# SYNOPSIS

| NAME OF SPONSOR/COMPANY: | INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER | (FOR NATIONAL AUTHORITY USE ONLY) |
|---|---|---|
| Johnson & Johnson Pharmaceutical Research & Development, L.L.C.<br>NAME OF FINISHED PRODUCT:<br>ER OROS® Paliperidone<br>NAME OF ACTIVE INGREDIENT(S):<br>Paliperidone | Volume:<br><br>Page: | |

**Protocol No.:** R076477-SCH-702

**Title of Study:** A Randomized, 6-Week Double-Blind, Placebo-Controlled Study With an Optional 24-Week Open-Label Extension to Evaluate the Safety and Tolerability of Flexible Doses of Extended Release OROS® Paliperidone in the Treatment of Geriatric Subjects With Schizophrenia – Open Label Phase

**Coordinating Investigator:** Tzimos Andreas, MD - Mental Hospital of Thessaloniki, Thessaloniki; Greece

**Publication (Reference):** None

**Study Initiation/Completion Dates:** 21 September 2004 to 15 November 2005 | **Phase of development:** 3

**Objectives:** The primary objective of the open-label extension phase was the long-term assessment of safety and tolerability of Extended Release (ER) OROS paliperidone (3 mg to 12 mg/day) in subjects (≥65 years of age) with schizophrenia, and the secondary objective was the assessment of long-term efficacy.

**Methodology:** The 24-week, open-label extension study that followed a 6-week, double-blind, placebo-controlled study (R076477-SCH-302) was conducted in Czech Republic, Greece, Russia, Slovakia, South Africa, and the Ukraine. Subjects in the open-label phase received flexibly dosed ER OROS paliperidone (3 mg to 12 mg/day) for 24 weeks.

**Number of Subjects (planned and analyzed):** No formal sample size calculation was performed for this study, since it was the open-label extension of the preceding study, R076477-SCH-302. Of the 114 subjects randomized in R076477-SCH-302, 88 subjects were enrolled into the open-label phase. This included 30 subjects who had previously received placebo and 58 subjects who had previously received ER OROS paliperidone. All 88 enrolled subjects received study medication, provided safety data, and had baseline and post-baseline efficacy assessments during the open-label phase; thus all subjects were included in the safety and intent-to-treat analysis sets.

**Diagnosis and Main Criteria for Inclusion:** Subjects who had completed the double-blind phase or discontinued due to lack of efficacy after at least 21 days of treatment, who signed the informed consent for the open-label phase, and who the investigator agreed that open-label treatment was in the best interest of the subject were eligible to participate in the open-label phase.

**Test Product, Batch No., Dose and Mode of Administration:** ER OROS paliperidone (one 3-mg tablet [3 mg dosage], two 3-mg tablets [6 mg dosage]; one 9 mg-tablet [9 mg dosage]; or one 3-mg tablet and one 9-mg tablet [12 mg dosage]) were administered orally once a day in the morning. The following batches were used: 3-mg tablet, MV0301019, MV0332871, and 0426911; 9-mg tablet, MV0301025, MV0406657, and 0426912. The initial dosage for all subjects was 6 mg/day. After 7 days, subjects who tolerated the 6-mg dose had their dosage increased to 9 mg/day; otherwise, the dose could be reduced to 3 mg/day at any time during the first week of treatment. After the initial 7 days, dosages were flexible within the 3 mg to 12 mg/day range. Dose increases were allowed no more frequently than every 7 days, in increments of ≤3 mg/day. Decreases were made as necessary, to a dosage ≥3 mg/day, in decrements of ≤3 mg/day. The minimum dose was 3 mg/day.

**Reference Therapy, Dose and Mode of Administration:** This was an open-label study and no reference therapy was administered.

**Duration of Treatment:** Open-label study drug (ER OROS paliperidone 3 mg to 12 mg/day) was administered for 24 weeks.

**Criteria for Evaluation:**

Efficacy: The efficacy variables included the change from baseline (double-blind) and baseline (open-label) to end point (last postbaseline assessment) in the following: Positive and Negative Syndrome Scale (PANSS) total score; Personal and Social Performance Scale (PSP); Clinical Global Impression Scale – Severity (CGI-S); Symptoms and Quality of Life in Schizophrenia Scale (SQLS); and PANSS Marder factor scores.

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Safety: Safety was based on the incidence of treatment-emergent adverse events and on changes from baseline in physical examinations, vital sign measurements, clinical laboratory tests, electrocardiograms (ECGs), and extrapyramidal symptoms (EPS) rating scales.

Other Evaluations: Paliperidone plasma concentration data (sparse sampling) were obtained for a population pharmacokinetic analysis and pharmacokinetic/pharmacodynamic evaluations.

**Statistical Methods:** No formal sample size calculation was performed for this study, since the primary objective was an evaluation of safety and tolerability. All subjects who enrolled, received study medication, and had at least 1 postbaseline assessment on any of the following scales: PANSS, PSP, CGI-S, or SQLS were included in the intent-to-treat (ITT) analysis set. Analyses involving changes from the baseline value (double-blind and open-label) to the final postbaseline value in the open-label phase used the last observation carried forward (LOCF) approach. The change in PANSS total score, PANSS factor scores, PSP, and SQLS from baseline (double-blind and open-label) to end point was presented using descriptive statistics. For CGI-S scores, frequency counts of scores by severity were summarized. Changes from baseline (double-blind and open-label) were calculated using descriptive statistics.

Treatment-emergent adverse events, clinical laboratory analyte values, vital sign measurements, ECG data, and EPS rating scales results during the open-label phase were summarized.

Pharmacokinetics: Descriptive statistics were calculated on actual and dose-normalized paliperidone plasma concentrations at Visit 111 (Day 169) and per time point (before, 1 to 2 hours after and at least 4 hours after dosing).

Actual and/or dose-normalized paliperidone plasma concentrations were graphically displayed as a function of dosage in order to explore dose proportionality.

**SUMMARY – CONCLUSIONS**

SUBJECT AND TREATMENT INFORMATION: The study population was predominantly female (73%), and the mean age was 69.4 years (range, 64 to 81 years). All subjects were diagnosed with schizophrenia and the median age at the time of diagnosis was 34.5 years. Subjects received a mean ER OROS paliperidone dose of 8 mg/day (median dose, 8.3 mg/day). The median duration of treatment was 168 days and the mean duration was 121.1 days for subjects who previously received placebo and 138.1 days for those who previously received ER OROS paliperidone.

PHARMACOKINETIC RESULTS: Given the flexible dose regimen in this study, subjects were assigned to a dose level for the purpose of pharmacokinetic analysis if they were on that particular dose for at least 5 days prior to sampling, during which steady state should have been achieved. The average dose-normalized (to 9 mg) paliperidone plasma concentrations at predose, 1 to 2 hours postdose, and more than 4 hours postdose were 44.9, 46.8 and 44.6 ng/mL, respectively, with no apparent fluctuation within a dosing interval (once daily). These values were consistent with the results obtained in the Study R076477-SCH-302.

EFFICACY RESULTS: The mean PANSS total score decreased from baseline (open-label) to end point irrespective of previous treatment, indicating improvements in the severity of symptoms associated with schizophrenia. Improvements in all 5 PANSS factor scores at end point were noted. The biggest treatment effect during the open-label phase was observed in subjects previously treated with placebo (placebo/paliperidone group), as these subjects had notably higher PANSS scores at open-label baseline. There were improvements in personal and social functioning based on the PSP, and directional changes indicative of improvement in global severity of illness using the CGI from baseline (open-label) to end point. Most subjects during the open-label phase demonstrated a change of at least one 10-point PSP category (improvement) at end point from double-blind baseline. Improvements in subject-rated symptoms and well-being were demonstrated using the SQLS.

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| Paliperidone | | |

SAFETY: ER OROS paliperidone, at flexible doses between 3 mg and 12 mg/day, was well tolerated in elderly subjects with schizophrenia. There were no deaths reported during the study, although 1 subject died later (4 days post-treatment), due to a non-treatment-emergent adverse event of bronchopneumonia that was judged as not related to study drug. The incidence of serious adverse events and adverse event resulting in discontinuation was low.

| | Pla/Pali (N=30) n (%) | Pali/Pali (N=58) n (%) | Total (N=88) n (%) |
|---|---|---|---|
| Any treatment-emergent adverse event | 24 (80) | 43 (74) | 67 (76) |
| Possibly related treatment-emergent adverse event | 12 (40) | 26 (45) | 38 (43) |
| Deaths | 0 | 0 | 0 |
| Any serious treatment-emergent adverse event | 2 ( 7) | 3 ( 5) | 5 ( 6) |
| Adverse event leading to permanent discontinuation | 3 (10) | 3 ( 5) | 6 ( 7) |

The most common adverse events reported in subjects were asthenia (14%), sinus tachycardia (11%), and insomnia (11%). Sinus tachycardia was reported more frequently in subjects who had previously received placebo (13% vs. 10%) and insomnia was more frequently reported in subjects who had previously received ER OROS paliperidone (16% vs. 3%). A review of subjects with insomnia indicates that the insomnia was either a symptom of worsening schizophrenia or psychosis or a result of the fluctuating nature of the underlying illness. Notably, no subjects had an adverse event of neuroleptic malignant syndrome, cerebrovascular disorders or events, seizures/convulsions, or tardive dyskinesia. There were also no cases of suicidal ideation/thoughts or potentially prolactin-related adverse events reported as an adverse event.

Somnolence was reported in 2 subjects, and no subjects discontinued due to somnolence. Two subjects had a glucose-related adverse event, although no subject met the criteria for treatment-emergent markedly elevated glucose values. Overall, long-term treatment with ER OROS paliperidone was associated with a low incidence of EPS. EPS-related adverse events were reported in 6% of subjects; none were serious and only tremor resulted in treatment discontinuation. Based on adverse events, orthostatic vital sign changes and elevations in plasma prolactin levels were considered to be of limited clinical relevance during long-term treatment.

There were no notable mean changes from baseline (open-label) in standing or supine systolic or diastolic blood pressure values. The incidence of abnormal increases in standing and supine pulse rates was higher in the placebo/paliperidone group than in the ER OROS paliperidone/paliperidone group (standing: 17% vs. 10%; supine: 10% vs. 3%). These results are in agreement with the adverse event reports of sinus tachycardia that were slightly higher in the placebo/paliperidone group than in the ER OROS paliperidone/paliperidone group (13% vs. 10%). They are also consistent with the fact that these adverse events occur early in treatment as illustrated by the higher incidence in the group naïve to paliperidone treatment. All events of sinus tachycardia were either mild or moderate in severity, none were serious or resulted in discontinuation of treatment; most cases occurred early in treatment and were transient. Treatment-emergent orthostatic hypotension, based on orthostatic changes in blood pressure and pulse rate, occurred only in 3 subjects. None of these subjects reported hypotension as an adverse event, suggesting that these findings are of limited clinical relevance. No noteworthy mean changes in body weight or BMI were noted. Three subjects had a body weight increase that exceeded the predefined upper limit of 7%, and for 1 of these subjects, this was reported as an adverse event. One additional subject also experienced weight increase as an adverse event.

Clinically significant instances of QT interval prolongation were to be reported as adverse events using MedDRA preferred terms “ECG QTc interval prolonged” and “ECG QT prolonged”. Seven subjects had a QT interval prolongation-related adverse event, although only 1 subject (Subject 200214) had QTcLD values ≥480 msec at any registered time point during open-label treatment. This subject discontinued the study due to ECG QTc interval prolonged that was also a serious event.

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CONCLUSION: In this 24-week open-label extension study, flexibly-dosed ER OROS paliperidone 3 mg to 12 mg/day was safe and well tolerated in elderly subjects with schizophrenia. The safety profile in this elderly population was generally consistent with that reported in adult subjects after short-term use and was consistent with the known pharmacological properties of paliperidone. No unexpected adverse events emerged that appear to be related to long-term exposure. Findings using rating instruments to assess long-term effectiveness were consistent, and showed improvements in the severity of symptoms associated with schizophrenia (PANSS), personal and social functioning (PSP), global severity of illness (CGI-S), and subject-rated symptoms and well-being (SQLS) in both treatment groups

Date of the report: 03 April 2006

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