CLINICAL STUDY REPORT SYNOPSIS

Document No.: EDMS-PSDB-6241435:2.0

Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development	
Name of Finished Product	ER OROS® Paliperidone	
Name of Active Ingredient(s)	paliperidone	

Protocol No.: R076477-SCH-701

Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study With an Open-Label Extension Evaluating Extended Release OROS® Paliperidone in the Prevention of Recurrence in Subjects With Schizophrenia

Coordinating Investigator: Kashinath Yadalam, M.D. - Lake Charles Clinical Trials, Lake Charles, LA; United States.

Publication (Reference):

Study Period: 09 Sep 2004 – 28 Aug 2006 | **Phase of Development:** 3

Objectives: The primary objective of the open-label extension was the long-term assessment of safety and tolerability of ER OROS paliperidone 3 to 15 mg/day in subjects diagnosed with schizophrenia. In addition, the long-term efficacy and effect of ER OROS paliperidone on overall functioning and personal and social functioning, as well as quality of life, health economics, and subjective sleep measures, was explored.

Methodology: This open-label extension study followed a recurrence prevention study (R076477-SCH-301) that had both an open-label run-in/stabilization phase and a double-blind, placebo-controlled phase. The study was conducted in the United States, Latvia, Lithuania, Romania, Turkey, and India. Subjects in the open-label phase received flexibly dosed ER OROS paliperidone (3 mg to 15 mg/day) for 52 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-301 (run-in phase, 530 subjects; stabilization phase, 312 subjects; double-blind phase, 207 subjects). A total of 235 subjects enrolled in the open-label extension, including 152 who had participated in the double-blind phase (80 treated with placebo treated and 72 treated with flexibly dosed ER OROS paliperidone 3 to 15 mg/day) and 83 subjects who were enrolled in the run-in or stabilization phases at the time of study termination and thus had no double-blind treatment. In the open-label extension, all subjects received ER OROS paliperidone, provided safety data, and were included in the safety analysis set, and 232 of these subjects also had baseline and post-baseline efficacy assessments and were included in the intent-to-treat analysis set.

Diagnosis and Main Criteria for Inclusion: Subjects who had experienced a recurrence event during the double-blind phase of Study R076477-SCH-301, remained recurrence free until the end of the double-blind phase, or were in the run-in or stabilization phases when the study was terminated; who signed the informed consent for the open-label extension, 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 extension.

Test Product, Dose and Mode of Administration, Batch No.: ER OROS paliperidone (one 3-mg tablet [3 mg dosage], two 3-mg tablets [6 mg dosage]; one 9 mg-tablet [9 mg dosage]; one 3-mg tablet and one 9-mg tablet [12 mg dosage]); or two 3-mg capsules and one 9-mg capsule (15 mg dosage) were administered orally once a day in the morning. The following batches were used: 3-mg tablet, 0426909, Mv0301019, Mv0332871, and Mv0332891; 9-mg tablet, 0426912, MV0301025, and MV0406657. The dosage of ER OROS paliperidone in the open-label extension started at 9 mg once daily and was titrated as needed within the 3 mg to 15 mg/day range based on the clinical observation of response and tolerability.

Reference Therapy, Dose and Mode of Administration, Batch No.: 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 15 mg/day) was administered for 52 weeks.

SYNOPSIS (CONTINUED)

Criteria for Evaluation:

Efficacy: The efficacy variables included the change from baseline (run-in, double-blind, and open-label) to end point open-label (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-R4); and PANSS Marder factor scores.

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.

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-R4 were included in the intent-to-treat analysis set. Analyses involving changes from the baseline value (run-in, 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-R4 from baseline (run-in, 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.

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.

SUMMARY - CONCLUSIONS

SUBJECT AND TREATMENT INFORMATION: The study population was predominantly male (66%), and the mean age was 35.8 years (range, 18 to 58 years). All subjects were diagnosed with schizophrenia and the median age at the time of diagnosis was 24.0 years. Subjects received a mean ER OROS paliperidone dose of 11.2 mg/day (median dose, 11.9 mg/day). The median duration of treatment was 363 days, and the mean duration was 269.4 days. Overall, 142 (60%) subjects completed the open-label extension, including 50 (63%) subjects previously treated with placebo, 48 (67%) previously treated with ER OROS paliperidone, and 44 (53%) who did not receive double-blind treatment. The most frequent reason for discontinuation was subject choice (21%). Treatment discontinuation due to adverse events occurred in 6% of subjects; this rate was greatest in subjects previously treated with double-blind placebo (11%) and lowest in those previously treated with double-blind ER OROS paliperidone (1%).

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 of the 5 PANSS factor scores at end point were noted. As expected, the largest treatment effect during the open-label extension was observed in subjects treated with double-blind placebo, 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-S from baseline (open-label) to end point. In addition, improvements in subject-rated symptoms and well-being were demonstrated using the SQLS-R4.

SAFETY RESULTS: There were no safety concerns or unexpected adverse events noted with ER OROS paliperidone in this open-label extension phase. Treatment-emergent adverse events occurred in 69% of subjects. The most common treatment-emergent adverse events (in 10% or more of all subjects) were tremor (13%) and akathisia (11%). One death, resulting from convulsion and pulmonary embolism, was reported during the open-label extension. The investigator considered the events to be probably related to study drug. The incidence of treatment-emergent serious adverse events was 6%, and the incidence of adverse events resulting in discontinuation was 5%. Ten subjects experienced tachycardia or sinus tachycardia, and 11 subjects experienced somnolence or sedation; none were severe, serious or resulted in discontinuation. No subject had a glucose-related adverse event or treatment-emergent markedly elevated glucose value. One subject experienced an adverse event of orthostatic hypotension that did not meet the prespecified definition of orthostatic hypotension. Of note, there were no subjects who experienced neuroleptic malignant syndrome or tardive dyskinesia. Three subjects experienced an adverse event related to suicidality, 1 of which (suicide attempt) was serious and resulted in permanent discontinuation from open-label treatment. Two subjects had non-serious events of suicidal ideation, one of which resulted in permanent discontinuation, the other resulted in temporary discontinuation of study medication. Tremor and akathisia were the most frequently reported EPS-related adverse events reported in 13% and 11% of all subjects, respectively. Two subjects discontinued due to an EPS-related event, but no event was considered serious. Results of EPS rating scales, including SAS, BARS, and AIMS, did not reveal a change over time in either the incidence or severity of movement disorders. Long-term use is associated with lower incidence of new-onset EPS events, as supported by the higher incidence of such events among the treatment group with the

SYNOPSIS (CONTINUED)

shortest duration of exposure to ER OROS paliperidone.

For most analytes, there were no noteworthy mean changes from baseline (open-label), incidence of treatment-emergent markedly abnormal laboratory findings was very low, and adverse events related to such findings were reported at a low incidence. There was a decrease in mean CK values among subjects who had received double-blind ER OROS paliperidone, compared with increased mean values among subjects who received double-blind placebo and those who did not receive double-blind treatment. There was a low incidence of increased CK values reported as a treatment-emergent markedly abnormal laboratory finding, and none were recorded as an adverse event nor were these findings consistently associated with EPS-related events. These results suggest that most of the observed increase in CK levels were benign and asymptomatic. These findings are consistent with the asymptomatic serum CK elevations that have been observed both as a phenomenon in chronic schizophrenics and reported in approximately 10% of schizophrenic patients taking antipsychotic drugs.

Median plasma prolactin levels increased during open-label treatment in subjects previously treated with double-blind placebo, but remained stable in subjects previously treated with double-blind ER OROS paliperidone and among subjects who did not receive double-blind treatment. At end point, median prolactin levels remained somewhat higher in subjects previously treated with placebo and were elevated in all treatment groups, more so among females than males. Thirteen (6%) female subjects experienced at least 1 potentially prolactin-related adverse event. No event was serious or severe, and 1 subject discontinued treatment due to amenorrhea.

There were no notable mean changes from baseline (open-label) in standing or supine SBP or DBP values. Overall, 19% of subjects experienced an abnormally high standing pulse rate, and 9% of subjects had an abnormally high supine pulse rate. As assessed by orthostatic changes in blood pressure and pulse rate, treatment-emergent orthostatic hypotension occurred in 21 (9%) subjects. None of these subjects reported hypotension as an adverse event, suggesting that these findings are of limited clinical relevance.

There was a modest mean change (increase) in body weight (1.5 kg). Thirty-seven (19%) subjects had a body weight increase that exceeded the predefined upper limit of 7%. Nine subjects experienced weight increase as an adverse event.

The incidence of treatment-emergent abnormalities in recorded ECG parameters (PR interval and QRS interval) was low. Based on ECG recordings, the incidence of abnormally high heart rate was 19% and was lowest among subjects previously treated with double-blind ER OROS paliperidone. These findings are consistent with pulse rate data.

No subject had a treatment-emergent abnormally high (≥500 ms) QT interval or QTc interval, using any of the correction methods. Most subjects had normal QTcLD values at baseline (open-label) and throughout the open-label extension phase. No subjects shifted from a QTcLD baseline of normal to ≥480 ms during open-label treatment. Four subjects had ECG QTc interval prolongation or ECG QT prolonged reported as adverse events, and none of these subjects had QTcLD interval values ≥450 ms at any registered time point. The ECG-related adverse events resulted in study withdrawal for 2 of these 4 subjects. No subjects experienced a serious event of QTc interval prolonged.

CONCLUSION: In this 52-week open-label extension study, flexibly-dosed ER OROS paliperidone 3 mg to 15 mg/day was safe and well-tolerated in subjects with schizophrenia. The safety profile was generally consistent with that observed in subjects after short-term use in the double-blind studies and was consistent with the known pharmacologic 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 further 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-R4) in both treatment groups

Issue Date of the Clinical Study Report: 12 February 2007

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.