CLINICAL STUDY REPORT SYNOPSIS

Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.	
Name of Finished Product	Extended-Release ER OROS® paliperidone	
Name of Active Ingredient(s)	paliperidone	

Protocol No.: R076477-SCH-705 (CR002944)

Title of Study: A Randomized, Double-Blind, Placebo- and Active-Controlled, Parallel-Group, Dose-Response Study to Evaluate the Efficacy and Safety of 3 Fixed Dosages of Extended Release OROS® Paliperidone (3, 9, and 15 mg/day) and Olanzapine (10 mg/day), With Open-Label Extension, in the Treatment of Subjects With Schizophrenia.

Coordinating Investigator: Robin Emsley, M.D. - Stikland Hospital, Research Centre, Belville, Cape Town; South Africa

Publication (Reference): None

Study Period: 15 June 2004 to 31 May 2006

Phase of Development: 3

Objectives: The primary objective of the open-label extension was the long-term assessment of safety and tolerability of flexibly-dosed ER OROS paliperidone (3 to 15 mg/day) in subjects with a diagnosis of schizophrenia.

Other measures assessed in the extension study included: change in the total Positive and Negative Syndrome Scale (PANSS) score; change in PANSS subscale (positive and negative) scores; overall functioning, as measured by the Clinical Global Impression Scale-Severity (CGI-S); personal and social functioning, as measured by the Personal and Social Performance Scale (PSP); and quality of life parameters, as measured by the Schizophrenia Quality of Life Scale, Revision 4 (SQLS-R4). In addition, a Healthcare Resource Use questionnaire was administered. Results of this questionnaire will be presented in a separate report.

Methodology:

Subjects who completed the 6-week, double-blind phase of the study (R076477-SCH-305) or who discontinued due to lack of efficacy after a minimum of 21 days, and who fulfilled the inclusion/exclusion criteria for the open-label extension, were entered in the 52-week open-label extension (R076477-SCH-705). Subjects participated in the open-label phase at 69 centers in United States, Canada, Mexico, Eastern Europe (Bulgaria, Poland, Romania, Ukraine), Israel, Asia (Hong Kong, Malaysia, Republic of Korea, Singapore, Taiwan) and South Africa.

In the open-label phase (R076477-SCH-705), subjects received flexibly dosed ER OROS paliperidone (3, 6, 9, 12, and 15 mg) administered once daily for 52 weeks. Treatment with open-label ER OROS paliperidone was to be initiated on the first day of the open-label extension at a starting dosage of 9 mg/day for all subjects. To obtain the optimal level of efficacy and tolerability for each subject, the dosage could be increased by 3 mg/day to a maximum of 15 mg/day, or decreased by the amount and frequency deemed necessary in the clinical judgment of the investigator.

Number of Subjects (planned and analyzed): Of the 618 subjects randomized into the double-blind phase (Study R076477-SCH-305), 408 subjects were enrolled into the open-label phase, 407 subjects were included in the safety analysis set (received study drug), and 406 subjects were included in the intent-to-treat analysis set.

Diagnosis and Main Criteria for Inclusion: Study R076477-SCH-305 enrolled male or female patients 18 years of age or older who met the DSM-IV criteria of schizophrenia for at least 1 year. Eligible subjects were experiencing active symptoms at the time of enrollment and had a PANSS total score between 70 and 120. The open-label extension study population comprised subjects who had completed the 6-week double-blind phase of the study or who had discontinued due to lack of efficacy after at least 21 days of treatment.

Test Product, Dose and Mode of Administration, Batch No.: ER OROS paliperidone 3-mg tablet (batch numbers 0426911/F016, MV0301019/F016, MV0307085/F016, MV0332871B/F016, MV0332891/F016) and ER OROS paliperidone 9-mg tablets (0426912/F017, MV0301025/F017, MV0406657/F017) were provided in perforated blister cards to allow for flexible dosing. Subjects were to be maintained on a flexible dosage as follows, 3 mg/day: one 3 mg tablet; 6 mg/day: two 3 mg tablets; 9 mg/day: one 9 mg tablet; 12 mg/day: one 3 mg tablet + one 9 mg tablet; 15 mg/day: two 3 mg tablets + one 9 mg tablet.

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

Duration of Treatment: Study drug was administered for 52 weeks.

SYNOPSIS (CONTINUED)

Criteria for Evaluation:

Efficacy: Changes from baseline (double-blind) and baseline (open-label) to end point were summarized for the following efficacy assessments during the 52-week open-label phase of the study: PANSS total score (sum of the scores of all 30 PANSS items), PSP (assessing socially useful activities, personal and social relationships, self-care, and disturbing and aggressive behavior), and SQLS scales (addressing emotional problems and vitality).

CGI-S frequency counts of scores by severity (mild, moderate, etc.) were summarized at each assessed time point. Changes from baseline (double-blind) and baseline (open-label) were calculated using descriptive statistics based on the numerical scores for both observed cases and LOCF values.

PANSS factor scores, including positive symptoms, negative symptoms, disorganized thoughts, uncontrolled hostility/excitement, and anxiety/depression, were calculated.

Safety: Evaluations of safety and tolerability included assessment of treatment-emergent adverse events (TEAE), extrapyramidal symptoms (EPS) rating scales, clinical laboratory tests (hematology, serum chemistry, and urinalysis), vital sign measurements, physical examinations, body weight and body mass index, and 12-lead ECGs.

Statistical Methods: The primary objective of this open-label extension study was to assess long term safety and tolerability of ER OROS paliperidone. Long-term efficacy assessment constituted one of the secondary objectives of the study. No statistical hypothesis was specified for this open-label extension study. Descriptive statistics were generated for exploratory purposes.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

The mean (SD) PANSS total score (-8.0 [20.63]) decreased from baseline (open-label) to the open-label end point for all subjects treated with open-label ER OROS paliperidone, indicating improvements in the severity of symptoms associated with schizophrenia. Subjects previously treated with double-blind placebo had the most improvement with a mean (SD) change of -16.1 (24.83). With the exception of the former ER OROS paliperidone 15 mg group, continued improvement was noted during open-label treatment for all 5 PANSS factor scores.

Findings on the PANSS were consistent with results on other investigator rated scales. The mean (SD) PSP score (6.0 [16.20]) increased from baseline (open-label) to the open-label end point for all subjects treated with open-label ER OROS paliperidone indicating improved functioning during open-label treatment.

The median CGI-S score in all treatment groups was either 3 or 4 at baseline (open-label) denoting mild or moderate severity of the subjects' psychotic condition. The median change from baseline (open-label) to end point for the CGI-S score was 0.0 (range, -5 to 4) across all ER OROS paliperidone-treated subjects.

The median and mean SQLS total scores decreased from open-label baseline to the open-label end point indicating continued improvement in subject-rated symptoms and well-being in all ER OROS paliperidone-treated subjects while on open-label treatment. The mean (SD) change from baseline (open-label) to end point in SQLS total score indicated greatest improvement in subjects previously treated with double-blind placebo (-4.7 [21.39]) or double-blind paliperidone 3 mg group (-4.2 [13.54]).

SAFETY RESULTS:

There were no deaths reported during the open-label phase. Treatment-emergent serious adverse events occurred in 53 subjects (most commonly psychotic disorder and schizophrenia) and most were judged by the investigators as either unrelated or doubtfully related to ER OROS paliperidone.

Summary of Treatment-Emergent Adverse Events During Open-Label Phase

	Pla/Pali (N=73) n (%)	Pali3/Pali (N=78) n (%)	Pali9/Pali (N=82) n (%)	Pali15/Pali (N=84) n (%)	Olan/Pali (N=90) n (%)	Total (N=407) n (%)
TEAE	63 (86)	62 (79)	66 (80)	62 (74)	75 (83)	328 (81)
Possibly related TEAE [(a)]	51 (70)	44 (56)	43 (52)	41 (49)	55 (61)	234 (57)
1 or more serious TEAE	8 (11)	9 (12)	16 (20)	11 (13)	9 (10)	53 (13)
TEAE leading to permanent stop	6 (8)	4 (5)	6 (7)	4 (5)	11 (12)	31 (8)

(a) Study drug relationships of possible, probable, and very likely are included in this category.
Olan=olanzapine; Pali=paliperidone; Pla=placebo; TEAE=treatment-emergent adverse event

A total of 31 subjects were discontinued due to TEAE (most commonly psychotic disorder and depression). More than half of these events were judged by the investigators as either unrelated or doubtfully related to ER OROS paliperidone.

TEAE events occurred in 81% of subjects; the most common events in ER OROS paliperidone-treated subjects

SYNOPSIS (CONTINUED)

were headache (18%), insomnia (17%), akathisia (11%), and anxiety (10%).

Overall, there were few cases of severe or serious EPS-related events or of EPS-related events that resulted in discontinuation. Results of EPS rating scales, EPS-related adverse events, and anti-EPS medication use were generally consistent regardless of previous treatment. Fourteen subjects, including 1 subject previously treated with double-blind placebo, experienced an adverse event related to suicidality. These events were serious in 7 subjects; additionally, 1 subject had a serious adverse event of self-injurious ideation. No subjects had neuroleptic malignant syndrome, anaphylactic reaction, peptic ulcer, or transient ischemic attack. One subject had an adverse event of convulsion that was serious, judged as possibly drug-related, and resulted in discontinuation.

There were no noteworthy mean changes from baseline (open-label) to the final visit for most laboratory analytes, including liver function, renal function, glucose, serum lipids, or hematology test values. For most analytes, the incidence of treatment-emergent markedly abnormal laboratory findings was very low. Two subjects (one with hypokalemia and one with hyponatremia) had laboratory-related adverse events that were reported as serious.

Mean increases in CK levels were observed for ER OROS paliperidone-treated subjects with high variability across the treatment groups. The mean increase for CK was greater in subjects previously treated with double-blind placebo versus those previously treated with any double-blind active treatment.

Median prolactin levels increased during open-label treatment in subjects previously treated with double-blind placebo and double-blind olanzapine. At all time points, median prolactin levels tended to be higher for females compared with males.

There were no clinically relevant changes from baseline (open-label) to end point in mean vital sign changes in ER OROS paliperidone-treated subjects during the open-label phase. The incidence of subjects who experienced increases or decreases in supine or standing systolic or diastolic blood pressure or decreases in supine or standing pulse rate was low (0 to 10%). Increases in standing or supine pulse rate were observed in 28% and 16% of ER OROS paliperidone-treated subjects, respectively.

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 22% in ER OROS paliperidone-treated subjects, and was slightly higher in subjects previously treated with double-blind placebo (33%) or double-blind olanzapine (26%) vs. double-blind paliperidone treatment (16 to 18%). These findings are consistent with pulse rate data.

No subject had a treatment-emergent abnormally high (≥500 ms) QT interval or QTc interval value during open-label treatment. Most subjects had normal QTcLD values at baseline (open-label) and throughout the open-label phase. No subject shifted from a normal QTcLD interval value to ≥480 ms and no subjects had a QTcLD baseline (open-label) value ≥480 ms.

Seven subjects had instances of ECG QT interval prolongation reported as adverse events. No subjects discontinued open-label treatment due to QTc interval prolonged or experienced a serious or severe 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 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 stability of symptoms or 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) regardless of prior treatment group.

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