CLINICAL STUDY REPORT SYNOPSIS

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Name of Sponsor/Company Johnson & Johnson Pharmaceutical Research & Development, LLC	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product ER OROS® paliperidone	Volume:	
Name of Active Ingredient(s) Paliperidone	Page:	

Protocol No.: R076477-SCH-703

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 (6, 9, and 12 mg/day) and Olanzapine (10 mg/day), With Open-Label Extension, in the Treatment of Subjects With Schizophrenia – Open Label Phase

Coordinating Investigator: Jaroslaw Strzelec, M.D., Ph.D, - Institution/Clinic, City, State; Country

Publication (Reference): None

Study Initiation/Completion Dates: 11 May 2004 to 29 December 2005	**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 12 mg/day) in subjects diagnosed with schizophrenia. The secondary objective was the assessment of long-term efficacy expressed as a function of change in the total Positive and Negative Syndrome Scale (PANSS) score, effect on positive and negative symptoms of schizophrenia by means of change in PANSS factor scores, and personal and social functioning, overall functioning, and quality of life parameters as measured by Personal and Social Performance Scale (PSP), Clinical Global Impression Scale – Severity (CGI-S), and Schizophrenia Quality of Life Scale (SQLS), respectively.

Methodology: This 52-week, open-label extension study followed a 6-week, double-blind, placebo- and active-controlled study (R076477-SCH-303) was conducted at 52 sites in 11 countries. Subjects in the open-label phase received flexibly dosed ER OROS paliperidone (3 mg to 12 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-303). Of the 630 subjects randomized in R076477-SCH-303, 473 were enrolled into the open-label phase. All 473 subjects received study medication and provided safety data and were thereby included in the safety population. The efficacy population included 472 subjects; 1 subject did not have a post-baseline efficacy measurement and was therefore not included in the analyses.

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, 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], or one 3-mg tablet plus 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, MV0307085, 0426911, V0332871B

9-mg tablet: 0426912, MV0301025, MV0406657

All subjects began dosing in the open-label phase with 9 mg. After 7 days, subjects who tolerated the 9-mg dose had their dosage increased to 12 mg/day. Dose decreases were made, as deemed necessary by the investigator, at any time point and by an increment, to a minimum dosage of 3 mg/day. After the initial 7 days, dosages were flexible within the 3 to 12 mg/day range. Dosages could be increased no more frequently than every 7 days, by increments of no larger than 3 mg/day each.

Reference Therapy, Dose and Mode of Administration, Batch No.: No reference therapy was administered.

Duration of Treatment: Open-label ER OROS paliperidone 3 mg to 12 mg/day was administered for 52 weeks.

SYNOPSIS (CONTINUED)

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.

Safety: Safety was evaluated 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 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.

SUMMARY – CONCLUSIONS

SUBJECT AND TREATMENT INFORMATION: The study population was approximately half female (51%) and half male (49%) and the mean age was 36.9 years. All subjects were diagnosed with schizophrenia and the median age at the time of diagnosis was 25 years (range, 5 to 60 years). Subjects received a mean ER OROS paliperidone dose of 9.3 mg/day (median dose, 9.0 mg/day). The median total duration of exposure to ER OROS paliperidone during the open-label phase was 359 days and the total mean duration was 254.1 days.

EFFICACY RESULTS: The mean PANSS total score decreased from baseline (open-label) to end point, irrespective of treatment, indicating improvements in the severity of symptoms associated with schizophrenia. Improvements in almost all 5 PANSS factor scores at end point were noted (2 treatment groups experienced no change for 2 PANSS factor parameters). Improvements during the open-label treatment phase were more prominent for subjects treated with placebo during the double-blind phase, although incremental improvement was also noted in subjects previously treated with ER OROS paliperidone and olanzapine. Findings on the PANSS were consistent with results on other investigator-rated scales, PSP (mean changes) and CGI-S (median changes), and showed improvements from baseline (open-label) to end point. There was an improvement in personal and social functioning based on the PSP, and directional changes indicative of improvement in global severity of illness using the CGI. 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. In addition, improvements in subject-rated symptoms and well-being were demonstrated using the SQLS. Taken together, results of the efficacy evaluations during 52 weeks of open-label treatment indicate that flexibly dosed ER OROS paliperidone (3 mg to 12 mg/day) was associated with clinically meaningful improvements in symptoms, global severity of the illness, and personal and social performance in subjects with schizophrenia, suggesting long-term symptomatic effects.

SAFETY RESULTS: ER OROS paliperidone, at flexible doses between 3 mg to 12 mg/day was well tolerated and no safety concerns were identified in this subject population. Two subjects died during the study, both of completed suicide events considered unrelated to study drug. Overall, the incidence of serious adverse events (13%) and adverse events that resulted in study discontinuation (6%) was low. Psychiatric disorders were the most common adverse events that caused discontinuation.

SYNOPSIS (CONTINUED)

Subjects with Treatment Emergent Adverse Events						
	Pla/Pali (N=88)	Pali6/Pali (N=87)	Pali9/Pali (N=91)	Pali12/Pali (N=101)	Olan/Pali (N=106)	Total (N=473)
Any TEAE	66 (75)	61 (70)	65 (71)	72 (71)	82 (77)	346 (73)
Possibly related TEAE[a]	51 (58)	42 (48)	46 (51)	45 (45)	55 (52)	239 (51)
Any serious TEAE	8 (9)	11 (13)	11 (12)	13 (13)	20 (19)	63 (13)
TEAE leading to permanent discontinuation	4 (5)	6 (7)	7 (8)	2 (2)	9 (8)	28 (6)
TEAE leading to death	0	1 (1)	0	0	1 (1)	2 (<1)

TEAE=treatment-emergent adverse event

[a] Study drug relationships of possible, probably, and very likely are included in this category.

Overall, the most common treatment-emergent adverse events were insomnia (14%), akathisia (12%), and tachycardia, depression, and psychotic disorder (10% subjects for each event). The incidence of these common treatment-emergent adverse events appeared to be relatively comparable across treatment groups. Psychiatric disorders were reported by a total of 42%; nervous system disorders were reported by a total of 36%. Cardiac disorders were reported by a total of 17% subjects. The incidence of cardiac disorders was higher in subjects who previously received ER OROS paliperidone 12 mg and olanzapine (21%) compared with subjects who previously received ER OROS paliperidone 6 mg (16%), placebo (15%) and 9 mg (11%).

The incidence of somnolence was comparable across treatment groups, with a total incidence of 35 (7%) subjects. There were no events of somnolence considered serious or that led to study discontinuation. Sinus tachycardia was reported as an adverse event in 20 (4%) subjects, with the highest incidence in subjects who previously received placebo. Two subjects (both in the olanzapine/ER OROS paliperidone group) experienced SAEs of tachycardia/sinus tachycardia, one of whom was discontinued from the study. Based on adverse events, orthostatic vital sign changes and elevations in plasma prolactin levels were as expected and were considered to be of limited clinical relevance during long-term treatment.

A total of 4 (1%) subjects experienced a glucose-related adverse event (including increased blood glucose, diabetes mellitus, and hyperglycemia). None of the glucose-related events were considered serious and none resulted in study discontinuation.

Clinically significant instances of QTc interval prolongation were to be reported by the investigator as adverse events. Of the 10 subjects who had clinically significant instances of QT interval prolongation recorded as adverse events, only 1 had a treatment-emergent QTcLD value =480 ms.

CONCLUSION: In this 52-week open-label extension study, flexibly-dosed ER OROS paliperidone 3 mg to 12 mg was safe and well tolerated in subjects with schizophrenia. The safety profile in this study 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, PSP, CGI-S, and SQLS) across all treatment groups.

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