SYNOPSIS

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

Protocol No.: CR004426

Title of Study: A Randomized, Double-Blind, Placebo- and Active-Controlled, Parallel-Group, Dose-Response Study to Evaluate the Efficacy and Safety of 2 Fixed Dosages of Extended Release OROS® Paliperidone (6 and 12 mg/day) and Olanzapine (10 mg/day), With Open-Label Extension, in the Treatment of Subjects With Schizophrenia

Coordinating Investigator: Adam Lowy, M.D.- Comprehensive NeuroScience, Inc., Washington, DC; USA

Publication (Reference): None

Study Initiation/Completion Dates: 18 March 2004 to 20 December 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 with schizophrenia, and the secondary objective was the assessment of long-term efficacy.

Methodology: The 52-week, open-label extension study that followed a 6-week, double-blind, placebo-controlled study (R076477-SCH-304) was conducted in the U.S. 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-304. Of the 444 subjects randomized in R076477-SCH-304, 203 subjects were enrolled into the open-label phase. This included 45 subjects who had previously received placebo, 59 subjects who had previously received ER OROS paliperidone 6 mg, 46 who had previously received ER OROS paliperidone 12 mg, and 53 who had previously received olanzapine 10 mg. All enrolled subjects received ER OROS paliperidone, provided safety data, and were included in the safety analysis set and 199 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 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, MV0307085, and MV0332891; 9-mg tablet, MV0301025 and MV0406657. The initial dosage for all subjects was 9 mg/day. Based on clinical observations of response and tolerability, this dosage could be increased by 3 mg/day at any time (although investigators were encouraged to wait ≥7 days to allow maximum effectiveness) to a maximum dose of 12 mg/day, or the dose could be reduced to the amount and frequency deemed necessary by the investigator at any time. After the initial dose, dosages were flexible within the 3 mg to 12 mg/day range. 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 52 weeks.

SYNOPSIS (CONTINUED)

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Criteria for Evaluation:

Efficacy: The efficacy variables included the change from baseline (double-blind) and baseline (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); 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 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.

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 (73%), and the mean age was 41.5 years (range, 20 to 76 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 10.2 mg/day (median dose, 10.1 mg/day). The median duration of treatment was 81 days and the mean duration was 143.5 days.

EFFICACY RESULTS: Subjects entering the open-label phase had previously experienced significant decreases in the mean PANSS total score during double blind treatment. Despite this improvement already realized at the start of the open-label phase, continued improvement was observed during open-label treatment. The mean PANSS total score decreased from baseline (open-label) to end point, indicating improvements in the severity of symptoms associated with schizophrenia. Improvements in 4 of the 5 PANSS factor scores at end point were noted, and the exception was uncontrolled/hostility excitement. Improvements during the open-label phase were most pronounced in subjects previously treated with double-blind placebo, as these subjects had notably higher PANSS scores at open-label baseline. There was an improvement in personal and social functioning based on the PSP with most subjects during the open-label phase demonstrating a change of at least one 10-point PSP category (improvement) at end point from double-blind baseline. Directional changes indicative of improvement in global severity of illness using the CGI from baseline (open-label) to end point were observed. Improvements in subject-rated symptoms and well-being were demonstrated using the SQLS.

SAFETY: ER OROS paliperidone, at flexible doses between 3 mg and 12 mg/day, was well tolerated in subjects with schizophrenia. There were no deaths reported during the open-label phase. The incidence of treatment-emergent serious adverse events was 27%, and the incidence of adverse events resulting in open-label discontinuation was 10%. As expected, schizophrenia and psychotic disorder were the most common adverse events considered serious or that resulted in discontinuation. Most of these events were judged by the investigators as either unrelated or doubtfully related to ER OROS paliperidone, and more likely related to the underlying psychiatric disorder.

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	Pla/Pali (N=45) n (%)	Pali6mg/Pali (N=59) n (%)	Pali12mg/Pali (N=46) n (%)	Olan/Pali (N=53) n (%)	Total (N=203) N (%)
Any treatment-emergent AE	36 (80)	45 (76)	37 (80)	36 (68)	154 (76)
Possibly related treatment-emergent AE	21 (47)	28 (47)	15 (33)	25 (47)	89 (44)
Any serious treatment-emergent AE	13 (29)	12 (20)	11 (24)	18 (34)	54 (27)
AE leading to permanent discontinuation	4 (9)	9 (15)	1 (2)	6 (11)	20 (10)
Deaths	0	0	0	0	0

The most common adverse events reported in subjects were headache (12%), psychotic disorder (10%), schizophrenia (10%), akathisia (9%), agitation (9%), and insomnia (9%). Notably, no subjects had an adverse event of neuroleptic malignant syndrome or seizures/convulsions. One subject had mild tardive dyskinesia. Eight subjects, including 4 subjects previously treated with double-blind placebo, experienced an adverse event related to suicidality. These events were serious in 5 subjects and caused discontinuation in 3 subjects (was serious in 2 of these 3 subjects). Additionally, 1 subject had a serious adverse event of self-injurious ideation and another subject had a non-treatment-emergent serious adverse event of suicidal ideation after completing the open-label phase.

Tachycardia was reported in 4 subjects (2%) and somnolence was reported in 11 subjects (5%). No event of tachycardia or somnolence was severe, serious, or resulted in discontinuation. Two subjects had a glucose-related adverse event, and 1 event met the criteria for treatment-emergent markedly elevated glucose. Overall, long-term treatment with ER OROS paliperidone was associated with a low incidence of EPS-related adverse events. None were serious and only 2 subjects discontinued due to an EPS-related adverse event. Twelve subjects (6%) experienced at least 1 potentially prolactin-related adverse event; none were serious and 1 subject discontinued due to erectile dysfunction. 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 pulse rates was higher in subjects previously treated with double-blind placebo. Treatment-emergent orthostatic hypotension, based on orthostatic changes in blood pressure and pulse rate, occurred only in 14 subjects (7%). 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. Nineteen subjects (13%) had a body weight increase that exceeded the predefined upper limit of 7%, and for 3 of these subjects, this was reported as an adverse event. Eight additional subjects 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”. Three subjects had a QT interval prolongation-related adverse event using the QTcB correction method, and none of these subjects had QTcLD interval values ≥480 ms at any registered time point. No events of QTc interval prolonged were severe, serious, or resulted in discontinuation.

CONCLUSION: In this 52-week open-label extension study, flexibly-dosed ER OROS paliperidone 3 mg to 12 mg/day was safe and well tolerated in subjects with schizophrenia. The safety profile in this population 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 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) in both treatment groups.

Date of the report: 13 June 2006

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