SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: ER OROS® 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.: R076477-SCH-302 CR004381

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

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

Publication (Reference): None

Study Initiation/Completion Dates: 04 August 2004 to 24 May 2005 | **Phase of development:** 3

Objectives: The primary objective of the double-blind phase of this study was to evaluate the safety and tolerability of flexibly dosed Extended Release (ER) OROS paliperidone (3 to 12 mg/day) compared with placebo in elderly subjects (≥65 years of age) with schizophrenia. Secondary objectives were to assess the improvement on psychotic symptoms (based on Positive ad Negative Syndrome Scale [PANSS]); the global improvement in severity of illness; the benefits in patient-reported symptoms and well-being related to schizophrenia; the benefits to personal and social performance; and the improvement to sleep associated with the use of ER OROS paliperidone compared with placebo. Additional objectives were to explore the pharmacokinetics (PK) and the relationship between PK and efficacy (PANSS) and safety parameters (extrapyramidal symptoms [EPS], adverse events), and the genes/genotypes that may be related to the response or metabolism of ER OROS paliperidone.

Methodology: This randomized, double-blind, placebo-controlled study was conducted in Czech Republic, Greece, Russia, Slovakia, South Africa, and the Ukraine. Following a screening phase, subjects were randomized to receive either placebo or flexibly dosed ER OROS paliperidone (3 to 12 mg/day) in double-blind fashion for 6 weeks.

Number of Subjects (planned and analyzed): The planned total sample size was approximately 105 subjects (2:1 ratio ER OROS paliperidone: placebo). 132 subjects were screened; 114 eligible subjects were randomly assigned to receive flexibly dosed ER OROS paliperidone (n=76) or placebo (n=38). All 114 randomized subjects received study medication, provided safety data, and had both baseline and post-baseline efficacy assessments; thus, all were included in both the safety and intent-to-treat analysis sets.

Diagnosis and Main Criteria for Inclusion: Male or female patients aged 65 years or older with a DSM-IV diagnosis 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.

Test Product, Batch No., Dose and Mode of Administration: ER OROS paliperidone (one 3-mg capsule [3 mg dosage], two 3-mg capsules [6 mg dosage]; one 9 mg-capsule [9 mg dosage]; or one 3-mg capsule and one 9-mg capsule [12 mg dosage]) were administered orally once a day in the morning. The following batches were used: 3-mg capsule, 03J01/F022 and 04D05/F022; 9-mg capsule, 03J13/F023 and 04E04/F023. The initial dosage was 6 mg/day. After 7 days, subjects who tolerated the 6-mg dose had dosage increase 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 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.

Reference Therapy, Dose and Mode of Administration: ER OROS paliperidone matching placebo (one 3-mg capsule; two 3-mg capsules; one 9 mg-capsule, or one 3-mg capsule and one 9-mg capsule) were administered orally once a day in the morning (batches 03I08/F027 and 04A12/F027).

Duration of Treatment: Study drug was administered for 6 weeks.

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Criteria for Evaluation:

Efficacy: The efficacy variables included the change from baseline to end point (Day 43 or last postbaseline assessment) in the following: 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); as well as in quality of sleep and daytime drowsiness visual analog scale (VAS) and PANSS Marder factor and subscale scores. Other variables included onset of therapeutic effect and treatment responders.

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, ECGs, and EPS scale scores.

Other Evaluations: Paliperidone plasma concentration data (sparse sampling) were obtained for a population pharmacokinetic analysis and pharmacokinetic/pharmacodynamic evaluations. Genotyping of *CYP2D6* was performed for a subset of subjects.

Statistical Methods: Tolerability of the flexible dosing regimen was evaluated from 2 perspectives: 1) the maximum dose reached by the subjects (based on the percentage of subjects who reached dose levels of 6 mg, 9 mg, or 12 mg for at least 1 day during the double-blind phase) and 2) the dose maintained (the dose most frequently taken in the last 14 days of the double-blind treatment). Efficacy assessment was a secondary objective. Since no formal calculation was performed for sample size and power, the 95% confidence interval (CI) inferential approach was used in the analysis of efficacy variables without adjustment for multiple intervals. The change in PANSS total score from baseline to end point for the ER OROS paliperidone group was compared with that in the placebo group by use of an analysis of covariance (ANCOVA) model with treatment, analysis center, and age group (≥65 to <70, ≥70 to ≤75, and >75 years of age) factors, and the baseline PANSS total score as a covariate. Using this model, least squares (LS) means of the difference and 2-sided 95% CI were presented for the change in the ER OROS paliperidone group versus placebo. For CGI-S scores, the median difference between groups in the score change at end point was estimated using the Hodges-Lehmann procedure. For CGI-S, PSP, SQLS, and sleep VAS scores, 95% CI for the mean difference between treatment groups in the score change was produced using ANCOVA on the change with factors for treatment, age group, and analysis center as well as the baseline score as a covariate. A 95% CI analysis was performed for each of the PANSS factor scores as described by Marder. Onset of therapeutic effect was defined as the first time point at which the treatment groups became different (i.e. when 95% CI for the difference between groups in LS means did not include zero) and remained different until end point with regard to the estimated LS mean change from baseline in the PANSS total score (LOCF). Responders were defined as subjects with a 30% or more reduction from baseline in the PANSS total score at the last postbaseline assessment in the double-blind phase. The cumulative response rate, defined as the percentage of subjects experiencing at least a given value of percent reduction from baseline in PANSS total score, was presented graphically.

SUMMARY – CONCLUSIONS

SUBJECT AND TREATMENT INFORMATION: The study population was predominantly female (73%); the mean age was 69.7 years (range, 64 to 81 years). The mean baseline PANSS total score was 92.6 (range, 75-119). The most commonly used doses of ER OROS paliperidone were 6 mg/day and 9 mg/day. The dose of 6 mg/day was maintained by 34% of all subjects. The use of the modal dose of 6 mg/day and the percentage of subjects who maintained their dose level at 6 mg/day increased with age. The higher doses of 9 mg/day and 12 mg/day were reached by approximately one-third of the subjects each and maintained by 29% and 25% of subjects, respectively. Across the prespecified dose levels of 6, 9, and 12 mg/day, most subjects (between 65% and 76%) were able to maintain the maximum dose they achieved without the need for dose reduction.

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PHARMACOKINETIC RESULTS: Given the flexible dose regimen, subjects were assigned to a particular dose level if they were receiving that dose for ≥5 days prior to sampling, at which time steady state should have been achieved. The paliperidone plasma concentrations increased in a dose-proportional manner for the 6, 9 and 12 mg/day doses. The average dose-normalized (to 9 mg) paliperidone plasma concentrations at predose, 1 to 2 hours postdose, and more than 4 hours post-dose were 50.3±33.7, 48.6±33.2 and 47.9± 30.4 ng/mL, respectively, on Day 15 and 48.3±36.0, 50.2± 36.0 and 47.1± 31.6 ng/mL, respectively, on Day 36, with no apparent fluctuation within a dosing interval and no accumulation of paliperidone over a period of 5 weeks. These values were generally within the expected concentration range for adults, although the average concentrations were higher than those observed with a 9 mg dose in adults in a previous trial (Study R076477-P01-102) (maximum, 40.2±24.1 ng/mL; average, 31.7±19.3 ng/mL). Given that paliperidone is mainly excreted unchanged by the kidneys, a higher exposure can be expected in elderly subjects due to age-related deterioration of the renal function. There were no noteworthy differences in dose-normalized plasma concentrations across the age groups, although the number of subjects in the older age groups was too small for definite conclusions.

EFFICACY RESULTS: In both treatment groups, PANSS total scores decreased from baseline to end point, indicating improvement in the severity of schizophrenia symptoms. Despite high placebo response, flexibly dosed ER OROS paliperidone was superior to placebo with regard to improving PANSS total scores at end point. This clinically notable result was consistent with the numerically higher response rate observed in the ER OROS paliperidone group (38%, compared to 29% in the placebo group). Placebo-treated subjects discontinued treatment due to lack of efficacy at a higher rate (16%) than subjects receiving ER OROS paliperidone (4%). ER OROS paliperidone showed directional changes on CGI-S at end point indicative of improvement in global severity of illness. There was no difference between the treatment groups in the change from baseline in either PSP or SQLS scores. Compared to placebo, ER OROS paliperidone treatment led to improvements in PANSS factor scores, (positive and negative symptoms of schizophrenia and anxiety/depression); no differences between the treatment groups were observed in factor scores on disorganized thoughts and uncontrolled hostility/excitement. Based on the results of a self-administered VAS, ER OROS paliperidone treatment was numerically superior to placebo with regard to improving the subjects' quality of sleep, and was not associated with an increase in daytime drowsiness.

SAFETY: ER OROS paliperidone, at flexible doses between 3 and 12 mg/day, was generally well tolerated by elderly subjects with schizophrenia. There were no deaths among subjects receiving ER OROS paliperidone, and the incidence of serious adverse events in that group was lower than in the placebo group. The incidence of adverse events resulting in treatment discontinuation was similar between treatment groups.

	Placebo (N=38) n (%)	ER OROS PAL (N=76) n (%)	Total (N=114) n (%)
Any treatment-emergent adverse event	27 (71)	51 (67)	78 (68)
Possibly related treatment-emergent adverse event	17 (45)	38 (50)	55 (48)
Treatment-emergent adverse event leading to death	2 (5)	0	2 (2)
Any serious treatment-emergent adverse event	3 (8)	2 (3)	5 (4)
Adverse event leading to permanent discontinuation	3 (8)	5 (7)	8 (7)

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Overall, treatment-emergent adverse events occurred at similar rates in the 2 treatment groups. Common adverse events that occurred more frequently in subjects treated with ER OROS paliperidone were tachycardia, somnolence, dizziness, ECG abnormal specific, and hypotension; those events more frequently reported by subjects in the placebo group included extrapyramidal disorder, psychosis, T-wave inversion, vomiting, and upper respiratory tract infection. Notably, there were no reports of neuroleptic malignant syndrome, cerebrovascular disorders or events, or tardive dyskinesia. There were also no cases of suicidal ideation/thoughts, glucose-related or potentially prolactin-related adverse events, or orthostatic hypotension reported as an adverse event. The adverse events reported for the 3 subjects treated in error with ER OROS paliperidone 15 mg/day were transient and consistent with the safety profile in the rest of the study population.

Somnolence, mostly mild in severity, was reported at a higher rate in the ER OROS paliperidone group; no subjects discontinued due to somnolence. Overall, ER OROS paliperidone was associated with a low incidence of EPS. EPS-related adverse events were reported at the same incidence in both groups; none were serious or resulted in treatment discontinuation. Based on adverse events, orthostatic vital sign changes and elevations in serum prolactin and creatine kinase in the ER OROS paliperidone groups were considered to be of limited clinical relevance.

Both standing and supine pulse rates in the ER OROS paliperidone group showed slight mean increases on Days 5 and 6, compared to the corresponding decreases in the placebo group; these increases were more pronounced and persistent in the older subjects. Consistent with the observations in the adults, there was a higher incidence of abnormally high pulse rates and abnormally high heart rates in the ER OROS paliperidone group. These data were in agreement with the reports of tachycardia as an adverse event (16% in ER OROS paliperidone group vs. none in the placebo group). All cases of tachycardia were either mild or moderate in severity, none were serious or resulted in discontinuation of treatment; most cases occurred early in treatment, were transient and brief in duration. Based on orthostatic changes in blood pressure and pulse rate, treatment-emergent orthostatic hypotension during the double-blind phase occurred only in the ER OROS paliperidone group (3 subjects, 4%). None of these subjects reported hypotension as an adverse event, suggesting that these findings are of limited clinical relevance. There was no evidence of significant weight increases, and no changes in body weight were reported as adverse events in ER OROS paliperidone group; no noteworthy mean changes in body weight or BMI were noted.

Overall, the ECG findings were comparable between the 2 groups. Clinically significant instances of QTc interval prolongation were reported by the investigators as adverse events using preferred terms “ECG abnormal specific” (ER OROS paliperidone: 7%; placebo: 3%) and “QT prolonged” (ER OROS paliperidone: 1%; placebo: 3%). Two of the 5 subjects who experienced the adverse event of ECG abnormal in the ER OROS paliperidone group were withdrawn from the study (the event was reported on Day 4 in both cases), including 1 subject who had QTcB and QTcF values of 500 msec or higher. Consistent with the observed increases in heart rate, only QTcB values, but not values derived from other QTc corrections, were classified as borderline or prolonged in 3 of these 5 cases. In the ER OROS paliperidone group, 13 subjects experienced a shift in QTcLD duration from normal at baseline to borderline or prolonged and/or had instances of QTc interval prolongation reported as adverse events (ECG abnormal specific or QT prolonged). Twelve of these 13 subjects had a significant prior history of cardiovascular disorders and/or cardiovascular adverse events or QTc prolongation reported before initiation of treatment.

PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS: The correlation of paliperidone plasma concentrations with safety parameters (EPS rating scales: AIMS, BARS and SAS, and cardiovascular safety parameters: QTcLD) was explored graphically. There was no apparent relationship between plasma concentration and any of the EPS and cardiovascular safety parameters or their respective shifts from baseline.

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CONCLUSION: ER OROS paliperidone, administered at flexible doses of 3, 6, 9, and 12 mg/day to elderly schizophrenic subjects, was superior to placebo with respect to improvement in PANSS total score at end point and was associated with a numerically higher response rate. Compared to placebo, ER OROS paliperidone treatment led to significant improvements in PANSS factor scores at end point, including positive and negative symptoms of schizophrenia and anxiety/depression symptoms. These observations were consistent with the directional changes indicative of improvement in global clinical state at end point for subjects receiving ER OROS paliperidone versus placebo. Overall, ER OROS paliperidone treatment was associated with a clinically meaningful reduction in symptoms in elderly subjects with schizophrenia.

ER OROS paliperidone, administered at flexible doses of 3, 6, 9, and 12 mg/day, was generally safe and well tolerated by elderly subjects with schizophrenia. The safety profile of ER OROS paliperidone in this population was generally consistent with that reported in adult subjects. With the exception of higher and more persistent increases in pulse rates observed in the older subjects, no clinically important differences across age groups were observed.

Date of the report: 28 October 2005

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