SYNOPSIS

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

Protocol No.: CR0004384

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; U.S.A.

Publication (Reference): None

Study Initiation/Completion Dates: 13 April 2004 to 31 August 2005	**Phase of development:** 3

Objectives: The primary objectives of the double blind (DB) phase of this study were to evaluate the efficacy of paliperidone extended release tablets (referred to as ER OROS paliperidone in this report) compared with placebo in the prevention of recurrence of symptoms of schizophrenia, and to assess the safety and tolerability of ER OROS paliperidone in subjects with schizophrenia. The efficacy evaluation was based on time to recurrence of symptoms of schizophrenia (based on predefined criteria) during the DB phase. Secondary objectives were to evaluate subject improvement in symptoms associated with schizophrenia (Positive and Negative Syndrome Scale for Schizophrenia [PANSS]); to assess global improvement in severity of illness (Clinical Global Impression Scale – Severity [CGI-S]), the benefits in personal and social performance (PSP), the benefits in patient-reported symptoms and well-being related to schizophrenia (Quality of Life in Schizophrenia Scale [SQLS]), and the improvement in quality of sleep (self-administered Visual Analog Scale [VAS]); and to explore the genes/genotypes that may be related to the response or metabolism of ER OROS paliperidone. Safety of ER OROS paliperidone compared with placebo was assessed using adverse events, physical examinations, vital sign measurements, clinical laboratory evaluations, electrocardiograms (ECGs), and EPS rating scales (Abnormal Involuntary Movement Scale [AIMS], Barnes Akathisia Rating Scale [BARS], and Simpson Angus Scale [SAS]).

Methodology: The study was conducted in the USA, Latvia, Lithuania, Romania, Turkey, and India. Following a screening phase, subjects entered an 8-wk run-in (RI) phase during which they received open-label (OL), flexibly dosed ER OROS paliperidone. Those subjects who achieved control of their acute schizophrenic symptoms and maintained a stable dose regimen during the last 2 wks of the RI phase entered the OL 6-wk stabilization (ST) phase, where they received the same dose of ER OROS paliperidone. Subjects who remained on that stable dose and continued to meet the eligibility criteria with regard to symptom control qualified for entry into the DB phase of variable duration, where they were randomly assigned to receive either flexibly dosed ER OROS paliperidone (3 to 15 mg/day) or placebo (in a 1:1 ratio) in DB fashion until they experienced a recurrence event, withdrew from the study, or until the DB phase was terminated.

Number of Subjects (planned and analyzed): The planned sample size was 432 subjects, based on the expectation that 216 randomized subjects would provide 86 recurrence events during the DB phase. If necessary, up to 600 subjects could be enrolled to achieve the required number of recurrence events. Of the 530 subjects enrolled in the RI phase (all treated analysis set), 312 (59%) subjects entered the ST phase, and 207 (39%) subjects were randomized to DB treatment (placebo, n=102; ER OROS paliperidone, n=105). The intent-to-treat (ITT) efficacy analysis set for the final analysis included 205 subjects (placebo, n=101; ER OROS paliperidone, n=104); the DB safety analysis set included 206 subjects (placebo, n=102; ER OROS paliperidone, n=104). At the time of the interim efficacy analysis (which was considered primary efficacy analysis, see Statistical Methods section of this synopsis), 113 subjects were randomized into the DB phase of the study and received at least 1 dose of double blind study medication (placebo, n=55; ER OROS paliperidone, n=58); the interim analysis ITT analysis set included 111 subjects (placebo, n=55; ER OROS paliperidone, n=56).

Diagnosis and Main Criteria for Inclusion: Male or female patients 18 to 65 years of age who met the DSM-IV criteria of schizophrenia for at least 1 year and were experiencing active symptoms at the time of enrollment into the RI phase (with a PANSS total score between 70 and 120). To enter the DB phase, the subjects had to first achieve symptom control during the 8-wk RI phase, while receiving a stable dose of ER OROS paliperidone during the last 2 wks of that phase; and then to maintain symptom control on the same dose during the 6-wk ST phase.

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Test Product, Dose and Mode of Administration, Batch No.: During the RI/ST phases, subjects received ER OROS paliperidone tablets in OL fashion (3-mg and 9-mg; flexible dose [range, 3 to 15 mg/day] during first 6 wks of RI phase; fixed dose during the last 2 wks of RI phase and 6-wk ST phase). During DB phase, subjects received overencapsulated ER OROS paliperidone tablets as one 3-mg capsule (3 mg dosage); two 3-mg capsules (6 mg dosage); one 9 mg-capsule (9 mg dosage); one 3-mg capsule and one 9-mg capsule (12 mg dosage); or two 3-mg capsules and one 9-mg capsule (15 mg dosage) orally once a day in the morning. The batch numbers were MV0301019/ F016, MV0332871B/ F016, 03I10/ F022, 03J01/ F022, 04D05/ F022, 05A03/ F022 for 3-mg capsule and MV0301025/ F017, MV0406657/ F017, 03I22/ F023, 03G14/ F023, 03J13/ F023, 04E04/ F023, 05A10/ F023 for 9-mg capsule. The starting dose was ER OROS paliperidone 9 mg/day, and was increased if needed to achieve symptom control, by 3 mg/day every 7 days up to a maximum of 15 mg/day. The dose was decreased as necessary for patient safety. The dose ranged between 3 mg to 15 mg. If required, the dose of study drug was adjusted during double-blind treatment within the range of 3 mg to 15 mg/day.

Reference Therapy, Dose and Mode of Administration, Batch No.: During the DB phase, subjects assigned to placebo received placebo capsules matching ER OROS paliperidone administered orally once a day in the morning (batch numbers, 03I08/ F027, 03J27/ F027, 04A19/ F027, 04A12/ F027, 04A26/ F027).

Duration of Treatment: Study medication was administered for 8 wks during the RI phase, 6 wks during the ST phase, and a variable length of time during the DB phase (until recurrence event, withdrawal, or DB phase termination; median duration, ER OROS paliperidone: 44.5 days [range, 3 to 330 days]; placebo, 28.5 days [range, 5 to 299 days]).

Criteria for Evaluation:

Efficacy: The primary efficacy variable was the time to the first recurrence event in the DB phase. Efficacy analyses in the DB phase were performed comparing ER OROS paliperidone with placebo. Secondary efficacy variables were assessed for the RI/ST phases based on the change from RI baseline and for DB phase based on the change from DB baseline. The secondary efficacy analyses included the change from baseline to endpoint in the PANSS total score and the change from baseline to corresponding end point in the following scores: CGI-S; PSP; SQLS; VAS; and PANSS subscale scores.

Safety: Safety assessment was based on the type and 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: No pharmacokinetic analysis was conducted. Genotyping of CYP2D6 was performed for a subset of subjects.

Statistical Methods: The primary efficacy variable was the time to recurrence during the DB phase. Subjects who met any of the predefined recurrence criteria were considered to have had a recurrence event; all other subjects were considered censored as of their last day of DB phase. The cumulative distribution function of the time to recurrence was estimated by the Kaplan-Meier method, time to recurrence was summarized, and treatments were compared using a 2-sided log-rank test. The estimate of the hazards ratio and its 95% confidence interval (CIs) was based on the Cox proportional hazards model with treatment as a covariate. An additional sensitivity analysis including any follow-up data without medication, if available, was performed. In addition, Cox proportional hazards model with treatment, region, and baseline body mass index (BMI) as covariates was performed. The overall significance level across treatment groups for all secondary analyses was 0.05 (2-sided) with no multiplicity adjustments. Analyses of DB data involving changes from baseline used the last observation carried forward (LOCF) approach. Using an analysis of covariance (ANCOVA) model with treatment and analysis center and DB baseline PANSS total score as a covariate, the change from baseline to end point for the ER OROS paliperidone treatment group was compared to the change of the placebo group for the DB phase. For the PANSS total, PANSS subscales, CGI-S, PSP, SQLS, and sleep VAS total scores, at each DB assessment time point, except baseline, the p-values for the test of a difference between the ER OROS treatment group and placebo were determined using an ANCOVA model on the change (on the ranked data for CGI-S) with factors for treatment and analysis center, and with baseline score as a covariate.

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The 2-stage group sequential design allowed for early termination of the study in order to limit the number of potential recurrences if the preplanned interim analysis yielded significant evidence of efficacy. At the time of the 43rd recurrence event (50% of the planned recurrence events), interim analysis was performed by the independent data monitoring committee (IDMC). The interim analysis demonstrated a statistically significant difference in favor of ER OROS paliperidone, and the decision was made on August 01, 2005 to terminate the study per the IDMC recommendation. Since the study was terminated because of the significant results of the interim analysis, this analysis is considered the primary analysis as prespecified in the study protocol, and the analysis of the final efficacy data is considered confirmatory.

SUMMARY – CONCLUSIONS

SUBJECT AND TREATMENT INFORMATION: The 530 subjects who entered the study were mostly male (68%) and white (53%); the mean age was 37.9 years (range, 17 to 64 years). Most subjects (82%) had a diagnosis of paranoid schizophrenia. At RI baseline, the mean PANSS total score was 92.1 (range, 70-132). Based on CGI-S, most subjects' psychotic condition at RI baseline was either moderate (49%), or marked (40%). The starting RI dose of ER OROS paliperidone was 9 mg/day. The mean mode dose was 10.8 mg/day during the RI phase, 11.2 mg/day during ST phase, and 10.8 mg/day during the DB phase.

EFFICACY RESULTS: Based on interim analysis, ER OROS paliperidone was superior to placebo (p=0.0053) with regard to the primary efficacy endpoint of time to recurrence of symptoms of schizophrenia and the number of recurrence events (Table 1). This was confirmed in the final analysis (p<0.001), where the rate of recurrence was 51.5% (placebo) vs. 22.1% (ER OROS paliperidone), and the estimated time point at which 25% of subjects experienced a recurrence event was 23 days (placebo) vs. 68 days (ER OROS paliperidone).

Table 1: Number of Subjects Experiencing Recurrence Events and Time to Recurrence During the Double-Blind Phase

			Overall		
Descriptive[a]	Placebo	ER OROS PAL	Chisq	DF	P-value[b]
Primary Efficacy Analysis (Interim Analysis)					
Number Assessed	55	56			
Number Censored (%)	26 (47.3)	42 (75.0)			
Number Recurred (%)	29 (52.7)	14 (25.0)			
25% Quantile (95% CI)	23.0 (14.0; 42.0)	83.0 (32.0; NE)			
Median (95% CI)	62.0 (42.0; 119.0)	NE[c] (97.0; NE)			
75% Quantile (95% CI)	NE[d] (116.0; NE)	NE[d]			
Statistical Test			7.7713	1	0.0053
Confirmatory Analysis (Final Analysis)					
Number Assessed	101	104			
Number Censored (%)	49 (48.5)	81 (77.9)			
Number Recurred (%)	52 (51.5)	23 (22.1)			
25% Quantile (95% CI)	23.0 (15.0; 29.0)	68.0 (50.0; NE)			
Median (95% CI)	58.0 (44.0; 114.0)	NE[c]			
75% Quantile (95% CI)	261.0 (116.0; NE)	NE[d]			
Statistical Test			18.709	1	<0.001

[a] Based on Kaplan-Meier product limit estimates.
[b] Log rank test.
[c] Less than 50% of subjects experienced a recurrence event.
[d] Less than 75% of subjects experienced a recurrence event.
NE = not estimable

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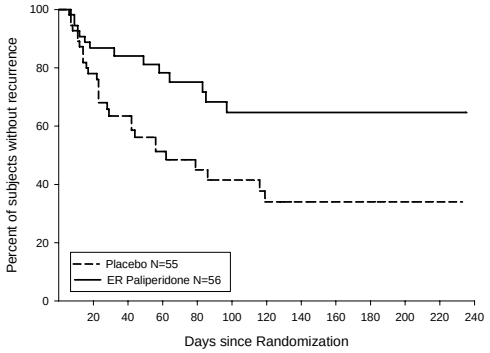
Kaplan-Meier plot of the time to recurrence for primary efficacy analysis (Figure 1) shows that a higher proportion of subjects in the ER OROS paliperidone group, compared to placebo, did not experience a recurrence event.

Figure 1. Kaplan-Meier Plot of Time to Recurrence (Interim Analysis)



During the 14-wk OL treatment in RI/ST, substantial improvements in symptom control, compared to RI baseline, were observed for the all treated analysis set based on the decrease in the PANSS total score (mean change [SD], -38.0 [16.03]) and decrease in the global severity of clinical impairment (median change in CGI-S rating, -2.0 points). The final PSP scores at end of the RI/ST OL treatment were consistent with a mild degree of impairment. Improvement was also observed in all PANSS factor scores and the SQLS scores. Based on self-administered VAS, ER OROS paliperidone improved quality of sleep and did not produce or exacerbate daytime drowsiness.

Symptom stability was achieved for subjects entering the DB phase (DB baseline PANSS total score, 53.4 [placebo] and 51.0 [ER OROS paliperidone]; DB baseline median CGI-S rating, 3.0 in both groups). During the DB phase, a statistically significant advantage over placebo was observed for ER OROS paliperidone with regard to changes from DB baseline to end point in each of the secondary efficacy variables, including PANSS total score (mean change in total score [SD]: placebo, 15.1 [19.10] vs ER OROS paliperidone, 6.0 [13.62]) and PANSS subscales; CGI-S (median change: placebo, 1.0 vs ER OROS paliperidone, 0.0); PSP score (mean change [SD]: placebo, -8.0 [12.58] vs ER OROS paliperidone, -3.0 [10.40]), as well as SQLS and VAS scores. Placebo-treated subjects experienced a statistically significant worsening of symptoms compared to subjects who continued to receive ER OROS paliperidone and maintained symptom control.

SAFETY RESULTS: AEs reported in at least 10% of subjects during RI/ST phases were tremor, headache, hyperkinesia, and insomnia. During DB phase, only psychosis, aggressive reaction, and insomnia were reported in 5% of subjects or more in any treatment group. Psychosis and aggressive reaction occurred more frequently in subjects treated with placebo. The rate of discontinuations due to AEs was low (RI/ST phases: 5%; DB phase: ER OROS paliperidone, 3%; placebo, 1%). No deaths were reported during RI/ST phases. One subject, withdrawn from ST phase due to suicidal ideation, committed suicide the day after withdrawal. During DB phase, 2 deaths were reported in the placebo group (1 suicide and 1 death due to non self-inflicted multiple gunshot wounds). Serious treatment-emergent adverse events (AEs) were reported at the rates of 6% during RI/ST phases; and at the rates of 8% (ER OROS paliperidone) vs. 16% (placebo) during DB phase; most serious AEs across phases were psychiatric disorders, most likely related to the underlying psychotic disorder.

There were no reports of neuroleptic malignant syndrome, cerebrovascular disorders or events, or tardive dyskinesia. EPS-related AEs were reported in 31% of the 530 subjects during the RI/ST phases; the EPS-related AEs with an onset during RI/ST phases were mostly reported early in treatment (58% within 3 weeks, 76% within 5 weeks). Of the EPS-related AEs, 73% that had the onset during RI/ST resolved during either RI/ST or DB treatment. Of the EPS-related AEs that resolved, 75% did so within 3 weeks of onset. Based on AE reports, orthostatic changes in vital signs and elevations in serum prolactin, glucose, and creatine kinase were of limited clinical relevance.

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SAFETY RESULTS (Cont.) For most laboratory analytes, the incidence of treatment-emergent, markedly abnormal laboratory findings was low and suggested no between-group difference in incidence during DB phase. Prolactin levels increased after treatment with ER OROS Paliperidone and returned to normal when it was withdrawn. Increased prolactin levels were uncommonly associated with reported adverse events. Both standing and supine pulse rates showed mean increases at early evaluations of the RI phase. In DB phase, mean standing pulse rates showed increases at most evaluations in the ER OROS paliperidone group vs. decreases in the placebo group. Despite the high incidence of abnormally high heart rates, tachycardia was reported as an AE in only 7% of subjects during RI/ST phases. Mean body weight increases were observed in both groups from RI baseline to DB endpoint (ER OROS paliperidone, 1.8 kg vs. placebo, 0.2 kg). The incidence of AEs related to abnormal laboratory findings or vital sign parameters was low.

The majority of subjects had normal QTcLD values throughout the study. There were no cases of postbaseline increases in QTcLD interval values above 60 ms. During DB, there were no clinically significant differences between the groups with regard to changes in QTcLD values from baseline. QTcLD shifted from normal to prolonged during RI/ST phases in 2 subjects, 1 of whom was withdrawn from the study due to an AE ("QT prolonged"). During the RI/ST phases, clinically significant QTc interval prolongation was reported using WHOART preferred terms "ECG abnormal specific" (4 subjects; 1%) and "QT prolonged" (2 subjects; <1%). No such AEs were reported during the DB phase.

CONCLUSIONS: During double-blind, placebo-controlled treatment of up to 11 months (median duration, 44.5 days in the ER OROS paliperidone group, 28.5 days in the placebo group), ER OROS paliperidone effectively prevented recurrence of symptoms of schizophrenia in patients who achieved symptom stability. During the double-blind period, ER OROS paliperidone treatment maintained symptom control as measured by the efficacy scales including PANSS, CGI-S, and PSP.

The study also demonstrated that 14-wk OL treatment with ER OROS paliperidone resulted in considerable improvement in the symptoms of schizophrenia in subjects with acute exacerbation at the time of enrollment.

In this long-term study, flexibly dosed ER OROS paliperidone (3 mg/day to 15 mg/day) was generally well tolerated by subjects with schizophrenia.

Date of the report: 15 MARCH 2006

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