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.: CR004378

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: 17 February 2004 to 22 December 2005 | **Phase of development:** 3

Objectives: The primary objective of the double-blind phase of this study was to evaluate the efficacy and safety of 2 fixed dosages of Extended-Release (ER) OROS paliperidone (6 and 12 mg/day) compared with placebo in subjects with schizophrenia. The efficacy response was measured by the change in the Positive and Negative Syndrome Scale (PANSS) total score from start of treatment to the end of the double-blind phase. Secondary objectives were to assess benefits in personal and social performance, global improvement in severity of illness, the benefits in patient-reported symptoms and well-being related to schizophrenia. Additional objectives were to assess the improvement to sleep associated with the use of ER OROS paliperidone compared with placebo, and to explore the dose-response relationship of ER OROS paliperidone, the relative efficacy of the ER OROS paliperidone groups versus the olanzapine group, the pharmacokinetics and the relationship between pharmacokinetics and efficacy (PANSS) and safety parameters (extrapyramidal symptoms [EPS], adverse events) of interest, and the genes/genotypes that may be related to the response or metabolism of ER OROS paliperidone. Safety of ER OROS paliperidone 6 or 12 mg/day compared with placebo and olanzapine 10 mg/day, was assessed using adverse events, physical examinations, vital sign measurements, clinical laboratory evaluations, electrocardiograms (ECGs), and EPS rating scales.

Methodology: This randomized, double-blind, placebo- and active-controlled, parallel-group, dose-response study was conducted in the U.S. Following a screening phase, subjects were randomized to receive placebo, ER OROS paliperidone 6 or 12 mg, or olanzapine 10 mg in double-blind fashion for 6 weeks. The primary reason for inclusion of the olanzapine 10 mg treatment group in the study was to have a concurrent active control group to confirm that the study was adequate to detect a drug effect (i.e., assay sensitivity) in case the 2 ER OROS paliperidone treatment groups had failed to show efficacy.

Number of Subjects (planned and analyzed): 440 subjects (110 per group) were planned for enrollment. 570 subjects were screened for the study, 444 subjects were randomly assigned to a treatment group (110 to placebo, 112 to 6 mg ER OROS paliperidone, 112 to 12 mg ER OROS paliperidone, and 110 to 10 mg olanzapine). 432 subjects were analyzed for efficacy (received study drug and had at least 1 postbaseline efficacy assessment), 439 subjects were analyzed for safety (received study drug).

Diagnosis and Main Criteria for Inclusion: Male or female patients 18 years of age or older and 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.

Test Product, Dose and Mode of Administration, Batch No.: ER OROS paliperidone two 3-mg capsules (batch numbers 03G09/F022. 04C29/F022, 04D13/F022; 6 mg dosage group) and ER OROS paliperidone one 3-mg capsule and one 9-mg capsule (batch numbers 03G14/F023, 03D26/F023; 12 mg dosage group) were administered orally once a day in the morning.

Reference Therapy, Dose and Mode of Administration, Batch No.: Olanzapine 10-mg capsule (two 5-mg tablets overencapsulated into a single capsule; batch numbers 03G31/F291, 03J23/F291, 04B26/F291) and 1 placebo capsule (olanzapine 10 mg dosage group) or 2 placebo capsules (placebo group; batch numbers 03F02/F125, 03J20/F125, 04B09/F125, 04B16/F125) were administered orally once a day in the morning.

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

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Criteria for Evaluation:

Efficacy: Key efficacy analyses were performed comparing results for each ER OROS paliperidone group with placebo. The criterion for the primary efficacy variable was the change from baseline in PANSS total score at the end of the double-blind phase (Day 43 or last postbaseline assessment). The secondary efficacy analyses included the change from baseline in the variable score at the end point (Day 43 or last postbaseline assessment): Personal and Social Performance Scale (PSP), Clinical Global Impression Scale – Severity (CGI-S), and Symptoms and Quality of Life in Schizophrenia Scale (SQLS). Other efficacy variables included the change from baseline to end point in sleep visual analog scale (VAS) and PANSS subscale scores, onset of therapeutic effect, and treatment responders. (An additional analysis compared the change from baseline in PANSS total scores for each ER OROS paliperidone group with the olanzapine group.)

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 and olanzapine 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: The change in PANSS total score from baseline to end point for each ER OROS paliperidone group was compared with placebo and between the ER OROS paliperidone 6 mg and 12 mg groups by use of an analysis of covariance (ANCOVA) model with treatment and analysis center as factors, and the baseline PANSS total score as a covariate (primary analysis). A similar analysis was performed for each of the PANSS factor scores as described by Marder and the PANSS subscale scores. For each ER OROS paliperidone group that was shown to be superior to placebo in the primary analysis, the comparison between this group and placebo was performed for PSP, CGI-S, and SQLS. Statistical comparisons between each ER OROS paliperidone group and placebo for the change from baseline in PSP scores (ANCOVA), CGI-S scores (ANCOVA on the ranks of change), and in SQLS were performed using the unconditional randomization resampling algorithm to adjust for multiple testing. An additional analysis for the change from baseline to end point in PSP scores was performed using the Dunnett procedure to adjust for multiple comparisons. Statistical comparisons between each ER OROS paliperidone group and the placebo group for the change from baseline in sleep VAS scores using an ANCOVA model were performed. Onset of therapeutic effect was calculated as the first time point at which a change from baseline in PANSS total score in subjects treated with ER OROS paliperidone 6 or 12 mg was significantly different (nominal significance level of 5%, 2-tailed) and remained different for the remainder of the study, than the change from baseline in PANSS total score in subjects treated with placebo. Responders were defined as subjects who show a 30% or more reduction from baseline in the PANSS total score at the last postbaseline assessment in the double-blind phase. Differences between each ER OROS paliperidone group and placebo were compared using a Cochran-Mantel-Haenszel test controlling for analysis center. (Also, an analysis of the change from baseline in PANSS total scores comparing each ER OROS paliperidone group with olanzapine was performed using an ANCOVA model with treatment and analysis center as factors and with baseline as a covariate.)

SUMMARY - CONCLUSIONS

PHARMACOKINETIC RESULTS:

For the 6 mg ER OROS paliperidone treatment group, mean paliperidone plasma concentrations at predose, 1-2 hours postdose, and more than 4 hours postdose were 22.2, 20.2, and 19.6 ng/mL, respectively, at Visit 6 and 19.0, 18.3, and 18.3 ng/mL, respectively, at Visit 9. For the 12 mg ER OROS paliperidone treatment group, mean paliperidone plasma concentrations at predose, 1-2 hours postdose, and more than 4 hours postdose were 37.6, 38.0, and 34.6 ng/mL, respectively, at Visit 6 and 35.8, 34.6, and 35.3 ng/mL, respectively, at Visit 9. Plasma concentrations of olanzapine at predose, 1-2 hours postdose, and more than 4 hours postdose were 16.2, 20.3, and 25.0 ng/mL, respectively, at Visit 6 and 15.7, 19.2, and 24.6 ng/mL, respectively, at Visit 9.

EFFICACY RESULTS: As shown below, ER OROS paliperidone, 6 mg/day and 12 mg/day, demonstrated significant improvement compared to placebo with regard to changes from baseline to end point in PANSS total score (primary efficacy variable) as well as CGI-S. Results of additional analyses of PANSS scores were consistent with the primary efficacy analysis. Improvement in PANSS total score vs. placebo was first observed early with ER OROS paliperidone (Day 4 for the 6 mg group and Day 15 for the 12 mg group); statistical superiority over placebo was maintained for the duration of the 6-week double-blind phase. At end point, significantly more subjects who received ER OROS paliperidone 6 mg (50%) or 12 mg (51.4%) compared to placebo (34.3%) demonstrated a 30% or greater reduction from baseline in PANSS total score (i.e., "treatment response"). Discontinuation rates due to lack of efficacy were lower in the ER OROS paliperidone groups compared to the placebo group, and a higher proportion of subjects completed the double-blind phase in the ER OROS paliperidone 12 mg group versus the 6 mg group.

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paliperidone		

EFFICACY RESULTS (continued): Both ER OROS paliperidone groups had directional changes (indicative of improvement) from baseline to end point in PSP scores; a statistically significant advantage over placebo was observed for the 6 mg dose group but not the 12 mg group. Improvement in quality of sleep VAS scores without exacerbation of daytime drowsiness was observed for both doses of ER OROS paliperidone.

	Placebo (N=105)	ER OROS PAL 6 mg (N=111)	ER OROS PAL 12 mg (N=111)
PANSS total score (primary end point) (n)	105	110	111
Mean change (SD)	-8.0 (21.48)	-15.7 (18.89)*	-17.5 (19.83)*
PSP (n)	88	93	91
Mean Change (SD)	2.9 (13.04)	8.8 (13.92)*,#	6.6 (13.06)
CGI-S (n)	105	111	111
Median Change (Range)	0.0 (-4;2)	-1.0 (-4;1)#	-1.0 (-3;1)#
SQLS (n)	100	107	107
Mean Change (SD)	-3.3 (16.31)	-6.7 (16.62)	-5.7 (14.19)
PANSS Subscales (n)	105	111	111
Mean change (SD)			
Positive symptoms	-2.9 (7.07)	-5.2 (5.95)†	-6.0 (6.68)†
Negative symptoms	-2.2 (6.59)	-4.4 (5.87)†	-3.9 (5.56)†
Disorganized thoughts	-1.7 (5.13)	-2.7 (4.33)	-3.7 (4.98)†
Uncontrolled hostility/excitement	0.3 (3.90)	-1.2 (3.92)†	-1.5 (3.91)†
Anxiety/depression	-1.5 (4.36)	-2.3 (3.67)	-2.4 (3.75)
Quality of Sleep (n)	101	106	107
Mean change (SD)	-3.3 (36.16)	8.3 (33.40)†	6.8 (35.03)†
Daytime Drowsiness (n)	101	107	107
Mean change (SD)	-2.6 (29.93)	0.9 (31.57)	1.2 (31.96)

* Denotes a statistically significant ($p<0.05$) improvement in score versus placebo using Dunnett's procedure to adjust for multiple comparisons.

# Denotes a statistically significant ($p<0.05$) improvement in score versus placebo using Unconditional Randomization Resampling Algorithm to adjust for multiple comparisons.

† Denotes a statistically significant ($p<0.05$) improvement with no adjustment for multiple comparisons.

A comparison between the olanzapine 10 mg group and the ER OROS paliperidone 6 mg and 12 mg groups in terms of the primary efficacy end point showed similar directional changes and no statistically significant between-group differences.

SAFETY RESULTS:

ER OROS paliperidone, 6 and 12 mg/day, was well tolerated by subjects with schizophrenia. There were no deaths, and the incidence of serious adverse events and adverse events resulting in discontinuation was similar across treatment groups.

Treatment-Emergent Adverse Events	Placebo (N=106) n (%)	ER OROS PAL 6 mg (N=112) n (%)	ER OROS PAL 12 mg (N=112) n (%)	Olanzapine 10 mg (N=109) n (%)
Any event	82 (77)	82 (73)	89 (79)	79 (72)
Events related to study drug	45 (42)	52 (46)	59 (53)	61 (56)
Serious events	11 (10)	10 (9)	8 (7)	12 (11)
Events leading to study drug discontinuation	5 (5)	7 (6)	5 (4)	7 (6)

Of the more common adverse events, somnolence was reported more frequently by subjects who received olanzapine (28%) compared to other treatments (13% for placebo and both ER OROS paliperidone groups). A higher incidence of hypertonia, dystonia, tongue paralysis, extrapyramidal disorder, and hyperkinesia was observed in the ER OROS paliperidone 12 mg group compared to other treatment groups; the incidence and severity of these events was similar for the placebo and the ER OROS paliperidone 6 mg groups. Overall, the incidence and severity of EPS-related adverse events and results of EPS rating scales indicated that the study drugs were associated with a low incidence of EPS. Isolated cases of severe EPS-related events, suicidal ideation/thoughts, anaphylactic reaction, and seizure occurred, and there were no reports of neuroleptic malignant syndrome or cerebrovascular disorders/events. No tardive dyskinesia was reported in subjects receiving active treatment. Based on adverse event reports, orthostatic changes in vital signs and elevations in serum prolactin, glucose, and creatine kinase in the ER OROS paliperidone groups were of limited clinical relevance.

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SAFETY RESULTS (continued):

For most laboratory analytes, the incidence of treatment-emergent, markedly abnormal laboratory findings was low and suggested no between-group difference in incidence; there was also a low incidence of adverse events related to abnormal laboratory findings. The percentage of subjects with abnormally high pulse rates was higher in the ER OROS paliperidone groups versus the placebo group and in the ER OROS paliperidone 12 mg group versus the 6 mg group, but the incidence of adverse events of tachycardia showed only a small difference between ER OROS paliperidone (5% in both dose groups) and placebo (3%). Mean body weight increases were observed in all treatment groups; these increases were greatest among subjects who received olanzapine (3.3%), followed by ER OROS paliperidone 12 mg (2.5%) and ER OROS paliperidone 6 mg (1.3%), and lowest in the placebo group (0.5%).

Clinically significantly prolonged QTc intervals were to be reported as adverse events (preferred term: ECG abnormal specific). The incidence of these adverse events was similar across treatment groups (3-6%). Two subjects with treatment emergent QTcB values ≥500 ms—1 in the ER OROS paliperidone 6 mg group and 1 in the olanzapine group (who also had severe hypokalemia and prolonged QTcLD, QTcF, and QTlc)—were withdrawn from the study, in part due to prolonged QT values. In both cases, resolution of the prolonged QT values occurred 3 to 4 days later.

PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS

Graphical display of pharmacokinetic-pharmacodynamic relationships showed no apparent relationship between paliperidone plasma concentrations and any of the assessed safety parameters (AIMS, BARS, SAS total scores) or their respective shifts from baseline.

CONCLUSIONS:

ER OROS paliperidone, administered at doses of 6 mg and 12 mg per day, was significantly more effective than placebo in improving PANSS total scores at end point (primary efficacy variable) in this 6-week double-blind trial in subjects with schizophrenia. The treatment effect was observed as early as Day 4 with ER OROS paliperidone 6 mg and Day 15 with ER OROS paliperidone 12 mg.

Improvements were noted in PSP score with ER OROS paliperidone; these reached statistical significance for the 6 mg group.

Significant effects of both doses of ER OROS paliperidone were noted on the positive and negative symptoms and uncontrolled hostility/excitement scores of the PANSS subscales, and the clinical relevance of these observed effects was confirmed by a significant decrease in the CGI-S score versus placebo. Also noteworthy is the improvement in quality of sleep VAS scores without exacerbation of daytime drowsiness, which was observed for both doses of ER OROS paliperidone.

ER OROS paliperidone, administered at doses of 6 mg and 12 mg per day for 6 weeks, was generally safe and well tolerated in subjects with schizophrenia. The highest dose studied (12 mg per day) was associated with a higher incidence of selected EPS-related adverse events and a greater mean increase in prolactin level, pulse rate, and body weight.

Date of the report: 28 October 2005

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