CLINICAL STUDY REPORT SYNOPSIS

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Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development	
Name of Finished Product	INVEGA®	
Name of Active Ingredient(s)	Paliperidone	

Protocol No.: CR010855

Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy and Safety of Flexibly-Dosed Extended-Release Paliperidone as Adjunctive Therapy to Mood Stabilizers in the Treatment of Acute Manic and Mixed Episodes Associated With Bipolar I Disorder

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Publication (Reference): None

Study Period: 24 April 2006 to 29 August 2007 | **Phase of Development:** 3

Objectives: The primary objectives of this study were to demonstrate antimanic efficacy and assess the safety and tolerability of paliperidone extended-release (ER) relative to placebo during 6 weeks of treatment in subjects with Bipolar I Disorder who experience acute manic or mixed episode(s) (with or without psychotic features) while taking lithium or valproate. The key secondary objective of the study was to assess the effect of paliperidone ER on global functioning as compared to placebo during 6 weeks of treatment. Other objectives were to: 1) assess the onset of antimanic clinical response to paliperidone ER as compared to placebo; 2) assess the global improvement in severity of illness associated with the use of paliperidone ER as compared to placebo; 3) evaluate the impact of paliperidone ER therapy on health-related functional status, using the Short Form (SF-36), as compared to placebo; 4) assess the impact of paliperidone ER on depressive symptoms as compared to placebo; 5) assess the impact of paliperidone ER on psychotic symptoms as compared to placebo using a symptom-rating scale; and 6) explore the pharmacokinetics of paliperidone ER in subjects with Bipolar I Disorder. Pharmacokinetic evaluations included the assessment of the time of study drug administration relative to food intake and the type of meal during the first 6 days of study treatment and the assessment of the pharmacokinetics in relationship to the efficacy and safety of paliperidone ER.

Methodology: This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter clinical study in subjects with Bipolar I Disorder. Subjects who experienced acute manic or mixed episodes and who may or may not have been taking lithium or valproate were screened for study entry eligibility. The study consisted of a screening period of no more than 14 days, a 6-week double-blind treatment phase, and a 1-week posttreatment visit. The screening period included a washout period of no more than 7 days during which antimanic and mood-stabilizing treatments other than lithium or valproate were discontinued. For those subjects entering the study not taking lithium or valproate, treatment with either mood stabilizer was initiated at the start of screening and extended for up to 2 weeks (including 7 days of washout). Subjects completing the screening/washout phase entered a 6-week double-blind, treatment phase after a balanced, and random assignment to 1 of 2 treatment groups: flexibly-dosed oral paliperidone ER (3 to 12 mg/day) or flexibly-dosed placebo once daily added to the mood stabilizers lithium or valproate. End-of-study/early-withdrawal assessments were completed on Day 42 after the last dose of study drug was administered. A follow-up (posttreatment) visit was scheduled approximately 1 week after the end-of-study/early-withdrawal visit.

Number of Subjects (planned and analyzed): The planned sample size was 296 subjects (148 per treatment group). A total of 438 subjects were screened for this study, and 300 subjects (150 each in the flexibly-dosed and placebo and paliperidone ER groups) were randomized to 1 of 2 treatment groups (flexibly-dosed placebo and flexibly-dosed paliperidone ER 3 to 12 mg/day). The safety and intent-to-treat analysis sets consisted of 150 subject in the placebo group and 149 subjects in the paliperidone ER group. One subject, randomized to the paliperidone ER (3 to 12 mg/day) group, did not receive the double-blind medication.

Diagnosis and Main Criteria for Inclusion: Male and female subjects were eligible for this study if they were 18 to 65 years of age, inclusive; met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for Bipolar I Disorder, most recent episode manic or mixed (with or without psychotic features) at screening; had a history of at least 1 documented manic or mixed episode requiring medical treatment within 3 years of screening; had a total score of at least 20 on the Young Mania Rating Scale (YMRS) at screening and baseline (Day 1); and had taken the mood stabilizers lithium or valproate as part of their treatment for Bipolar I Disorder for a minimum of 2 weeks prior to randomization.

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Test Product, Dose and Mode of Administration, Batch No.: Paliperidone ER was supplied as 3- and 9-mg over-encapsulated tablets (Batch Nos. 0500130/F16 and 0500236/F017, respectively). Oral doses of paliperidone ER ranging from 3 to 12 mg per day were achieved by combining, where appropriate, 3 and 9 mg paliperidone ER tablets (1 or 2 tablets).

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo (Batch Nos. 05F03/F027 and 06C20/F027) was supplied as over-encapsulated tablets identical to the paliperidone ER capsules. Doses consisted of 1 or 2 capsules taken orally once daily.

Duration of Treatment: The study consisted of a 14 day screening/washout period, a 42 day double-blind treatment period, and a follow-up visit approximately 1 week after the end-of-study/early withdrawal visit.

Criteria for Evaluation:

Efficacy: The following parameters were used to evaluate efficacy: YMRS, Global Assessment of Functioning (GAF), Clinical Global Impression-Bipolar Disorder-Severity of Illness Scale (CGI-BP-S), Positive and Negative Syndrome Scale (PANSS), Short Form 36 (SF-36), and Sleep Visual Analog Scale (VAS).

Safety: The following parameters were used to evaluate safety: adverse events, clinical laboratory tests, vital signs, weight, waist circumference, and body mass index (BMI), ECGs, physical examination, rating scales for extrapyramidal symptoms, Montgomery-Asberg Depression Rating Scale (MADRS), and Scale for Suicidal Ideation (SSI).

Pharmacokinetics: Plasma concentrations of paliperidone were determined from blood samples taken at baseline (Day 1), Day 6, and Day 21; prior to study drug administration and at least 8 hours after study drug administration on Day 6.

Pharmacogenomics: Approximately 10 mL of whole blood was obtained for genetic analysis from subjects who provided specific written informed consent to participate in the genetics portion of the study. No genetic analysis was performed at the time of this report.

Statistical Methods: For the primary (YMRS) and key secondary efficacy (GAF) assessments, an analysis of covariance (ANCOVA) model was used to analyze the change from baseline score with treatment, country, and mood stabilizer (i.e., lithium or valproate) as factors, and baseline YMRS or GAF scores as covariate. The last observation-carried-forward (LOCF) method was used. Treatment effects were estimated based on the least-squares means of the difference. Two–sided 95% confidence intervals (CIs) were presented for the mean change of the paliperidone ER group versus placebo. At each time point, descriptive statistics of the numerical scores and change from baseline were presented. The analysis of the key secondary endpoint was declared significant only if the analysis of the primary endpoint (YMRS) was also significant. At each CGI-BP-S assessment time point and endpoint, frequency counts of scores by severity label (mild, moderate, etc.) were produced by treatment group for both observed case and LOCF data. Descriptive statistics (N, median, and range) of the numerical scores and the change from baseline were presented. At each assessment time point except baseline and follow-up, the p-values for the test of a difference between paliperidone ER and placebo were produced using an ANCOVA model on the ranks of the change with treatment, country, and mood stabilizer as factors and baseline score as a covariate. Onset of therapeutic effect was defined as the first time point at which the treatment groups (paliperidone ER versus placebo) were different (at the 2–sided 5% level of significance) and remained different thereafter until endpoint based on the change from baseline in the total YMRS score (LOCF). The between-group comparison of the change from baseline in Sleep VAS, total PANSS score, and PANSS individual subscales scores were analyzed by means of an ANCOVA model with treatment, country, and mood stabilizer as factors and baseline score as a covariate. The between-group comparison of the change from baseline in the 2 summary scale scores of the SF-36 as well as the 8 domain subscale scores were analyzed by means of an ANCOVA model with treatment, country, and mood stabilizer as factors and baseline score as a covariate. The safety assessments were evaluated using descriptive statistics and frequency tabulations.

SUMMARY - CONCLUSIONS

Thirty-three percent of subjects entered the study with a diagnosis of Bipolar I Disorder, most recent episode mixed, and 67% entered the study with a most recent episode of manic. Thirty-eight percent of subjects received lithium as the mood stabilizer and 62% received valproate. The median modal dose of paliperidone ER used in this study was 6 mg/day.

EFFICACY RESULTS: The treatment of Bipolar I Disorder subjects with paliperidone ER at dosages of 3 to 12 mg/day (mean final dose of 8.1 mg/day) for 6 weeks did not result in a statistically significant improvement in total YMRS score relative to placebo at endpoint (p=0.160). The mean (SD) change from baseline to endpoint in YMRS score was -14.3 (10.01) in the paliperidone ER group and -13.2 (10.91) in the placebo group. While this change was not statistically significant relative to placebo, a statistically significant treatment-by-country interaction was seen in the primary efficacy YMRS model. Specifically, there was little to no difference in the

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change from baseline in total YMRS score between treatment groups among subjects at centers in the United States of America and Russia, where the majority (46% and 23%, respectively) of subjects were enrolled. Other participating countries had too few subjects to draw definitive conclusions. There was insufficient evidence to indicate that the choice of mood stabilizer (lithium or valproate) differentially affected the change from baseline to endpoint in total YMRS score across treatment groups. There was no statistically significant difference in the proportion of YMRS responders and remitters between treatment groups. Consistent with the primary efficacy analysis (YMRS), there was no statistically significant difference between paliperidone ER and placebo for the following efficacy variables: global functioning (GAF), severity of illness (CGI-BP-S), psychotic features (PANSS), quality of sleep, (Sleep VAS), and health-related functional status (SF-36). A statistically significant increase in daytime drowsiness (Sleep VAS) was observed in the paliperidone ER-treated subjects (p=0.021).

SAFETY RESULTS:

Adverse Events

As shown in the table below, treatment-emergent adverse events occurred more frequently in the paliperidone ER group (70%) as compared to placebo (54%). This includes treatment-emergent adverse events possibly related to the study medication, 42% (paliperidone ER) as compared to 26% (placebo), and treatment-emergent adverse events leading to a permanent stop in the double-blind medication, 8% (paliperidone ER) as compared to 1% (placebo).

Overall Summary of Treatment-Emergent Adverse Events - Double-Blind Phase
(Study R076477-BIM-3003: Safety Analysis Set)

	Placebo (N=150) n (%)	PALI ER (N=149) n (%)
TEAE	81 (54)	104 (70)
Possibly related TEAE [a]	39 (26)	62 (42)
1 or more serious TEAE	7 (5)	7 (5)
TEAE leading to permanent stop	2 (1)	12 (8)

[a] Study drug relationships of possible, probable, and very likely are included in this category.
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Of the treatment-emergent adverse events that occurred in ≥2% of the subjects in any treatment group, the following were more common (i.e., group differences of ≥3%) in the paliperidone ER group: somnolence, akathisia, extrapyramidal disorder, weight increased, and increased appetite. Most treatment-emergent adverse events were mild or moderate in severity and not related or doubtfully related to the study drug.

Deaths, Serious Adverse Events, and Adverse Events Leading to Discontinuation

No subject died during the study. During the double-blind phase of the study, serious treatment-emergent adverse events were reported for 7 subjects each in the paliperidone ER and placebo groups. The majority of these events appeared to be related to the subjects' underlying psychiatric disorder. Five subjects in the paliperidone ER group and 2 subjects in the placebo group had serious adverse events after completion of the double-blind phase of the study. All but 1 (gastrointestinal hemorrhage) of these events appeared to be related to the subjects' underlying psychiatric disorder. Fourteen subjects discontinued due to adverse events: 12 subjects (8%) in the paliperidone ER group as compared to 2 subjects (1%) in the placebo group. Psychiatric disorders were the most common events leading to discontinuation. Single incidence events occurring only in the paliperidone ER-treated group included anxiety, Bipolar I Disorder, insomnia, mania, hypothyroidism, vomiting, ALT increased, AST increased, blood glucose increased, torticollis, and akathisia.

Depression

Two subjects each in the paliperidone ER- and placebo-treated groups reported adverse events coded as depression. The percentage of subjects who switched to depression was higher in the placebo group (14%) as compared to the paliperidone ER group (7%), suggesting that paliperidone ER does not increase the risk of switching from mania to depression.

Extrapyramidal Symptoms (EPS)

Most EPS-related adverse events were mild to moderate in severity. The incidences of extrapyramidal disorder (4% of paliperidone ER and 1% of placebo subjects) and akathisia (8% of paliperidone ER and 1% of placebo subjects) were higher in the paliperidone ER group. The percentage of subjects receiving anticholinergic medications during the double-blind phase was higher in the paliperidone ER group (10%) than in the placebo group (3%).

SYNOPSIS (CONTINUED)

Glucose- and Prolactin-Related Adverse Events

Glucose-related adverse events occurred in 2 paliperidone ER-treated subjects, and potentially prolactin-related adverse events occurred in 1 paliperidone ER-treated subject.

Clinical Chemistry, Hematology, and Urinalysis

There were no clinically relevant mean changes from baseline during the double-blind period for hematology and urinalysis parameters evaluated in this study. Increases from baseline to endpoint in AST, ALT, and LDH values in the paliperidone ER group were small but apparent when compared to placebo. The mean increase from baseline to endpoint in creatine kinase values in the paliperidone ER group was 63.0 U/L as compared to -9.5 U/L in the placebo group. Prolactin levels increased from baseline in both males and females in the paliperidone ER group, as expected. Only 1 male subject (paliperidone ER) had a treatment-emergent potentially prolactin-related adverse event (sexual dysfunction).

Vital Sign and ECG Measurements

There was a greater number of subjects in the paliperidone ER group with standing and supine pulse rates above the clinically important limits as compared to placebo. More subjects with abnormally high heart rates were reported in the paliperidone ER-treated group (12%) as compared to the placebo group (5%). There were slight mean increases in body weight and BMI in the paliperidone ER group, and weight increases of ≥7% were more common among the paliperidone ER subjects as compared to placebo.

PHARMACOKINETICS:

Dose normalized paliperidone plasma concentrations were comparable between fasted subjects and subjects who had consumed a standard continental or a high-caloric breakfast between 2 hours before and 1 hour after their medication intake. Dose normalized paliperidone plasma concentrations were comparable between subjects who received valproate and those who received lithium as mood stabilizer. Paliperidone plasma exposure was also comparable to that observed in other Phase 3 studies in subjects who received no concomitant mood stabilizer, suggesting the absence of significant impact of the coadministered mood stabilizer on paliperidone exposure.

CONCLUSION: In this study, paliperidone ER in a flexible dose range of 3 to 12 mg/day was not statistically superior to placebo in the treatment of subjects with Bipolar I Disorder who experienced acute manic or mixed episodes while taking lithium or valproate, as measured by the primary efficacy variable (YMRS). Paliperidone ER in a flexible dose range of 3 to 12 mg/day was generally safe and well tolerated. The overall safety findings in this study were similar to those observed in previous studies with paliperidone ER in schizophrenia, and no new safety signal was detected.

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