CLINICAL STUDY REPORT SYNOPSIS

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Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.	
Name of Finished Product	INVEGA®	
Name of Active Ingredient(s)	paliperidone	

Protocol No.: CR010834

Title of Study: A randomized, double-blind, placebo-controlled, parallel-group, dose-response, multicenter study to evaluate the efficacy and safety of three fixed doses of extended-release paliperidone (3, 6, and 12 mg/day) in the treatment of subjects with acute manic and mixed episodes associated with Bipolar I Disorder

Coordinating Investigator: Andrew Cutler, MD - Florida Clinical Research Center, Bradenton, FL; USA

Publication (Reference): None.

Study Period: 16 February 2006 to 25 June 2007 | **Phase of Development:** 3

Objectives: The primary objectives were to demonstrate the efficacy and to assess the safety of 3 different doses of extended-release (ER) paliperidone compared with placebo. The key secondary objective was to assess the effect of paliperidone ER on global functioning compared with placebo. Other objectives were to assess the onset of antimanic clinical response to paliperidone ER, to assess the global improvement in severity of illness associated with the use of paliperidone ER, to evaluate the impact of paliperidone ER therapy on patient-reported outcomes (via the Short Form 36 [SF-36]), to assess the impact of paliperidone ER on depressive symptoms and on psychotic symptoms, to explore the pharmacokinetics (PK) of paliperidone ER, to assess the differential effect of the time of study drug administration relative to food intake and the type of meal eaten during the first 6 days of study treatment, and to assess the possible relationship of PK to the efficacy and safety of paliperidone ER.

Methodology: This was a randomized, double-blind, placebo-controlled, parallel-group, dose-response, multicenter, efficacy and safety study. The study began with a screening and washout phase of no more than 7 days during which subjects' current antimanic, mood-stabilizing treatment and other excluded medications were discontinued. Subjects may have been hospitalized at any time during this phase or been followed as outpatients. Eligible subjects who completed the washout phase entered a 3-week double-blind treatment phase after balanced, random assignment to 1 of 4 double-blind study drugs (3, 6, or 12 mg/day of oral paliperidone ER, or placebo once daily). Subjects were hospitalized for at least the first 7 days of double-blind treatment. As early as Day 7, subjects could be discharged and followed as outpatients if they were believed by the investigator to be at no significant risk of violent or suicidal behavior. End-of-study/early-withdrawal assessments were done on Day 21 after the last dose of study drug had been received and PK sampling had been completed, or upon early withdrawal from the study. A follow-up visit for safety evaluations was scheduled approximately 1 week later.

Number of Subjects (planned and analyzed): The planned sample size was 464 subjects (116 per treatment group). A total of 467 randomized subjects (121 in the placebo group, 112 in the paliperidone ER 3-mg group, 119 in the 6-mg group, and 115 in the 12-mg group) received at least 1 dose and were included in the safety analysis set. A total of 465 subjects (121, 112, 118, and 114, respectively) from the safety analysis set also provided efficacy data and were included in the intent-to-treat (ITT) analysis set.

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); had a history of at least 1 documented manic or mixed episode requiring medical treatment within the 3 years before screening; and had a total score of at least 20 on the Young Mania Rating Scale (YMRS) at screening and baseline (Day 1).

Test Product, Dose and Mode of Administration, Batch No.: Paliperidone ER was supplied as overencapsulated 3-mg tablets (batch numbers 05A24/F022, 05E23/F022, and 06G03/F022) or 6-mg tablets (batch numbers 05F02/F061 and 06D24/F061). Doses consisted of 2 capsules taken orally once daily.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo (batch numbers 05F03/F027, 06B21/F027, and 06F07/F027) was supplied as overencapsulated tablets identical to the paliperidone capsules. Doses consisted of 2 capsules taken orally once daily.

Duration of Treatment: The study consisted of a screening and washout phase (up to a maximum of 7 days), a 3-week double-blind treatment phase, and a follow-up visit approximately 1 week after the end of double-blind treatment (or early withdrawal).

SYNOPSIS (CONTINUED)

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), Sleep Visual Analog Scale (VAS), and SF-36.

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

Pharmacokinetics: Plasma concentrations of paliperidone were determined from blood samples taken at baseline on Day 1, on Days 6 and 21 before 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 had been performed when this report was written.

Statistical Methods: The change from baseline to end point (last observation carried forward [LOCF]) in YMRS (primary efficacy variable) and GAF (key secondary efficacy variable) was compared between treatment groups using an analysis of covariance (ANCOVA) model with treatment and country as factors and baseline score as a covariate. The closed testing based parallel gatekeeping procedure using Dunnett's test and Bonferroni adjustment was applied to adjust for multiplicity in testing of the 3 doses versus placebo for the primary and key secondary efficacy variables. A similar ANCOVA model was used to analyze the changes in CGI-BP-S, PANSS, Sleep VAS, SF-36, MADRS, and SSI and to compare the YMRS results between paliperidone ER groups without adjustment for multiplicity. A Cochran-Mantel-Haenszel test controlling for country was used to analyze the percentages of YMRS responders (≥50% reduction from baseline in YMRS total score), YMRS remitters (YMRS total score of ≤12 at end point), and subjects who switched to depression (MADRS score ≥18, with an increase from baseline of ≥4, at any 2 consecutive assessments or at the last observation). The remaining efficacy and safety variables were evaluated using descriptive statistics and frequency distributions.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS: From baseline to end point, there were decreases in YMRS total scores in all treatment groups, indicating improvement in the severity of manic symptoms. The mean (SD) change was -9.9 (10.22) in the placebo group, -9.6 (11.30) in the paliperidone ER 3-mg group, -11.7 (10.04) in the paliperidone ER 6-mg group, and -13.9 (9.19) in the paliperidone ER 12-mg group. The least-squares mean differences from placebo were +0.3, -1.9, and -4.0, respectively. The improvement in the paliperidone ER 12-mg group reached statistical significance ($p=0.005$) when compared with the placebo group. The paliperidone ER 3-mg and 6-mg groups did not achieve statistical superiority to the placebo group (3 mg: $p=0.992$; 6 mg: $p=0.302$). The improvement from baseline in the paliperidone ER 12-mg group was significantly ($p<0.001$) larger than that in the paliperidone ER 3-mg group but did not differ significantly ($p=0.102$) from that in the paliperidone ER 6-mg group. The onset of therapeutic effect based on the YMRS total score was Day 2 for the 12-mg dose.

There was a significant treatment-by-country interaction for the change in YMRS total score at end point ($p<0.001$). To further explore the interaction, country was categorized as United States vs. non-U.S. All 3 doses were tested using the 2-sided Gail-Simon interaction test. There was insufficient evidence to indicate that the interaction for any of the 3 doses and country was qualitative as indicated by the non-significance ($p\geq0.2499$) of the Gail-Simon test (2-tailed).

The median CGI-BP-S score at baseline was 4 (denoting moderate severity) in all treatment groups. Although the magnitude of the median change from baseline was the same in all 4 treatment groups (-1), there was a statistically significant difference between the paliperidone ER 12-mg group and the placebo group ($p=0.046$). This reflects a noticeably larger decrease from baseline in the percentage of markedly/severely/very severely ill subjects in the paliperidone 12-mg group than in the other groups.

There was improvement in the quality of sleep in each treatment group. The mean (SD) increase from baseline to end point was 8.3 (36.28) in the placebo group, 12.6 (33.25) in the paliperidone ER 3-mg group, 17.6 (30.79) in the paliperidone ER 6-mg group, and 20.6 (33.93) in the paliperidone ER 12-mg group. Statistical superiority to the placebo group was achieved by the 6-mg group ($p=0.034$) and the 12-mg group ($p<0.001$).

There were no significant differences between any paliperidone ER group and the placebo group in the following: change from baseline to end point in the GAF score, percentages of YMRS responders or remitters, PANSS total score, PANSS positive and negative subscales, PANSS Marder factors, daytime drowsiness, or SF-36 results.

SAFETY RESULTS: As shown in the table below, the incidence of treatment-emergent adverse events (TEAEs) increased with increasing paliperidone ER dose. Serious TEAEs were reported at a higher rate in the placebo group than in any of the paliperidone ER groups. The frequency of TEAEs leading to discontinuation was lower in

SYNOPSIS (CONTINUED)

the placebo and paliperidone ER 3-mg groups than in the 6- and 12-mg groups. No subject died during the double-blind phase of the study. One subject who received paliperidone ER 6 mg for 5 days died of unknown causes 1 week after withdrawing consent.

SAFETY RESULTS (CONTINUED):

Overall Summary of Treatment-Emergent Adverse Events During Double-Blind Phase
(Study R076477-BIM-3001: Safety Analysis Set)

	Placebo (N=121) n (%)	PALI ER 3 mg (N=112) n (%)	PALI ER 6 mg (N=119) n (%)	PALI ER 12 mg (N=115) n (%)	Total (N=467) n (%)
TEAE	85 (70)	68 (61)	89 (75)	100 (87)	342 (73)
Possibly related TEAE (a)	49 (40)	45 (40)	64 (54)	68 (59)	226 (48)
TEAE leading to death (b)	0	0	0	0	0
1 or more serious TEAE	10 (8)	4 (4)	5 (4)	5 (4)	24 (5)
TEAE leading to permanent stop	6 (5)	1 (1)	13 (11)	9 (8)	29 (6)

(a) Study drug relationships of possible, probable, and very likely are included in this category.
(b) Subject 605903 who was randomized to the paliperidone ER 6 mg group died 1 week after withdrawing from the study.
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Among the most common TEAEs, i.e., events that occurred in at least 5% of the subjects in any group, the following events occurred in paliperidone ER-treated subjects (total of all dose groups) at an incidence that was ≥3% higher (when calculated to 1 decimal place) than that in the placebo group: headache, somnolence, dizziness, sedation, akathisia, dystonia, and dyspepsia. Headache, somnolence, dizziness, sedation, and dystonia occurred more frequently (≥3% difference, when calculated to 1 decimal place) in the 6- and 12-mg paliperidone ER groups than in the 3-mg group. Mania occurred in placebo-treated subjects at an incidence that was ≥3% higher (when calculated to 1 decimal place) than that in the paliperidone ER-treated subjects (total of all dose groups). Most TEAEs were rated mild or moderate by the investigators.

Mania was the TEAE most commonly reported as serious. Such cases represent subjects who were hospitalized due to exacerbation of their underlying disease. The incidence of serious TEAEs of mania was higher for the placebo group (6%) than for any of the paliperidone ER groups (2% to 3%).

The incidences of EPS-related TEAEs grouped as parkinsonism, hyperkinesia, dystonia, and dyskinesia were higher in the paliperidone ER 12-mg group than in the paliperidone ER 3- and 6-mg groups; the incidences were higher in all 3 paliperidone ER groups than in the placebo group (except for dyskinesia). Distinct events (preferred terms) that occurred more frequently in at least 1 of the paliperidone ER groups than in the placebo group (i.e., ≥3% difference, when calculated to 1 decimal place) were hypertonia, akathisia, and dystonia. The incidences of extrapyramidal disorder, akathisia, dystonia, and dyskinesia were noticeably higher in the paliperidone ER 12-mg group than in the other 2 paliperidone ER groups. Although the 4 treatment groups had similar changes from baseline to end point in EPS rating scale scores, there was a clear dose-related increase in the percentage of subjects who used anticholinergic medications during the study: 9% in the placebo and paliperidone ER 3-mg groups, 13% in the paliperidone ER 6-mg group, and 28% in the paliperidone ER 12-mg group.

There were no clinically relevant changes in vital signs or ECG parameters. Prolactin levels increased in both males and females who received paliperidone ER, as expected. Only 3 subjects in the paliperidone ER groups and 1 subject in the placebo group had treatment-emergent potentially prolactin-related adverse events.

There were slight increases in mean body weight and BMI in all treatment groups from baseline to the end of the study, but the magnitude of the changes was greater in the paliperidone ER groups (increases of 1.1 kg in body weight and 0.4 kg/m^2 in BMI in each group) than in the placebo group (0.2 kg and 0.1 kg/m^2, respectively).

There was no evidence that paliperidone ER increased the risk of subjects switching from mania to depression or developing suicidal ideation.

PHARMACOKINETICS: The median plasma concentrations of paliperidone were dose proportional over the once daily dose range of 3, 6, and 12 mg. The median paliperidone plasma concentrations at 8 hours postdose on Day 6 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.

SYNOPSIS (CONTINUED)

CONCLUSION: Paliperidone ER 12 mg was efficacious in the treatment of subjects with Bipolar I Disorder who were experiencing an acute manic or mixed episode. Specifically, the results of the primary efficacy variable demonstrated statistical superiority of paliperidone ER 12 mg over placebo. Other efficacy variables showed some statistical improvements with the 6- and 12-mg doses, but the results were not consistent across efficacy variables. The overall safety findings were similar to those observed in previous studies with paliperidone ER in schizophrenia, and no new safety signal was detected.
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