CLINICAL STUDY REPORT SYNOPSIS

Document No.: EDMS-PSDB-7762251:3.0

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

Protocol No.: CR10858

Title of Study: A randomized, double-blind, active- and placebo-controlled, parallel group, multicenter study to evaluate the efficacy and safety of flexibly dosed, extended-release paliperidone compared with flexibly dosed quetiapine and placebo in the treatment of acute manic and mixed episodes associated with Bipolar I Disorder

Coordinating Investigator: Joseph Kwentus, M.D. - Precise Research Centers, Flowood, MS; USA

Publication (Reference): None

Study Period: 1 May 2006 to 16 November 2007 | **Phase of Development:** 3

Objectives: The primary objectives were to demonstrate the antimanic efficacy and to assess the safety of flexibly dosed paliperidone ER compared with placebo during 3 weeks of treatment in subjects with Bipolar I Disorder who were experiencing an acute manic or mixed episode. The key secondary objectives were to demonstrate that flexibly dosed paliperidone ER and quetiapine had comparable antimanic efficacy over a 12-week period; to assess the safety of flexibly dosed paliperidone ER over a 12-week period; and to assess the effect on global functioning associated with flexibly dosed paliperidone ER compared with placebo over a 3-week period. Other objectives were to assess the onset of antimanic clinical response to paliperidone ER compared with placebo over a period of 3 weeks; 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 subject-reported outcomes (via the Short Form-36 [SF-36]); to assess the impact of paliperidone ER on depressive symptoms during 3 weeks and 12 weeks of study treatment; to assess the impact of paliperidone ER on psychotic symptoms using a symptom rating scale during 3 weeks and 12 weeks of study treatment; and to explore the pharmacokinetics (PK) of paliperidone in subjects with Bipolar I Disorder (including assessment of the differential effect 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 assessment of the possible relationship of PK to the efficacy and safety of paliperidone ER).

Methodology: This was a randomized, double-blind, placebo- and active-controlled, parallel group, comparative efficacy and safety study conducted at multiple sites in the United States, Europe, and Asia that evaluated paliperidone ER in men and women 18 to 65 years of age, inclusive, with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnosis of Bipolar I Disorder, Most Recent Episode Manic or Mixed (with or without psychotic features). The study consisted of an up to 7-day screening and washout phase; a 3-week double-blind acute phase; a 9-week double-blind maintenance phase; and a follow-up phase 1 week after end-of-study or early-withdrawal assessments were completed. Following the screening/washout phase, subjects were randomly assigned to 1 of 3 treatment groups: paliperidone ER (3-12 mg/d, flexibly dosed; starting dose 6 mg/d), quetiapine (400-800 mg/d, initially titrated, and flexibly dosed; starting dose 100 mg/d), and placebo. Subjects were required to remain in the hospital for the first 7 days of the acute phase. Subjects who were initially assigned to treatment with paliperidone ER or quetiapine and completed the acute phase entered the 9-week maintenance phase and continued double-blind study drug; subjects assigned to placebo during the acute phase crossed over to receive paliperidone ER during the maintenance phase in a blinded fashion when they completed the acute phase. End-of-study/early-withdrawal assessments were done on Day 84 after the morning 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 after the end-of-study/early-withdrawal visit.

Number of Subjects (planned and analyzed): The planned total sample size was approximately 475 subjects, who were to be randomly assigned to receive 1 of 3 treatments in a 2:2:1 ratio: 190 paliperidone ER, 190 quetiapine, and 95 placebo. A total of 493 eligible subjects were randomly assigned to placebo (105 subjects), flexibly dosed paliperidone ER 3 to 12 mg/d (195 subjects), or flexibly dosed quetiapine 400 to 800 mg/d (193 subjects). Two subjects, 1 randomly assigned to the paliperidone ER group and the other assigned to the quetiapine group, did not receive the study drug. The remaining 491 subjects comprised the safety analysis set.

Diagnosis and Main Criteria for Inclusion: Eligible subjects were men and women 18 to 65 years of age, inclusive, with a DSM-IV diagnosis of Bipolar I Disorder, Most Recent Episode Manic or Mixed (with or without psychotic features). Eligible subjects had a history of at least 1 previously documented manic or mixed episode requiring medical treatment within the 3 years before the screening phase, and had a total score of at least 20 on

SYNOPSIS (CONTINUED)

the Young Mania Rating Scale (YMRS) at screening and at baseline.

Test Product, Dose and Mode of Administration, Batch No.: Oral Paliperidone ER 3 to 12 mg/d: 3-mg tablets, batch nos. 0426911, 0500130, 0602599, and 0620769; 6-mg tablets, batch nos. 0500129, 0607491, and 0617714.

Reference Therapy, Dose and Mode of Administration, Batch No.: Oral quetiapine 400 to 800 mg/d: 25-mg tablets, batch nos. LK0093, LM0092, MJ0009, CP245, CS976, and 06A02; 100-mg tablets, batch nos. LM0087, LL0096, LM0110, MK0050, MP0133, MC0002, MT0045, 06A01, 05K02, CT333, GK272A1, 06J02, and CV676.

Duration of Treatment: The study consisted of a 7-day screening and washout phase; a 3-week double-blind acute phase; a 9-week double-blind maintenance phase; and a follow-up phase 1 week after end-of-study or early-withdrawal assessments were completed.

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: Safety evaluations included the monitoring of adverse events, clinical laboratory testing, 12-lead electrocardiograms (ECGs), vital sign measurements, orthostatic changes in blood pressure and pulse, physical examination (including height, weight, and waist circumference), and monitoring of extrapyramidal symptoms (EPS) using the Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and Simpson-Angus Scale (SAS). Additionally, the Montgomery-Åsberg Depression Rating Scale (MADRS) and Scale for Suicidal Ideation (SSI) were utilized to evaluate subject tendencies toward depression and suicidality.

Pharmacokinetics: Plasma concentrations of paliperidone were determined from blood samples taken at baseline on Day 1, on Days 6, 21, and 84 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: Acute treatment phase: The intent-to-treat (ITT) analysis set included all randomized subjects who received at least 1 dose of double-blind study drug and had both the baseline and at least 1 postbaseline assessment in the double-blind phase on one of the assessment scales. The change from baseline to endpoint (last observation carried forward [LOCF]) in YMRS total score (primary efficacy variable), and the change from baseline to the last postbaseline assessment in GAF score (key secondary efficacy variable) were estimated and compared between treatment groups using an analysis of covariance (ANCOVA) model with treatment (included placebo and paliperidone ER groups only) and country as factors, and baseline score as a covariate. A 95% confidence interval was presented for the difference in least-squares (LS) mean change in YMRS and GAF scores between the paliperidone ER and placebo groups. To assess the sensitivity of the primary results at the 3-week endpoint, a mixed model repeated measures (MMRM) analysis was carried out on the observed case YMRS. For the change from baseline in PANSS total score at endpoint, the LS means were estimated and compared between the paliperidone ER treatment group and placebo using an ANCOVA model with treatment and country as factors, and baseline PANSS total score as a covariate. For CGI-BP-S, at each assessment time point and endpoint, frequency counts of scores by severity level were produced by treatment group for both observed case and LOCF data. For CGI-BP-S and the other efficacy endpoints, summary statistics were produced for scores and the changes from baseline. Differences between the paliperidone ER treatment group and placebo in the proportion of responders and the proportion of remitters were evaluated using a Cochran Mantel-Haenszel test controlling for country. The onset of effect was calculated as the first time point at which the treatment groups (paliperidone ER vs. placebo) were different (at the 2-sided nominal 5% level of significance) and remained different thereafter until endpoint, based on the change from baseline in the YMRS total score (LOCF). A descriptive comparison of the primary endpoint between quetiapine and placebo, and separately between quetiapine and paliperidone ER, was performed using 95% confidence intervals. Maintenance treatment phase: The per-protocol analysis set consisted of randomized subjects who had both a baseline and at least 1 postbaseline YMRS assessment during the acute and maintenance double-blind phases, and who did not have major protocol violations, such as violations of entry criteria, errors in treatment assignment, or use of prohibited medication. The point estimate and 2-sided 95% confidence interval based on ANCOVA (with missing values imputed using LOCF) approach was used to assess noninferiority of paliperidone ER relative to quetiapine. The LS mean difference between paliperidone ER (not including subjects who switched from placebo to paliperidone ER in the maintenance phase) and quetiapine in the change from baseline to the 12-week time point in YMRS total score was calculated using the per-protocol analysis set. Noninferiority of paliperidone ER to quetiapine was concluded if the lower limit of the 2-sided 95% confidence interval exceeded –4. An ANCOVA model using the 12-week ITT (LOCF) data as well as MMRM analyses were carried out to assess the robustness of the

SYNOPSIS (CONTINUED)

noninferiority results. For the other efficacy endpoints, descriptive statistics for the changes from baseline to endpoint were presented. Point estimates and 2-sided 95% confidence intervals using an ANCOVA model based on the ITT (with LOCF) analysis set were calculated for the difference between paliperidone ER and quetiapine. The proportion of responders and remitters among paliperidone ER and quetiapine subjects were presented and the 95% confidence interval of the difference was provided. All safety variables were evaluated using descriptive statistics and frequency distributions. Group differences between paliperidone ER and placebo at the 3-week endpoint and between paliperidone ER and quetiapine at the 12-week endpoint for the change from baseline in MADRS score were analyzed using an ANCOVA model, with treatment and country as factors and baseline MADRS score as a covariate.

SUMMARY - CONCLUSIONS

PHARMACOKINETICS: Paliperidone plasma exposure was comparable to that observed in other Phase 3 studies. Median dose-normalized paliperidone plasma concentrations at approximately 8 hours postdose on Day 6 were comparable between fasted subjects and subjects who had consumed a standard continental or high-caloric breakfast between 2 hours before and 1 hour after medication intake

EFFICACY RESULTS: For the primary efficacy variable, the mean (SD) change from baseline to the 3-week endpoint in YMRS total score was –7.4 (10.74) in the placebo group, –13.2 (8.68) in the paliperidone ER group, and –11.7 (9.28) in the quetiapine group. Based on ITT LOCF analysis of the primary efficacy variable using an ANCOVA model, paliperidone ER was statistically superior to the placebo group ($p<0.001$). The LS mean difference (95% confidence interval) from placebo was –5.5 (–7.57, –3.35) for the paliperidone ER group. The paliperidone ER group showed improvement over placebo as early as Day 2, and at every subsequent time point until Day 21. Further analysis using a MMRM analysis on the observed-case YMRS data was consistent with the primary efficacy results. At the end of the acute treatment phase, the percentage of responders was 55.8% for the paliperidone ER group, 34.6% for the placebo group, and 49.0% in the quetiapine group. The percentage of remitters was 52.1% for the paliperidone ER group, 28.8% for the placebo group, and 47.4% for the quetiapine group. The treatment-by-country interaction for the change in YMRS total score to the 3-week endpoint was statistically significant ($p<0.001$). To further explore the interaction, country was categorized as U.S. vs. non-U.S. There was insufficient evidence to indicate that the interaction was qualitative as indicated by the nonsignificance ($p=0.500$) of the Gail-Simon test (2-tailed). For the key secondary variable, the mean (SD) change from baseline to endpoint in GAF score at the 3-week endpoint was 6.7 (13.56) in the placebo group, 12.2 (11.17) in the paliperidone ER group, and 11.6 (11.96) in the quetiapine group. Based on the ITT LOCF analysis of this secondary efficacy variable and the prespecified sequential testing strategy, the improvement in the paliperidone ER dose group reached statistical significance ($p<0.001$) compared with placebo. At the 3-week endpoint, there were statistically significant improvements in the severity of illness (CGI-BP-S, $p<0.001$), in the severity of psychotic symptoms (PANSS, $p=0.002$), and in the quality of sleep (Sleep VAS, $p<0.001$) for paliperidone ER relative to placebo. There were no statistically significant differences for paliperidone ER relative to placebo in daytime drowsiness (Sleep VAS), and there were no improvements in SF-36 domain subscale or summary scale scores with paliperidone ER. For the noninferiority analysis at the 12-week endpoint, the mean (SD) change from baseline to the 12-week endpoint (LOCF) in YMRS total score was –15.2 (10.26) in the paliperidone ER group and –13.5 (11.02) in the quetiapine group. The difference in LS means in the change from baseline to the 12-week endpoint in YMRS total score between quetiapine and paliperidone ER was 1.7, with a 95% confidence interval of (–0.47, 3.96). As the lower limit of the 95% confidence interval was greater than –4 (the prespecified margin), paliperidone ER can be declared noninferior to quetiapine for the per-protocol analysis set. Similar results were obtained when the analyses were performed using the ITT analysis set. Further analyses using MMRM on the observed-case YMRS data were also consistent with these results for both the per-protocol and ITT analysis sets.

SAFETY RESULTS: As shown in the table below, treatment-emergent adverse events occurred with similar frequency during the combined double-blind phases (i.e., 12 weeks) in the placebo/paliperidone ER (71%) and paliperidone ER groups (70%), and with slightly higher frequency in the quetiapine group (82%). The treatment-emergent adverse events that occurred more commonly (≥5% of subjects) in the paliperidone ER group compared to the placebo group during the acute phase (i.e., first 3 weeks) were somnolence, akathisia, hypertonia, constipation, and dyspepsia. Most treatment emergent adverse events were mild or moderate in severity and possibly or probably related to the study drug.

SYNOPSIS (CONTINUED)

Overall Summary of Treatment-Emergent Adverse Events During the Double Blind (AC/MA) Phase

	Placebo/ PALI ER (N=105) n (%)	PALI ER/ PALI ER (N=194) n (%)	QUET/ QUET (N=192) n (%)	Total (N=491) n (%)
TEAE	75 (71)	136 (70)	157 (82)	368 (75)
Possibly related TEAE[a]	50 (48)	113 (58)	122 (64)	285 (58)
TEAE leading to death	1 (1)	0	1 (1)	2 (<1)
1 or more serious TEAE	8 (8)	16 (8)	14 (7)	38 (8)
TEAE leading to permanent stop	7 (7)	18 (9)	12 (6)	37 (8)

[a] Study drug relationships of possible, probable, and very likely are included in this category.
AC/MA=combined acute and maintenance phases

One subject assigned to the quetiapine group committed suicide during the maintenance phase, and 1 subject assigned to the placebo/paliperidone ER group died from complications of a suicide attempt 5 days after withdrawal from the study. During the combined acute and maintenance treatment phases, serious treatment-emergent adverse events were reported for 8 (8%) subjects in the placebo/paliperidone ER group, 16 (8%) subjects in the paliperidone ER group, and 14 (7%) subjects in the quetiapine group. A total of 37 subjects discontinued the study drug due to adverse events during the combined acute and maintenance phases: 7 (7%) in the placebo/paliperidone ER group, 18 (9%) in the paliperidone ER group, and 12 (6%) in the quetiapine group. Psychiatric disorders were the most common serious adverse events and events leading to discontinuation. Five (5%) subjects in the placebo/paliperidone ER group and 14 (7%) subjects in the paliperidone ER group reported adverse events coded as depression. No subjects in the quetiapine group reported adverse events coded as depression. The percentage of subjects who met predefined criteria for switching to depression during the combined acute and maintenance phases was higher in the placebo/paliperidone ER (18.0%) group compared to the paliperidone ER (13.9%) and quetiapine (7.5%) groups. There was a statistically significant improvement in MADRS score in the paliperidone ER group compared to the placebo group during the acute phase. Akathisia, hypertonia, drooling, extrapyramidal disorder, and muscle spasms occurred more frequently in the paliperidone ER group than in the placebo group. All of the EPS-related adverse events occurring during the study were mild or moderate in severity. The percentage of subjects receiving anticholinergic medications during the acute treatment phase was higher in the paliperidone ER group (17%) than in the placebo (5%) or quetiapine groups (7%). There was a low incidence (2%, 1%, and 2% in the placebo/paliperidone ER, paliperidone ER, and quetiapine groups, respectively) of treatment-emergent glucose-related adverse events during the combined double-blind phases. A total of 10 (5%) subjects in the paliperidone ER group experienced potentially prolactin-related adverse events during the combined acute and maintenance phases, compared to 3 (3%) subjects in the placebo/paliperidone ER group and 4 (2%) in the quetiapine group. There were differences between treatment groups in the mean changes from baseline in the level of creatine kinase at the 3- and 12-week endpoints; these differences were not likely to be clinically relevant. At the 3-week endpoint, there were mean (SD) increases in serum prolactin of 24.61 (23.98) ng/mL (males) and 89.77 (81.47) ng/mL (females) in the paliperidone ER group, compared to –1.03 (14.08) ng/mL (males) and 7.15 (31.82) ng/mL (females) in the placebo group. Mean prolactin levels did not increase in the quetiapine group. There were no notable mean changes from baseline to the 3- and 12-week endpoints in hematology or urinalysis parameters. Throughout the double-blind phase, there were larger proportions of paliperidone ER and quetiapine subjects with standing and supine pulse rates above clinically important limits (i.e., increase from baseline of ≥15 bpm to a value ≥100 bpm) compared to placebo treatment. Abnormally high heart rates were reported more frequently in subjects assigned to the paliperidone ER (20%) and quetiapine (19%) groups than subjects in the placebo/paliperidone ER group (10%). There were slight mean increases in body weight in the paliperidone ER and quetiapine groups relative to placebo. At the end of the maintenance phase, weight increases from baseline of greater than or equal to 7% were more common among subjects in the quetiapine group (17%) than the paliperidone ER (8%) or placebo/paliperidone ER (6%) groups.

CONCLUSION: Paliperidone ER in a flexible doses range of 3 to 12 mg/d over a 3-week period was efficacious in the treatment of subjects with Bipolar I Disorder who were experiencing an acute manic or mixed episode. Paliperidone ER in a flexible dose range of 3 to 12 mg/d over a 12-week period was noninferior to flexibly dosed quetiapine 400 to 800 mg/d in the treatment of subjects with Bipolar I Disorder who were experiencing an acute manic or mixed episode. The overall safety findings in this study were similar to those observed in previous studies with paliperidone ER in schizophrenia and Bipolar I Disorder, and no new safety signal was detected.

Issue Date of the Clinical Study Report: 17 April 2008

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.