SYNOPSIS

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

Protocol No.: R076477-BIM-3004

Title of Study: A Randomized, Double-Blind, Active- and Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy and Safety of Extended-Release Paliperidone as Maintenance Treatment After an Acute Manic or Mixed Episode Associated With Bipolar I Disorder

Coordinating Investigator: [redacted]

Publication (Reference): None

Study Period: 14 June 2006 to 30 April 2010

Phase of Development: 3

Objectives: The primary objectives of this study were to evaluate the efficacy of paliperidone extended-release (ER) compared with placebo in the prevention of the recurrence of any mood symptoms (ie, manic or depressive) associated with bipolar I disorder and to assess the safety and tolerability of paliperidone ER in subjects who maintain clinical stability after an acute manic or mixed episode. Secondary objectives were to evaluate the efficacy of paliperidone ER compared with placebo in the prevention of manic symptoms associated with bipolar I disorder and to evaluate the efficacy of paliperidone ER compared with placebo in the prevention of depressive symptoms associated with bipolar I disorder.

Additional objectives were to evaluate the global improvement in severity of illness associated with paliperidone ER treatment compared with placebo in subjects who maintained clinical stability after an acute manic or mixed episode associated with bipolar I disorder, as assessed by the Clinical Global Impression-Bipolar Disorder-Severity of Illness Scale (CGI-BP-S); to evaluate the impact of paliperidone ER compared with placebo on global functioning in subjects who maintained clinical stability after an acute manic or mixed episode associated with bipolar I disorder, as assessed by the Global Assessment of Functioning (GAF) scale; to evaluate the impact of paliperidone ER compared with placebo on health-related functional status in subjects who maintained clinical stability after an acute manic or mixed episode associated with bipolar I disorder, as assessed by the Short Form-36 (SF-36); and to document the efficacy and safety of paliperidone ER relative to olanzapine in the prevention of recurrent mood symptoms associated with bipolar I disorder on the basis of descriptive statistics.

Methods: This randomized, double-blind, active- and placebo-controlled, parallel-group, multicenter study was conducted in 79 centers in 17 countries (Bulgaria, China, Costa Rica, Germany, India, Malaysia, Morocco, Panama, Poland, Romania, Russia, Serbia, South Africa, Tunisia, Turkey, Ukraine, and the United States). There were 5 phases in this study: a screening phase (up to 7 days); a 3-week double-blind acute treatment (AC) phase; a 12-week double-blind continuation (CT) phase; a double-blind maintenance (MA) phase (until the subject experienced a recurrence); and a follow-up phase, with a visit approximately 1 week after the end-of-study/early withdrawal visit. Washout of all antipsychotics and all mood stabilizers other than study drug was to be completed before study drug administration on Day 1.

Following the screening phase, subjects were randomly assigned to double-blind AC phase where they received a flexible dosage range of paliperidone ER 3 to 12 mg/day (initial dosage 6 mg/day) or a flexible dosage range of

olanzapine 5 to 20 mg/day (initial dosage 10 mg/day) in a 4:1 ratio for 3 weeks. This was followed by a double-blind CT phase, in which subjects with clinical response continued to receive flexibly dosed paliperidone ER or olanzapine for 12 weeks. At the end of the 12-week CT phase, all subjects in the paliperidone treatment arm who remained clinically stable throughout the phase and achieved remission for each of the last 3 weeks of the CT phase were randomly assigned to paliperidone ER or placebo in a 1:1 ratio (double-blind MA phase). Subjects in the olanzapine treatment arm who met the same criteria continued on double-blind treatment with olanzapine in the double-blind MA phase. At the beginning of the MA phase, the dosage of paliperidone ER, olanzapine, or matching placebo was the same as that achieved at the end of the CT phase and remained unchanged throughout the phase. The MA phase lasted until the subject experienced a recurrence. Subjects then entered a follow-up phase, with a visit approximately 1 week after the end-of-study/early withdrawal visit.

The study included an optional pharmacogenomic component, with a single blood sample (10 mL) collected at baseline (or at any time before the follow-up phase) in countries where health authorities had approved pharmacogenomic testing. Subjects who completed the study or discontinued study drug for any reason were switched to appropriate alternative treatment, including re-titration if subjects were switched to treatment with olanzapine.

Number of Subjects (planned and analyzed): Planned: Initially approximately 650 subjects were planned for enrollment and randomization in a 4:1 ratio to flexibly-dosed paliperidone ER or olanzapine in the double-blind AC phase of the study. Among the 520 subjects who would be randomly assigned initially to paliperidone ER, it was expected that 284 subjects who maintained clinical stability would be re-randomized in a 1:1 ratio to treatment with paliperidone ER or placebo in the double-blind MA phase, of whom at least 140 subjects were expected to experience a recurrence event. If necessary, enrollment was to continue until as many as 710 subjects were randomly assigned to paliperidone ER or olanzapine in the double-blind AC phase. As periodic blinded monitoring indicated that the rate of recurrences declined over time, the protocol was amended to increase the maximum number of subjects who could be enrolled in the double-blind AC phase to 790. This was done to ensure that a sufficient number of subjects could potentially experience a recurrence to attain the pre-specified number of recurrences (140 across the paliperidone ER and placebo treatment arms) in order to terminate the study. Analyzed: A total of 766 eligible subjects were randomly assigned in a 4:1 ratio to receive paliperidone ER 3 to 12 mg/day (617 subjects) or olanzapine 5 to 20 mg/day (149 subjects) in the AC/CT phases. Four subjects (3 randomly assigned to the paliperidone ER group and 1 to the olanzapine group) did not receive the study drug. A total of 762 subjects comprised the safety analysis set. A total of 300 subjects in the paliperidone ER flexible dose group in the AC/CT phases were randomly reassigned in a 1:1 ratio to receive placebo (148 subjects) or paliperidone ER (152 subjects) in the MA phase. Of the 148 subjects who had received olanzapine in the AC/CT phases, 83 subjects entered the MA phase and continued to receive olanzapine. Four subjects (1 randomly assigned to the Pali/Placebo group and 3 to the Pali/Pali group) in the MA phase did not receive the study drug. A total of 379 subjects comprised the safety analysis set in the MA phase. Following an inspection of Site [redacted] conducted as part of an internal J&JPRD systems audit, it was concluded that the site could not be considered GCP compliant. Thus, subjects (12 in AC/CT phase and 7 in MA phase) at this site were excluded from the Intent-to-Treat (ITT) set for efficacy analysis. The ITT set consisted of 750 subjects in the AC/CT phase and 372 subjects in the MA phase.

Diagnosis and Main Criteria for Inclusion: Men or women between 18 and 65 years of age, inclusive, who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for bipolar I disorder with most recent episode manic or mixed (with or without psychotic features) at the time of screening (Days −7 to −1) and with a history of at least 2 previously documented mood episodes associated with bipolar I disorder (1 of which must have been a manic or mixed episode) that required medical treatment within the 3 years before screening. Subjects also had to have a total Young Mania Rating Scale (YMRS) of at least 20 at screening and at baseline (Day 1) to be included.

Test Product, Dose and Mode of Administration, Batch No.: Paliperidone ER based on a Push-Pull™ delivery system is a trilayer longitudinally compressed capsule-shaped tablet; supplied in 3- and 6-mg dose strengths. Paliperidone ER 3-mg tablet (Batch numbers: 06H14, 06J23, 06J30, 07E18, 07J01, 08C04, and 09E19) or paliperidone ER 6-mg tablet (Batch numbers: 06H15, 06K06, 07F08, 07J01, 07I127, 08C07, and 09E20) was administered orally in the morning.

Reference Therapy, Dose and Mode of Administration, Batch No.: Olanzapine was supplied as 5-mg round white coated tablets; administered orally once a day in the morning. The tablets were overencapsulated in size DB/AA capsules to preserve the blind. Batch numbers for 5 mg overencapsulated tablet were: 06B21, 06G27, 07C06, 07I11, 08B11, 09C04, 09D17, 09F25, 06B27, 06H01, 06J11, 07B05, and 08C11 and for 2x5 mg overencapsulated tablets were: 06B22, 06G28, 07C08, 07I12, 08B15, 09C05, 09D17, 09F30, 06B28, 06H02, 06J09, 07B07, 08C17, 09G16, 09G22, 09G17, and 09G16).

Placebo tablet was a bilayer longitudinal compressed tablet consisting of a placebo layer and a push layer to match paliperidone ER tablet.

Duration of Treatment: Paliperidone ER was administered in a flexible dosage range of 3 to 12 mg/day (initial dosage of 6 mg/day) and olanzapine was administered in a flexible dosage range of 5 to 20 mg/day (initial dosage of 10 mg/day) for the first 15 weeks (3 weeks in AC and 12 weeks in CT phase) followed by administration of the paliperidone, olanzapine, or placebo in the MA phase until the subject experienced recurrence (end point criterion).

Criteria for Evaluation:

Efficacy: Efficacy rating scales used in the study included YMRS, Montgomery-Asberg Depression Rating Scale (MADRS), CGI-BP-S, GAF, SF-36, and the sleep visual analog scale (VAS).

The primary efficacy endpoint was the time to first recurrence of any mood symptoms (ie, manic or depressive) associated with bipolar I disorder during the double-blind MA phase. Recurrence was defined based on the YMRS, MADRS, and CGI-BP-S scores for mania and depression, voluntary or involuntary hospitalization for any mood symptoms associated with bipolar I disorder, a therapeutic intervention to prevent or treat an impending mood episode, or any other clinically relevant event suggestive of a recurrent mood episode associated with bipolar I disorder.

The secondary endpoints included the time to the first recurrence of manic symptoms and the time to the first recurrence of depressive symptoms associated with bipolar I disorder. Other efficacy measures included change from baseline (Day 105) to the last postbaseline assessment in the double-blind MA phase for YMRS, MADRS, CGI-BP-S, GAF, SF-36, and sleep VAS.

Safety: Safety was based on the incidence of adverse events, clinical laboratory tests (including urine pregnancy testing and hemoglobin A_{1c}), 12-lead electrocardiogram, vital sign measurements, orthostatic changes in pulse and blood pressure, physical examination, and monitoring of extrapyramidal symptoms (EPS) using the Abnormal Involuntary Movement Scale (AIMS), the Barnes Akathisia Rating Scale (BARS), and the Simpson Angus Scale (SAS). In addition, the Scale for Suicidal Ideation (SSI) and the Columbia Suicide Severity Rating Scale (C-SSRS) were administered to assess potential suicidality.

Statistical Methods:

Sample Size Determination: Initially approximately 284 subjects were expected to be randomly assigned in the double-blind MA phase in a 1:1 ratio to either paliperidone ER or placebo in order to obtain at least 140 recurrence events to show that paliperidone ER was significantly different from placebo at the 1-sided significance level of 0.025, with 90% power to detect a relative risk of 0.57. The other assumptions were: uniform accrual (randomization) in the double-blind MA phase for a period of 14.2 months, randomization of approximately 20 subjects per month during the double-blind MA phase. The actual number of subjects to be enrolled would depend on the time that it took to obtain 140 recurrence events among paliperidone ER and placebo subjects. Monitoring of the total number of recurrence events in the double-blind MA phase was performed during the study to assess the appropriateness of the assumptions.

It was assumed that at least 45% of subjects who entered the double-blind AC and CT phases while being treated with paliperidone ER would not meet the criteria for randomization in the double-blind MA phase. To meet the expected number of 284 subjects (142 in paliperidone ER and placebo arms) to be randomly assigned in the double-blind MA phase, a total of 520 subjects were expected to be randomly assigned to paliperidone ER during the double-blind AC phase. With a 4:1 randomization ratio, 130 subjects were to be randomly assigned into the olanzapine arm and 520 subjects into the paliperidone ER arm, bringing the total number of subjects to be randomly

assigned during the double-blind AC phase to 650. The enrollment was to continue until 710 subjects were randomly assigned in the study. The maximum number of subjects that could be enrolled in the double-blind AC phase was increased to 790 since periodic monitoring showed a decline in the recurrence rate.

During the course of the study, the rate of recurrences slowed down over time to well below the expected rate. An Independent Data Monitoring Committee (IDMC) was employed to review the efficacy data and to provide recommendations on stopping or continuing the study based on the results of an interim efficacy analysis. If the study did not terminate based on the results from the interim analysis, an additional 80 subjects were to be enrolled and the study was to continue until a total of 140 recurrence events in the paliperidone ER and placebo treatment groups were obtained, at which time a final analysis was to be performed.

Efficacy Analysis: Following an inspection of Site [redacted] conducted as part of an internal J&JPRD systems audit, it was concluded that the site could not be considered GCP compliant. Thus, efficacy analyses were conducted using an ITT analysis set excluding the 12 subjects enrolled at this investigational site. Efficacy analyses including these 12 subjects were also performed and the results are provided in the clinical study report.

A group sequential approach was used for the analysis of primary and key secondary endpoint (time to recurrence of manic symptoms). Alpha spending function was used to control the overall type I error of 2.5% (1-sided). Analysis of all other endpoints was interpreted at significance level of 0.05 (2-sided). Analysis of the efficacy endpoints was restricted to subjects who received paliperidone ER or placebo during the double-blind MA phase. Data on olanzapine-treated subjects were summarized separately. There was no formal comparison between olanzapine- and paliperidone ER-treated subjects or between olanzapine- and placebo-treated subjects. Exploratory comparisons between olanzapine- and paliperidone ER-treated subjects were conducted on data from the double-blind AC phase and the combined AC/CT phases. In the double-blind AC/CT phases, the baseline value was defined as the last observation before receiving the first dose of study drug on Day 1. In the double-blind MA phase, the baseline value of a variable was defined as the last observation before receiving the first dose of maintenance study drug on Day 105.

The primary efficacy endpoint for the double-blind MA phase was the time to recurrence of any mood symptoms (ie, manic or depressive) associated with bipolar I disorder. For the primary analysis, time to recurrence was defined as the time between randomization to treatment in the double-blind MA phase and the first documentation of a recurrence (ie, the first time the subject met one of the recurrence criteria described under Efficacy Evaluations/Criteria). The analyses were restricted to subjects who received paliperidone ER or placebo during the double-blind MA phase. The cumulative distribution function of the time to recurrence was estimated by the Kaplan-Meier method, and the treatment groups were compared using a weighted Z statistic that was based on the log-rank test statistics from the interim and final data. Confidence intervals (CIs) for the recurrence rates at 6 months, at 1 year, and at the end of the study, were also determined.

The interim analysis was performed when approximately 87% of the 140 recurrences were reported in the placebo and paliperidone ER arms. A flexible group sequential approach was adopted that allowed for the implementation of the interim analysis. The exact information fraction was unknown at the time of interim analysis. The alpha spending approach that allowed for the control of the overall type I error when the information fraction was unknown was used. An IDMC reviewed the results of the interim analysis and safety data.

The secondary endpoints were the time to the first recurrence of manic symptoms and the time to first recurrence of depressive symptoms associated with bipolar I disorder. Time to recurrence of manic symptoms was considered to be the key secondary endpoint, and a flexible group sequential approach (similar to the one used for the primary endpoint) was applied. For the double-blind MA phase, change in the other efficacy measures (including YMRS, MADRS, GAF, and SF-36) from baseline (MA) to each visit and to the end-of-study/early withdrawal visit was analyzed based on an analysis of covariance (ANCOVA) model using both last-observation-carried-forward (LOCF) and observed cases. The model included treatment (excluding the olanzapine group) and country as factors and baseline (Day 105) value as a covariate. Treatment effects were estimated based on least-squares means, and the accompanying 95% CIs were presented. Between-group differences in CGI-BP-S were analyzed by means of an ANCOVA model on the ranks of change from baseline (MA), with treatment and country as factors and baseline (MA) score as a covariate.

RESULTS:

SUBJECT COMPLETION AND DEMOGRAPHIC RESULTS:

A total of 766 subjects were randomized in a 4:1 ratio to paliperidone ER (617 subjects) or olanzapine (149 subjects) in the AC and CT phases. Of the subjects randomized to paliperidone ER in the AC phase, 300 (49%) were re-randomized in a 1:1 ratio to receive placebo (148 subjects) or paliperidone ER (152 subjects) in the MA phase. Out of the 149 subjects randomized to olanzapine in the AC phase, 83 (56%) entered the MA phase, and continued to receive olanzapine. The diagnosis and psychiatric history at baseline was comparable between the intent-to-treat (ITT) analysis sets in the AC/CT and MA phases, except for the mean (SD) baseline MADRS score, which was lower for the ITT (MA) subjects entering the MA phase.

The rate of completion was 51% and 62% in the AC/CT and MA phases, respectively. The withdrawal rate from the AC/CT phases was high (67%) in the combined regions of North America and European Union compared to the Rest of the World (36%), due to a high rate of withdrawal of consent in these regions. The rate of discontinuation prior to entry in the MA phase was especially high among subjects enrolled at North American centers. The rate of completion in the MA phase was comparable between the combined regions of North America and European Union (58%) and Rest of the World (63%).

EFFICACY RESULTS:

Efficacy summaries are presented for the ITT analysis set excluding the 12 subjects enrolled at Site [redacted] found to be not GCP compliant. This ITT analysis set included 750 subjects in the AC/CT phase and 372 subjects in the MA phase. Additionally, efficacy results from analyses including the 12 subjects at Site [redacted] (762 subjects in AC/CT phase and 379 subjects in MA phase) are provided in the clinical study report. Exclusion of the 12 subjects at Site [redacted] from the analyses did not alter the overall conclusions of the study.

In the double-blind MA phase, paliperidone ER was statistically superior to placebo in delaying the time to recurrence of any mood symptoms in subjects with bipolar I disorder. There was a higher percentage of subjects who reported recurrence in the placebo group compared to the paliperidone ER group. Based on the interim analysis conducted by the IDMC after the 122nd recurrence event, there was a statistically significant difference between the treatment groups in the time to recurrence of any symptoms associated with bipolar I disorder in favor of paliperidone ER (p value: 0.014 at significance level (alpha=0.018). The median time to recurrence (the estimated time point at which 50% of subjects had experienced a recurrence event) was 283 days in the Pali/Placebo group and 511 days in the Pali/Pali group, based on the Kaplan-Meier estimates at the time of the interim analysis. The analyses conducted by the IDMC included subjects enrolled at Site [redacted] as the internal J&JPRD audit was carried out after the final database lock. Exclusion of the subjects at this site from the analysis did not change the conclusion of the original interim analysis.

Although the p value at the time of the interim analysis (p=0.014) was less than the prespecified significance level (alpha=0.018), the IDMC recommended continuation of the trial and indicated that continuing the study would have a greater influence on the p value, as well as providing insight into the recurrence of depressive symptoms in treated subjects. Subsequently, the protocol was amended to allow enrolment of an additional 80 subjects in the AC phase to ensure that at least 140 subjects experienced a recurrence during the MA phase (Protocol R076477-BIM-3004 Amendment INT-4).

The analysis conducted after the final database lock confirmed the findings of the interim analysis. There was a statistically significant difference between the paliperidone ER group and the placebo group in the time to recurrence of any mood symptoms in favor of paliperidone ER. There was a statistically significantly longer time to recurrence of any mood symptoms (manic or depressive) in subjects randomly assigned to the Pali/Pali group compared to the Pali/Placebo group (p=0.017 based on the weighted Z test from the log-rank test at 0.0195 level of significance). The median time to recurrence of any symptoms based on the Kaplan-Meier estimates was 283 days for subjects in the placebo group and 558 days in the paliperidone ER group.

Paliperidone ER showed superiority over placebo with respect to time to onset of manic symptoms associated with bipolar I disorder (p value <0.001 at significance level of 0.0198). The 25% quantile of time to recurrence of manic symptoms was 194 days in the placebo group and 498 days in the paliperidone ER group.

Analyses of other efficacy variables (based on assessment scales) provided further evidence of the efficacy of paliperidone ER in the maintenance treatment of subjects with bipolar I disorder. A statistically significant advantage over the placebo group was observed for the paliperidone ER group with regard to the mean changes from baseline (MA) to end point (MA) in the YMRS, CGI-BP-S, GAF, and VAS quality of sleep scores.

Paliperidone ER was not significanlty different from placebo with respect to rate of recurrence of depressive symptoms [hazard ratio (95% CI): 0.88 (0.53, 1.46)]. This was further noted in the analysis of the change from baseline (MA) in the MADRS total score, where differences between paliperidone ER and placebo were not statistically significant (p=0.763).

Overall, the proportion of subjects with a recurrence of any mood symptoms during the maintenance phase was smaller among those who were initially assigned to treatment with olanzapine (23%) in the acute treatment/continuation phases and subsequently met criteria for the maintenance phase than among subjects initially assigned to paliperidone ER and subsequently randomized on Day 105 to receive paliperidone ER during the maintenance phase (45%). The design of the study precluded any direct comparison, including inferential statistics, of subjects assigned to the Olan/Olan and Pali/Placebo groups for the primary endpoint during the maintenance phase.

Comparison of paliperidone ER with olanzapine for the change from baseline in YMRS and GAF scale scores during the 3-week AC phase showed a numerically greater improvement in the paliperidone ER group compared to the olanzapine group. The differences between the treatment groups were not statistically significant. There was no statistically significant difference between the paliperidone ER and olanzapine groups for the change from baseline in YMRS and GAF scores at the end of the combined 15-week AC/CT phases.

In the AC and AC/CT phases, the changes from baseline (AC) to end point (AC and AC/CT) in YMRS total score in both the paliperidone ER and olanzapine groups were similar for subjects from the US, the EU, and the overall population.

The results of the efficacy evaluations indicated that subjects in the paliperidone ER group had a significantly longer time to recurrence of any symptoms associated with bipolar I disorder and had a lower incidence of recurrence events at the time of the interim and final analyses, compared with the placebo group. Paliperidone ER was statistically significantly more effective than placebo in maintaining the symptomatic improvements achieved at the end of the acute treatment and continuation phases during the maintenance phase.

SAFETY RESULTS:

Flexibly dosed oral paliperidone ER (3 to 12 mg) administered daily for up to 15 weeks was safe and well tolerated in subjects with bipolar I disorder who were experiencing a manic or mixed episode. As shown in the table below, treatment-emergent adverse events occurred with similar frequency in the paliperidone ER and the olanzapine groups during the AC/CT phases of double-blind treatment. Treatment-emergent adverse events occurred with a higher frequency in the Olan/Olan group compared to the Pali/Pali group during the MA phase of the study.

Overall Summary of Treatment-Emergent Adverse Events - AC and CT Phases
(Study R076477-BIM-3004: Safety [AC/CT] Analysis Set)

	Pali (N=614) n (%)	Olan (N=148) n (%)	Total (N=762) n (%)
TEAE	471 (77)	111 (75)	582 (76)
Possibly related TEAE [a]	376 (61)	83 (56)	459 (60)
TEAE leading to death	2 (<1)	0	2 (<1)
1 or more serious TEAE	42 (7)	10 (7)	52 (7)
TEAE leading to permanent stop	65 (11)	13 (9)	78 (10)

[a]- Study drug relationships of possible, probable, and very likely are included in this category.
AC=acute treatment; CT=continuation; Pali=paliperidone ER; Olan=olanzapine; TEAE=treatment-emergent adverse event
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Overall Summary of Treatment-Emergent Adverse Events - MA Phase
(Study R076477-BIM-3004: Safety [MA] Analysis Set)

	Pali/Placebo (N=147) n (%)	Pali/Pali (N=149) n (%)	Olan/Olan (N=83) n (%)	Total (N=379) n (%)
TEAE	87 (59)	82 (55)	53 (64)	222 (59)
Possibly related TEAE [a]	49 (33)	45 (30)	32 (39)	126 (33)
TEAE leading to death	0	2 (1)	0	2 (1)
1 or more serious TEAE	33 (22)	16 (11)	8 (10)	57 (15)
TEAE leading to permanent stop	2 (1)	4 (3)	6 (7)	12 (3)

[a]- Study drug relationships of possible, probable, and very likely are included in this category.
MA=maintenance; Pali=paliperidone ER; Olan=olanzapine; TEAE=treatment-emergent adverse event
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Two subjects in the paliperidone ER group died during the AC/CT phase and 2 subjects in the Pali/Pali group died during the MA phase. The incidence of serious adverse events was similar between the Pali/Pali and Olan/Olan groups in the AC/CT and MA phases of the study. In the MA phase, the incidence of serious adverse events was higher in the Pali/Placebo group. Adverse events coded to the Psychiatric disorders SOC were the most common events leading to discontinuation during the AC/CT phases.

The incidence of adverse events coded as depression was similar in subjects receiving paliperidone ER and olanzapine in the AC/CT phases. In the MA phase, the incidence of adverse events coded as depression was higher in subjects randomly assigned to the Pali/Placebo and Pali/Pali groups (5% in each group) compared to the Olan/Olan (2%) group.

Most EPS-related adverse events were mild or moderate in severity. Akathisia, extrapyramidal disorder, dystonia, and tremor occurred at a greater incidence in the paliperidone ER group during the AC/CT phases. The percentage of subjects receiving anticholinergic medications during the AC/CT and MA phases was higher in subjects treated with paliperidone ER compared to subjects treated with olanzapine.

The incidence of potentially prolactin-related adverse events was higher in subjects treated with paliperidone ER in the AC/CT and MA phases. There were greater mean decreases in serum prolactin levels from baseline of the MA phase at end point in both male and female subjects assigned to the Pali/Placebo group, indicating that prolactin levels decreased after subjects switched from paliperidone ER to placebo in the MA phase. Differences between treatment groups in the mean changes from baseline at end point in the levels of creatine kinase in the AC/CT and MA phases were not considered to be clinically relevant. There were no notable mean changes from baseline to the end points in hematology or urinalysis parameters.

In the MA phase, the proportion of subjects with abnormally high supine pulse rate was higher in subjects randomly assigned to the Pali/Pali and Olan/Olan groups compared to subjects assigned to the Pali/Placebo group. In the AC/CT phases, 1 subject in the paliperidone ER group had a postbaseline QTcB value of 505 msec, which was considered to be clinically significant. No subject in the MA phase had QTc values greater than 500 msec.

Glucose-related adverse events occurred at a low incidence across treatment groups during the AC/CT and MA phases. During the AC/CT phases, weight increases of 7% or greater from baseline were more common in subjects receiving olanzapine compared to subjects receiving paliperidone ER. In the MA phase, weight increases of 7% or greater from baseline (AC) were more common in subjects randomly assigned to the Olan/Olan group compared to the Pali/Pali and Pali/Placebo groups.

STUDY LIMITATIONS:

Since this study employed a randomized withdrawal design, limitations related to such a design, such as enrichment of the study population for responders to the study drug, apply to this study. Hence, the long-term efficacy data from this study cannot be extrapolated directly to a general population of patients without prior exposure to paliperidone ER.

CONCLUSION:

Paliperidone ER showed superiority over placebo in delaying time to recurrence of any mood symptoms. Similarly paliperidone ER was superior to placebo in delaying time to recurrence of manic symptoms, but not depressive symptoms. Paliperidone ER was more effective than placebo in maintaining the symptomatic improvements achieved at the end of the acute treatment/continuation phases, as reflected by mean changes for select outcome measures (e.g. YMRS but not MADRS) during the maintenance phase.

The overall safety findings in this study were similar to those observed in previous studies with paliperidone ER for the treatment of acute mania in subjects with bipolar I disorder, and no new safety signal was detected during long-term treatment.