SYNOPSIS

Issue Date: 14 December 2009
Document No.: EDMS-PSDB-10450120:3.0

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

Protocol No.: R076477-PSZ-3001

Title of Study: A Randomized, Multicenter, Double-Blind, Weight-Based, Fixed-Dose, Parallel-Group, Placebo-Controlled Study of the Efficacy and Safety of Extended Release Paliperidone for the Treatment of Schizophrenia in Adolescent Subjects, 12 to 17 Years of Age

Principal Investigator: Adelaide Robb, MD, Children's National Medical Center, Washington DC; United States

Publication (Reference): None

Study Period: 8 August 2007 to 30 March 2009

Phase of Development: 3

Objectives: The primary objective of this study was to evaluate the efficacy, safety, and tolerability of 3 weight-based, fixed-dose groups of paliperidone extended release (ER) (to fully explore the tolerability range) as compared with placebo in adolescent subjects 12 to 17 years of age, inclusive, with schizophrenia.

The secondary objectives were to assess the change in the global impression of severity of illness associated with the use of paliperidone ER compared with placebo as measured by the Clinical Global Impression Severity (CGI-S) scale; to assess the benefits in psychological, social, and school functioning associated with treatment with paliperidone ER compared with placebo as measured by the Children's Global Assessment Scale (CGAS); and to explore the pharmacokinetics (PK) of paliperidone ER and the relationship between its PK and the results of the efficacy parameters (eg, Positive and Negative Syndrome Scale [PANSS]) and safety parameters (eg, extrapyramidal symptoms [EPS], adverse events) of interest. An exploratory secondary objective was to assess the effect on sleep associated with treatment with paliperidone ER as measured by the sleep Visual Analog Scale (VAS).

Methods: This was a randomized, double-blind, parallel-group, placebo-controlled, multicenter study which consisted of 3 phases: a screening phase (with a possible overlapping washout period), a 6-week double-blind treatment phase with an end-of-study or early-withdrawal visit, and a 1-week follow-up visit for subjects who did not enter an optional, long-term, open-label safety study (R076477-PSZ-3002). The open-label safety study was offered to those subjects who completed the study or who completed a minimum of 21 days of double-blind treatment in the study and dropped out due to lack of efficacy and were expected to benefit from treatment with paliperidone ER. Subjects with schizophrenia who were in a state of acute exacerbation and not doing well on their current antipsychotics, and who met all entry criteria at screening, had their current disallowed psychotropic medications tapered and discontinued if necessary during the screening phase. Eligible subjects were then randomly assigned to 1 of 4 treatment groups (placebo, paliperidone ER Low, paliperidone ER Medium, paliperidone ER High) corresponding to nonoverlapping milligram per kilogram groups. Subjects weighing 29 to less than 51 kg at the baseline visit received placebo or 1.5, 3, or 6 mg of paliperidone ER daily and those weighing at least 51 kg received placebo or 1.5, 6, or 12 mg of paliperidone ER daily. The paliperidone ER Low treatment group included all subjects who received 1.5 mg. The paliperidone ER Medium treatment group included subjects who weighed 29 to less than 51 kg and received 3 mg plus those who weighed at least 51 kg and received 6 mg. The paliperidone ER High treatment group included subjects who weighed 29 to less than 51 kg and received 6 mg plus those who weighed at least 51 kg and received 12 mg.

A blood sample for pharmacogenomic research was collected from subjects who gave consent. Participation in pharmacogenomic research was optional. Blood samples were also collected for population PK analysis.

Number of Subjects (planned and analyzed): A total of approximately 200 subjects were planned to be enrolled. Two hundred one subjects were randomly assigned to receive placebo (N=51), paliperidone ER Low treatment (N=54), paliperidone ER Medium treatment (N=48), or paliperidone ER High treatment (N=48). All 201 subjects were included in the safety analysis set, and 200 subjects were included in the Intent-to-Treat (ITT) analysis set.

Diagnosis and Main Criteria for Inclusion: Males or females between 12 and 17 years of age, inclusive, with a body weight of at least 29 kg, who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for schizophrenia at least 1 year before screening and who had a PANSS total score between 60 and 120, inclusive, at screening and baseline. Eligible subjects were otherwise physically healthy based on medical history, physical examination, electrocardiogram (ECG), and laboratory test results.

Test Product, Dose and Mode of Administration, Batch No.: Paliperidone was supplied as oral tablets containing paliperidone ER 1.5 mg (Lots 0605432, 0701161), 3 mg (Lots 0620769, 0627123, 0706412, 0729774), 6 mg (Lots 0617714, 0707704, 0706413, 0729777), or 12 mg (Lots 0602596, 7AG1026-X).

Reference Therapy, Dose and Mode of Administration, Batch No.: Matching placebo tablets were supplied (Lots 0602143, 0602145).

Duration of Treatment: Subjects received double-blind treatment for 6 weeks.

Criteria for Evaluation: Pharmacokinetics: Venous blood samples of 2 mL were collected for the determination of plasma concentration of paliperidone enantiomers. A total of 5 samples were collected: 1 at baseline (predose) and 2 each at Visit 4 and Visit 7 (1 predose and 1 at least 2 hours postdose).

Efficacy: The primary efficacy variable was the change in the PANSS total score from baseline to the last postrandomization assessment in the double-blind period of the study (end point). The secondary efficacy variables were the change from baseline to end point in the CGI-S score, the CGAS score, the sleep VAS score, and the responder rate.

Safety: Safety was evaluated based on the changes from baseline in clinical laboratory testing (hematology, serum chemistry, urinalysis, prolactin), physical examinations, Tanner staging, vital sign measurements, measurements of weight gain and metabolic disturbances, ECGs, and monitoring for adverse events, including EPS using the Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and Simpson-Angus Rating Scale (SAS).

Statistical Methods: Efficacy analyses involving changes from baseline to end point used the last observation carried forward (LOCF) approach. All efficacy and safety analyses were performed according to the protocol using the randomly assigned, weight-based, fixed-dose treatment groups (placebo, paliperidone ER Low, paliperidone ER Medium, paliperidone ER High). Additional analyses were performed using the actual dose groups (placebo or paliperidone ER 1.5, 3, 6, or 12 mg).

Primary Variable: The primary efficacy variable was the change in the PANSS total score from baseline to end point. The primary efficacy variable was analyzed using an analysis of covariance (ANCOVA) model with treatment group and country as fixed factors and baseline PANSS total score as a covariate. A closed testing procedure using Dunnett's test was used to adjust for multiple comparisons in testing the 3 paliperidone ER treatment groups against placebo.

Secondary Variables: Changes from baseline to end point in CGI-S, CGAS, and sleep VAS were analyzed using an ANCOVA model with treatment and country as factors and the respective baseline scores as a covariate.

Other Variables:

- Responder Rate: Responders were defined as those subjects who showed a 20% or more reduction from baseline to end point in the PANSS total score. This variable was analyzed using the Cochran-Mantel-Haenszel test, controlling for country.
- PANSS Subscales: Changes from baseline for PANSS factors and subscales were analyzed using an ANCOVA model with treatment and country as factors and the respective baseline scores as a covariate.

Safety Analyses: Descriptive statistics were used to summarize adverse events including EPS, glucose-related events, potentially prolactin-related events, and other events of special interest; clinical laboratory tests; ECG data; vital sign measurements; weight, waist circumference, and body mass index (BMI). Additional analyses included a comprehensive clinical review of potential suicide-related events, homeostasis model assessment (HOMA), and standardized z-scores for weight, height and BMI.

RESULTS:

A majority (69%) of the 201 subjects randomly assigned to a weight-based, fixed-dose treatment group completed the study. The completion rate was higher in the paliperidone ER Medium (83%) and High (77%) treatment groups than in the placebo (51%) and paliperidone ER Low treatment (65%) groups. The most common reason for withdrawal was lack of efficacy, but the percentage of subjects who were withdrawn for that reason was higher in the placebo (39%) and paliperidone ER Low treatment (26%) groups than in the other groups (4% and 8%).

A majority of the subjects in this study were male (59%), white (68%), and had a baseline body weight of at least 51 kg (69%), a normal BMI (83%), and a diagnosis of paranoid schizophrenia (71%). The mean age at baseline was approximately 15 years, and the mean (SD) baseline PANSS total score was 91.1 (13.03). There were no differences between the treatment groups in demographic or baseline characteristics.

EFFICACY RESULTS: Efficacy analyses were based on the ITT analysis set, which included all randomized subjects who received at least 1 dose of double-blind study drug and had both a baseline and at least 1 postbaseline efficacy assessment in the double-blind phase.

The study had sufficient power to detect the true treatment effect, since statistical superiority with regard to the primary efficacy outcome was demonstrated using a conservative multiplicity adjustment (Dunnett's). Thus, the study achieved its protocol specified objective.

The mean change from baseline to end point in the PANSS total score (primary efficacy variable) was -7.9 in the placebo group, -9.8 in the paliperidone ER Low treatment group, -17.3 in the paliperidone ER Medium treatment group, and -13.8 in the paliperidone ER High treatment group. The improvement in the paliperidone ER Medium treatment group achieved statistical significance ($p=0.006$). For the paliperidone ER High treatment group, the p value for the comparison with placebo was 0.086. An additional analysis by actual dose revealed that the improvement in the 3, 6, and 12 mg dose groups achieved statistical significance. There were no significant treatment-by-country or treatment-by-baseline PANSS interactions, but there was a significant treatment-by-baseline weight category interaction. There was a lower treatment effect among subjects in the paliperidone ER High treatment group who weighed <51 kg than in the other paliperidone ER treatment groups and the placebo group. All 3 paliperidone ER treatment groups were evaluated using a 2-sided Gail-Simon test, which showed insufficient evidence to indicate a qualitative treatment-by-baseline weight category interaction.

The results for the secondary variables were consistent with those for the primary variable. The median change from baseline to end point in the CGI-S was 0.0 in both the placebo and paliperidone ER Low treatment groups and -1.0 in both the paliperidone ER Medium and High treatment groups. The results achieved statistical significance in both the paliperidone ER Medium treatment group ($p<0.001$) and the paliperidone ER High treatment group ($p=0.021$). The mean change from baseline to end point in the CGAS was 5.0 in the placebo group, 4.4 in the paliperidone ER Low treatment group, 13.1 in the paliperidone ER Medium treatment group, and 8.6 in the paliperidone ER High treatment group. The difference from placebo was statistically significant for the paliperidone ER Medium treatment group ($p<0.001$). For the paliperidone ER High treatment group, the p value for the comparison with placebo was

0.067. The mean change in quality of sleep (from the sleep VAS) was -0.3 in the placebo group, 6.6 in the paliperidone ER Low treatment group, 16.0 in the paliperidone ER Medium treatment group, and 14.4 in the paliperidone ER High treatment group. The results achieved statistical significance in both the paliperidone ER Medium and High treatment groups. There were no statistically significant effects of any paliperidone ER dose on daytime drowsiness (from the sleep VAS).

The results for the secondary variables by actual dose were consistent with those by treatment group. There was statistically significant improvement from baseline to end point in CGI-S and CGAS for the 3, 6, and 12 mg dose groups relative to the placebo group.

A reduction of at least 20% in the PANSS total score occurred in significantly higher percentages of subjects in the paliperidone ER Medium and High treatment groups than in the placebo group. Improvement from baseline to end point in the PANSS factors of positive symptoms and uncontrolled hostility/excitement achieved statistical significance in both the paliperidone ER Medium and High treatment groups. Improvement in the PANSS factors of negative symptoms and disorganized thoughts achieved statistical significance in the paliperidone ER Medium treatment group relative to the placebo group. Based on significant differences from placebo over time in the PANSS total score, the onset of therapeutic effect in the paliperidone ER Medium treatment group was Day 22 ($p=0.053$ on Day 15). For the paliperidone ER High treatment group, the p values for the comparison with placebo were less than 0.05 on Days 8, 15, 36, and at end point; 0.079 on Day 22; and 0.075 on Day 29.

PHARMACOKINETIC AND PHARMACOGENOMIC RESULTS: The PK data from this study will be used in a population PK analysis that will be reported in a separate document. No pharmacogenomic analysis was performed.

SAFETY RESULTS: Treatment-emergent adverse events (TEAEs) occurred in 58.8% of the subjects in the placebo group, 50.0% of those in the paliperidone ER Low treatment group, 60.4% of those in the paliperidone ER Medium treatment group, and 75.0% of those in the paliperidone ER High treatment group. There were dose-related trends in the incidences of somnolence, akathisia, tremor, dystonia, and tachycardia. Headache and weight increased occurred at incidences that were at least 5% higher in the paliperidone ER Low treatment group than in the placebo group. Somnolence, akathisia, and tremor occurred at incidences that were at least 5% higher in the paliperidone ER Medium treatment group than in the placebo group. Somnolence, akathisia, headache, tremor, dystonia, cogwheel rigidity, and tachycardia occurred at incidences that were at least 5% higher in the paliperidone ER High treatment group than in the placebo group. The proportion of subjects who experienced at least 1 TEAE was higher among those who weighed at least 51 kg than among those who weighed less than 51 kg in the paliperidone ER Medium and High treatment groups.

There were no deaths. Serious adverse events occurred in 1 subject in the placebo group and 1 or 2 subjects in each of the paliperidone ER treatment groups. TEAEs leading to discontinuation of study drug occurred in 3 subjects, 1 in each paliperidone ER treatment group.

Based on the comprehensive clinical review of both preferred and reported terms associated with potentially suicide-related adverse events and classification on the Columbia Classification Algorithm of Suicide Assessment (C-CASA), there were no reports of adverse events either coded to suicidality-related preferred terms or categorized as suicidal behavior. There was no indication of an increased suicidality risk in subjects receiving paliperidone ER, compared to placebo.

EPS-related adverse events occurred in a dose-related fashion, with the most common events being akathisia and dystonia. During the double-blind phase, anticholinergic medications were taken by 0% of the subjects in the placebo group, 4% of those in the paliperidone ER Low treatment group, 15% of those in the paliperidone ER Medium treatment group, and 29% of those in the paliperidone ER High treatment group. The results of the AIMS, BARS, and SAS showed little change from baseline to end point.

No subject in any group had neuroleptic malignant syndrome or TEAEs related to any of the following special categories of interest: suicidality, seizures and convulsions, cardiac arrhythmias, proarrhythmic potential, ischemia, gastrointestinal perforations/ulcers, pancreatitis, rhabdomyolysis, overdose, or drug withdrawal. The incidence of glucose-related TEAEs was low (<2%) in all 4 treatment groups. There were dose-related trends in the incidences of somnolence and sedation and of tachycardia, but not in the

incidences of agitation and aggression, TEAEs related to orthostatic hypotension, or TEAEs related to weight gain.

The incidence of potentially prolactin-related TEAEs was low (<5%) in all 4 treatment groups. Prolactin levels above the upper limit of the normal range occurred in greater percentages of subjects in the paliperidone ER treatment groups than the placebo group, consistent with the known pharmacology of paliperidone. Otherwise, there were no clinically meaningful effects of paliperidone ER on laboratory parameters. There was no evidence to suggest worsening of insulin resistance or an increase in glucose abnormalities in subjects treated with paliperidone ER, compared to those treated with placebo.

Only 1 subject (in the paliperidone ER High treatment group) had changes in both pulse and diastolic blood pressure that met the numeric criteria for orthostatic hypotension. The rates of abnormal values for pulse rate and blood pressure were generally higher in subjects who were 15 to 17 years old at baseline than in those who were 12 to 14 years old. The older subjects experienced dose-related increases in both standing and supine pulse rate.

There were dose-related increases from baseline to end point in measurements related to weight gain in both the analysis by weight-based, fixed-dose treatment group and the analysis by actual dose group. In the paliperidone ER High treatment group at end point, mean weight increased by 1.4 kg or 2.2%, mean BMI increased by 0.4 kg/m^2, and mean waist circumference increased by 0.9 cm. The corresponding values for the 12 mg dose group were 1.5 kg or 2.2%, 0.4 kg/m^2, and 1.2 cm. Increases in weight of ≥7% occurred in 2% of the subjects in the placebo group, 6% of those in the paliperidone ER Low treatment group, 13% of those in the paliperidone ER Medium treatment group, and 13% of those in the paliperidone ER High treatment group. Increases in weight of ≥7% occurred in 6% of the subjects who received 1.5 mg, 19% of those who received 3 mg, 7% of those who received 6 mg, and 18% of those who received 12 mg. There were no clinically significant changes in standardized z-scores for weight, height, or BMI in any treatment group from baseline to endpoint, and there was no evidence of a dose effect. This indicates that over the duration of this 6-week study, the growth observed (height, weight and BMI) was similar to that expected from normal adolescent maturation.

No subject had a QTcLD value greater than 450 msec or a change in QTcLD from average predose to end point of greater than 60 msec. Changes in QTcLD of greater than 30 to 60 msec occurred in 4% of the subjects in the placebo group, 0% of those in the paliperidone ER Low treatment group, 7% of those in the paliperidone ER Medium treatment group, and 2% of those in the paliperidone ER High treatment group. There were no clinically relevant effects of paliperidone ER on other ECG parameters.

The safety results by actual dose were consistent with those by treatment group; ie, there were dose-related trends in TEAEs, EPS-related adverse events, and measurements related to weight.

STUDY LIMITATIONS: This study investigated the efficacy and safety of paliperidone ER for acute treatment of schizophrenia over 6 weeks and does not provide information about longer-term efficacy and safety. Because the study was designed to enroll adolescent subjects 12 to 17 years of age, efficacy and safety in younger children with schizophrenia cannot be extrapolated from the data. Doses between 1.5 and 12 mg were evaluated, and results with higher or lower doses cannot be extrapolated from the data. The study was not designed to demonstrate efficacy for specific subgroups of subjects, such as those of a certain weight or from a particular country.

CONCLUSION: This was the first double-blind, placebo-controlled study of paliperidone ER in adolescent subjects with schizophrenia. For the primary efficacy analysis by weight-based, fixed-dose treatment group, the paliperidone ER Medium treatment group was statistically superior to the placebo group. When the primary efficacy variable was analyzed by actual dose group, improvement relative to placebo was observed with paliperidone ER doses of 3, 6, and 12 mg/day. All doses evaluated (1.5 to 12 mg/day) were safe and tolerable in adolescents with schizophrenia.

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