Janssen Research & Development

Synopsis
[Protocol R076477-PSZ-3002; Phase 3]

R076477 (paliperidone)

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SYNOPSIS

Issue Date: 29November 2012

Name of Sponsor/Company	Janssen Research & Development*
Name of Finished Product	INVEGA®
Name of Active Ingredient(s)	R076477 (paliperidone)

Protocol No.: R076477-PSZ-3002

Title of Study: A 2-Year, Open-Label, Single-Arm Safety Study of Flexibly Dosed Paliperidone Extended Release (1.5-12 mg/day) in the Treatment of Adolescents (12 to 17 Years of Age) With Schizophrenia

EudraCT Number: 2007-000577-38

NCT No.: NCT00488319

Clinical Registry No.: CR012616

Coordinating Investigator(s): [redacted] MD; [redacted] the United States

Study Center(s): Bulgaria (1 site), Estonia (2 sites), Finland (1 site), India (5 sites), Korea (6 sites), Poland (6 sites), Romania (1 site), Russia (12 sites), Ukraine (6 sites), and the United States of America (15 sites).

Publication (Reference): None

Study Period: 27 June 2007 to 18 July 2012

Phase of Development: 3

Objectives: The primary objective of the study was to evaluate the long-term (2-year) safety and tolerability of paliperidone extended release in at least 100 adolescent subjects 12 to 17 years of age, inclusive (ie, 12 to less than 18 years of age), with schizophrenia.

The long-term safety and tolerability was evaluated by studying the effects of paliperidone extended release (ER) on prolactin, growth and maturation. Effects on lipid levels, body weight and height, waist circumference, electrocardiograms (ECGs), fasting glucose, insulin, Tanner staging, extrapyramidal symptoms (EPS), sedation, and monitoring of psychiatric adverse events (suicide and related phenomena, homicidal ideation, depressed mood, and worsening of psychosis) and adverse events in general, was also included.

The exploratory secondary objectives of this study were to:

- Assess the effect of paliperidone ER on the long-term symptoms of schizophrenia as measured by the changes in Positive and Negative Syndrome Scale for Schizophrenia (PANSS) scores.
- Assess the effect of paliperidone ER on the long-term symptoms of schizophrenia as measured by the changes in the PANSS negative symptom scale based on Marder factors.[11]
- Assess the global improvement in severity of illness associated with treatment with paliperidone ER as measured by the Clinical Global Impression-Severity (CGI-S) scale.
- Assess the benefits in psychological, social, and school functioning associated with treatment with paliperidone ER as measured by the Children's Global Assessment Scale (CGAS).

- Assess the changes in multiple domains of cognitive functioning associated with treatment with paliperidone ER as assessed by the modified Measurements and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) cognition assessment battery.
- Assess the effect on sleep associated with treatment with paliperidone ER as measured by the sleep Visual Analog Scale (VAS).

Paliperidone ER is termed prolonged release (PR) in the European Union (EU). Paliperidone ER is used throughout this document.

Methodology: This was a 2-year open-label (OL), multicenter study of flexibly-dosed paliperidone ER in adolescents with a Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) diagnosis of schizophrenia. Subjects who had completed Study R076477-PSZ-3001 or had discontinued the study due to lack of efficacy, but completed a minimum of 21 days of Study R076477-PSZ-3001 and were expected to benefit from paliperidone ER, could be enrolled in this open-label study. Subjects who had not participated in Study R076477-PSZ-3001 could also be enrolled directly.

The study consisted of 3 phases: a screening phase and a washout phase (maximum of 21 days), an open-label treatment phase of up to 2 years, and a posttreatment (follow-up) visit, 1 week after the subject's final dose of the study drug. The total planned duration of the 2-year study was approximately 108 weeks. Eligible subjects were to begin the study at a starting dose of paliperidone ER 6 mg daily. The initial 6 mg daily dose was to be increased in increments of 3 mg (to 9 mg and then to 12 mg daily), not more frequently than once every 5 days until the maximum dose of 12 mg daily was reached. If 12.0 mg is not tolerated well, then the dose could be reduced down to 9 mg daily. Alternatively, if the 6 mg dose was not tolerated well, the dose could be decreased to 3 or 1.5 mg daily. Paliperidone ER was to be administered daily in the morning preferably before 10 AM and could be taken without regard to food. After amendment 6, the time of the medication could be adjusted to other times based on tolerability or convenience. However, study drug administration was to occur in a consistent manner relative to the intake of food (ie, either before or after breakfast, or without any breakfast) and to time throughout the study. A pharmacogenomic blood sample (up to 10 mL) was collected from subjects who entered this study directly without having participated in Study R076477-PSZ-3001 and whose parents or legal guardians gave separate written informed consent for this part of the study (where local regulations permitted). The total volume of blood drawn for laboratory evaluations and pharmacogenomics sampling throughout this study was approximately 100 mL for each subject.

The following treatment group designations were used for all (efficacy and safety) summary tables and listings:

- Placebo/Pali: subjects previously randomly assigned to placebo in Study R076477-PSZ-3001.
- Pali (DB)/Pali: subjects previously randomly assigned to any one of the paliperidone ER dose groups (low, medium, or high) in Study R076477-PSZ-3001. The protocol-specified treatment groups were 'Pali Low/Pali', 'Pali Medium/Pali', or 'Pali High/Pali'. These paliperidone ER treatment groups were combined and presented as the Pali (DB)/Pali group in this report (DB=double-blind).
- Pali (NO DB)/Pali: This group represented the subjects who enrolled in this study directly. The protocol-specified treatment group label was 'Pali Direct'.

All the summaries also included a Total group (ie, all treatment groups combined).

Number of Subjects (planned and analyzed): Planned: Approximately 400 subjects were planned to be enrolled in the study to have at least 100 evaluable subjects complete the 2-year open label study at or above the lowest effective dose (≤3 mg) that was identified in Study R076477-PSZ-3001.

Analyzed: A total of 400 subjects (39 subjects in the Placebo/Pali, 118 subjects in the Pali (DB)/Pali, and 243 subjects in the Pali (NO DB)/Pali treatment groups) were included in the safety analysis, and 393 subjects (39 subjects in the Placebo/Pali, 117 subjects in the Pali (DB)/Pali, and 237 subjects in the Pali (NO DB)/Pali treatment groups) were included in the efficacy analysis. A total of 109 evaluable subjects had exposure to paliperidone ER for the study duration of 2 years.

Diagnosis and Main Criteria for Inclusion: Subjects who were 12 and 17 years of age (inclusive, at the time of consent) and met the DSM-IV criteria for schizophrenia were eligible for enrollment in this study. Subjects with a weight of ≥29 kg, who had not been a danger to themselves or others, and who had family support available were maintained as outpatients. Subjects had to have a score of ≤2 for each item in the Kiddie-Sads-Present and Lifetime Version (K-SADS-PL) diagnostic interview: a) recurrent thoughts of death; b) suicidal thoughts; c) suicide attempts and their seriousness; d) suicide attempts and their lethality; and e) self-harming behavior. Subjects were excluded from the study if they met the DSM-IV criteria for dissociative disorder, bipolar disorder, major depressive disorder, schizoaffective disorder, schizophreniform disorder, autistic disorder, or primary substance-induced psychotic disorder at screening; if they had mild, moderate, or severe mental retardation; and if they had a known or suspected history of substance dependence according to the DSM-IV criteria in the 3 months preceding screening.

Test Product, Dose and Mode of Administration, Batch No.: Paliperidone ER, 1.5 mg, 3 mg, and 6 mg tablets. Paliperidone ER was administered at an initial 6 mg daily dose and could be increased as needed in increments of 3 mg (to 9 mg and then 12 mg daily) not more frequently than once every 5 days until the maximum dose of 12 mg daily was reached. (Batch numbers: 1.5 mg: 0605432, 0701161, 0818070, 0901616, 0915877, 1008456-X, 1013071; 3 mg: 0620766, 0677123, 0716337, 0706412, 0729774, 0811273, 9KD1190, 0MD2611-X; 6 mg: 0617714, 0707704, 0706413, 0729777, 0808305, 9JD1089, 0MD2605-X).

Duration of Treatment: The duration of the study, including the screening and posttreatment phase, was approximately 108 weeks.

Criteria for Evaluation:

Safety: The safety assessments included laboratory measurements (chemistry, fasting glucose, insulin, liver function tests, hematology, hormone, lipid assessments, prolactin [blinded], urinalysis, and urine drug screens), body weight and height, waist circumference, electrocardiograms (ECGs), and physical examinations (including Tanner staging used to investigate the impact of paliperidone ER treatment on growth and sexual maturation in relation to changes in prolactin). The Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and Simpson Angus Rating Scale (SAS) were used to assess EPS and dyskinesia. Adverse events (AEs) including psychiatric adverse events of interest (ie, suicide and related phenomena, homicidal ideation, depressed mood, and worsening of psychosis) and sedation that could have been associated with paliperidone ER in this population were monitored. In addition, the Columbia Suicide Severity Rating Scale (C-SSRS) was implemented after Study R076477-PSZ-3002 had been ongoing for approximately 2 years and 289 subjects had enrolled in the study to assess suicidality.

Efficacy: All efficacy analyses done for this study were exploratory. The primary efficacy variable was the change from baseline in the PANSS total score at the end of the open label phase (Week 104 or the last postbaseline assessment). Other measures of efficacy included the CGI-S, CGAS, the modified MATRICS cognition assessment battery, sleep VAS, and the PANSS negative symptom scale based on Marder factors.

Statistical Methods:

Sample size: No formal sample size calculation was performed for this study. Based on the discontinuation rate seen in a similar study evaluating risperidone in adolescents, approximately 400 subjects were to be enrolled into this open-label study so that at least 100 subjects completed the 2-year open-label study at or above the lowest effective dose (≤3 mg) that was identified in Study R076477-PSZ-3001.

Subjects who enrolled in this study were from 3 different sources: subjects who enrolled directly, subjects who were randomly assigned to placebo in Study R076477-PSZ-3001, and subjects who were randomly assigned to paliperidone ER in Study R076477-PSZ-3001. Due to the heterogeneity in this study population, and the lack of a control group, all analyses were descriptive only. Descriptive statistics of the change from baseline in PANSS total score and each PANSS subscale score to each time point (both observed and last-observation-carried-forward [LOCF]) were provided. Descriptive statistics of the changes from baseline in PANSS negative symptom scale based on Marder factors, CGI-S, CGAS, and sleep VAS, and each test in the modified MATRICS battery to each time point (both observed and LOCF) were provided. The efficacy and safety summaries of the data were generated when 100 subjects completed at least 6 months (Week 24) and 2 years (Week 104) in the study.

Safety analyses: All subjects who received at least 1 dose of the open-label study drug were included in the safety analyses. The percentage of subjects with specific treatment-emergent adverse events (TEAEs) was to be summarized. Extrapyramidal symptom-related Aes, glucose-related Aes, potentially prolactin-related Aes, and Aes of special interest were summarized by the treatment group. Descriptive statistics were to be provided for the clinical laboratory tests, vital signs, ECG, body weight, height, body mass index (BMI), and waist measurement at each scheduled time point and baseline. The frequency distributions of the physical examination findings (including Tanner Staging) at open-label and double-blind baseline and open-label end point were presented. Summary statistics for the total score at each assessment and end point was to be presented for the EPS Rating Scale of AIMS and SAS; the frequencies of the clinical global rating score of akathisia by treatment group for BARS were to be presented. The frequency distribution of the individual items of AIMS, SAS and BARS at each assessment time point and at end point was to be presented.

Efficacy analyses: The intent-to-treat (ITT) analysis set was used for the efficacy analyses. All enrolled subjects who received at least 1 dose of open-label study drug and had both the baseline and at least 1 postbaseline assessment in the open-label phase for either PANSS, CGI-S, or CGAS or sleep VAS were included in this analysis set. Descriptive statistics (n, mean, standard deviation, median, minimum, maximum) of the change from baseline to each time point (both observed and LOCF) were provided for PANSS, CGI-S, CGAS, sleep VAS, and for each test in the modified MATRICS battery test.

RESULTS:

STUDY POPULATION: A total of 400 subjects were assigned to the 3 treatment groups (39 subjects in the Placebo/Pali treatment group, 118 subjects in the Pali (DB)/Pali treatment group, and 243 subjects in the Pali (NO DB)/Pali treatment group).

Of the 400 subjects, 220 subjects (55%) completed the study (24 subjects in the Placebo/Pali treatment group, 75 subjects in the Pali (DB)/Pali treatment group, and 121 subjects in the Pali (NO DB)/Pali treatment group). A total of 180 subjects (45%) withdrew from the study due to subject choice (17%), lack of efficacy (11%), adverse event (7%), lost to follow up (6%), or other reasons (4%) in the Total treatment group. A total of 109 evaluable subjects had exposure to paliperidone ER for the study duration of 2 years.

A majority of the subjects were male (61%), white (67%), and had an open-label baseline body weight of ≥51 kg (76%) and a normal BMI (80%). The mean age of the subjects in the ITT analysis set was approximately 15.4 years.

Protocol deviations were reported in a total of 86 subjects in this study. A total of 400 subjects received at least 1 dose of the study drug and were included in the safety analysis set.

EFFICACY RESULTS:

Assessment of efficacy was not a primary objective of this study. The primary efficacy variable for the exploratory secondary objective was the change from open-label baseline to open-label end point in the PANSS total score. The efficacy analysis was based on the ITT analysis set which comprised of 393 subjects.

There were mean decreases in PANSS scores (indicating improvement) after administration of paliperidone ER from open-label baseline to open-label end point, the highest means (SD) change noted (-22.4 [22.25]) in the Pali (NO DB)/Pali treatment group and lowest change noted (-12.6 [19.92]) in the Pali (DB)/Pali treatment group. The mean (SD) change in PANSS total score from double-blind baseline to open-label end point was slightly higher in the Pali (DB)/Pali treatment group (-27.5 [19.09]) than in the Placebo/Pali treatment group (-25.7 [16.01]). In the Total group, the magnitude of the mean decrease (improvement) from open-label baseline to end point in PANSS total score was higher for non-US subjects than the US subjects, and was numerically slightly greater for the non-EU subjects (-19.6, N=315) than the EU subjects (-17.1, N=78). Other efficacy analyses including the CGI-S, CGAS, sleep VAS, and PANSS factor scores corroborated the findings of the primary efficacy variable. Small improvements in performance on tests of cognitive function were observed in all groups from open-label baseline to the 6-month time point for most domains.

SAFETY RESULTS:

The primary objective of the study was to assess the safety and tolerability of paliperidone ER. A total of 400 subjects received at least 1 dose of the study drug and were included in the safety analysis set. No deaths were reported in this study. Overall, 85.3% (341/400) of subjects experienced TEAEs in this open-label study; 82.1% in the Placebo/Pali treatment group, 74.6% in the Pali (DB)/Pali treatment group, and 90.9% in the Pali (NO DB)/Pali treatment group. The proportion of subjects with any possibly drug-related TEAE (67.5%, overall), and permanent discontinuation due to a TEAE (6.3%, overall) was higher in the Pali (NO DB)/Pali (76.1% and 9.5%, respectively) treatment group than in the other treatment groups. The most common (>10%) TEAEs reported in the Total group were somnolence and weight increased, followed by headache, insomnia, nasopharyngitis, akathisia, schizophrenia and tremor. The incidence of TEAEs was higher (88.0% versus 77.2%) in subjects who weighed 51 kg or more at open-label baseline than in subjects who weighed less than 51 kg in the Total group. Only 14.8% of subjects experienced SAEs. The proportion of subjects with SAEs was slightly higher in the Placebo/Pali treatment group (23.1%) than in the Pali (NO DB)/Pali treatment group (18.9%), and only 4 subjects (3.4%) in the Pali (DB)/Pali treatment group had a SAE.

The most commonly occurring EPS-related events were those grouped as parkinsonism and 15yperkinesias. The incidence of TEAEs related to cardiac arrhythmias (0.3%, overall), orthostatic hypotension (1.5%, overall), proarrhythmic potential (0.3%, overall), overdose (0.8%, overall), tachycardia (2.8%), and glucose-related (1.5%, overall) were low in this study. The incidence of suicidality-related events was 9.3% overall, and these events occurred in the Pali (NO DB)/Pali treatment group only. Agitation- and aggression-related Aes were reported only in the Pali (DB)/Pali and Pali (No DB)/Pali treatment groups, and the incidence of these was low. There was no reported TEAE of NMS in the study. The incidence of TEAEs related to weight gain was highest in the Pali (NO DB)/Pali treatment group (26.7%), followed by the Pali (DB)/Pali (12.7%), and the Placebo/Pali treatment groups (10.3%). The incidence of somnolence- and sedation-related Aes was higher in the Placebo/Pali (25.6%) and in the Pali (NO DB)/Pali (25.5%) treatment groups than in the Pali (DB)/Pali treatment group (16.9%). Overall, 9.3% of subjects (37/400) experienced a prolactin-related TEAE. The incidence of prolactin-related TEAEs was 18.5% (29/157) in females and 3.3% (8/243) in males. No remarkable changes in the AIMS, BARS, and SAS scores from open-label and double-blind baseline to open-label end point were observed.

The clinician review of all TEAE verbatim terms was only done for those subjects that did not have any C-SSRS data available from the eCRF (ie, they completed the study before initiation of the CSSRS). Sixteen of 111 subjects (14.4%) were identified with potentially suicide-related events (PSRE), with highest incidence in the Pali (NO DB)/Pali (25.5%) treatment group followed by the Placebo/Pali (14.3%) and Pali (DB)/Pali (2.2%) treatment groups. For subjects who completed the study after the initiation of the C-SSRS a total of 12.8% of subjects (37/289) were identified with PSRE. The highest incidence of PSRE was in the Pali (NO DB)/Pali (18.8%) treatment group, followed by the Placebo/Pali (4.0%) treatment group. No PSREs were identified in the Pali (DB)/Pali treatment group. No clinically relevant mean or median changes in heart rate, PR interval, QRS interval, QT interval, RR interval, QTcB, QTcF, QTlc, or QTcLD were observed. Overall, 43% of subjects experienced weight gain of at least 7% at open-label end point relative to open-label baseline. No clinically significant changes in z scores for height, weight, and BMI were observed. A majority of both male and female subjects in each treatment group had the same Tanner ratings at baseline and end point, and no noteworthy differences between the 3 treatment groups at end point in Tanner staging relative to the open-label or double-blind baseline were observed.

Overall, the safety and tolerability of paliperidone ER in adolescents with schizophrenia appeared to be similar to that observed in studies of risperidone in adolescents with schizophrenia and in the studies of paliperidone ER in adults with schizophrenia.

STUDY LIMITATIONS:

The study was an open label study. Limitations also included the lack of a concurrent placebo group and small number of subjects in the lower age group.

CONCLUSION(S):

Paliperidone ER in a dose range of 1.5 to 12 mg/day was safe and well tolerated for the long-term treatment of schizophrenia in adolescents. Administration of paliperidone ER in this dose range to adolescents with schizophrenia had a similar safety and tolerability profile to that of adults with schizophrenia and risperidone in adolescents.

Consistent with the known pharmacology of paliperidone, there were increases in prolactin levels in the paliperidone ER treatment groups. The incidence of potentially prolactin-related TEAEs was low (9.3% overall). Data on growth and maturation in this study indicate that there were no clinically significant changes in weight, height or body mass index (BMI) when adjusted for sex- and age-specific normative values. The growth observed in this study was generally similar to that expected for normal adolescent maturation. Extrapyramidal symptom-related Aes occurred at mildly higher rates in adolescents than adults, with the most frequent TEAEs in the group terms of parkinsonism and 16yperkinesias. The incidence of other psychiatric-related TEAEs (worsening of psychosis, depressed mood, agitation, and aggression) was relatively low for a severe mental illness in adolescents. No clinically meaningful changes in the vital sign values or ECG parameters were observed.

Data from the secondary efficacy end points demonstrate that paliperidone ER maintains symptom stability over the 2-year treatment period and support the efficacy of paliperidone ER in the maintenance treatment of schizophrenia in adolescents 12 to 17 years of age.