

Janssen Research & Development

Clinical Study Report Synopsis Protocol R076477-PSZ-3003; Phase 3

R076477 (paliperidone)

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SYNOPSIS**Issue Date:** 21 November 2012

<u>Name of Sponsor/Company</u>	Janssen Research & Development, LLC
<u>Name of Finished Product</u>	INVEGA®
<u>Name of Active Ingredient(s)</u>	R076477 (paliperidone)

Protocol No.: R076477-PSZ-3003**Title of Study:** A Randomized, Multicenter, Double-Blind, Active-Controlled, Flexible-Dose, Parallel-Group Study of the Efficacy and Safety of Extended Release Paliperidone for the Treatment of Symptoms of Schizophrenia in Adolescent Subjects, 12 to 17 Years of Age**EudraCT Number:** 2009-014811-11**NCT No.:** NCT01009047**Clinical Registry No.:** CR016675**Principal Investigator(s):** Dr [REDACTED], MD, PhD - [REDACTED], Russia.**Study Center(s):** India (6 sites), Romania (1 Site), Russian Federation (16 sites), Slovakia (1 site), Spain (3 sites), Ukraine (8 sites), and United States (6 sites).**Publication (Reference):** None**Study Period:** Study initiation date: 19 November 2009, Study end date: 11 June 2012, Database Lock date: 10 July 2012**Phase of Development:** 3**Objectives:** The primary objective of the study was to evaluate the efficacy of paliperidone extended release relative to aripiprazole in the treatment of symptoms of schizophrenia in adolescent subjects from 12 to 17 years of age, inclusive, (ie, 12 to less than 18 years of age) at the Week 8 (Day 56) end point as measured by the change from baseline in the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) total score.

The secondary objectives were to: 1) Evaluate the maintenance of clinical stability of paliperidone extended release (ER) compared with aripiprazole at the Week 26 (Day 182; as previously measured from Week 8 [Day 56]) end point based on a 20% improvement from baseline in the PANSS total score and Clinical Global Impression Severity (CGI-S) ≤ 4 , emergence of clinically significant suicidal or homicidal ideation, and the need for hospitalization due to psychiatric illness. 2) Compare the efficacy of paliperidone relative to aripiprazole in change from baseline in negative symptoms as measured by the PANSS negative symptom factor score (based on Marder factor) to the Week 8 (Day 56) and Week 26 (Day 182) end points. 3) Assess the change in the PANSS total score of paliperidone ER compared with aripiprazole from baseline to Week 26 (Day 182) end point. 4) Assess the change in the global impression of severity of illness associated with the use of paliperidone ER compared with aripiprazole as measured by the CGI-S scale at the Week 8 (Day 56) and Week 26 (Day 182) end points. 5) Assess the change associated with the use of paliperidone ER compared with aripiprazole in social functioning as measured by the personal and social performance scale (PSP) at the Week 8 (Day 56) and Week 26 (Day 182) end points. 6) Overall safety was assessed.

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

Methodology: This was a randomized, double blind, active controlled, parallel group, flexible dose, multicenter study designed to determine the efficacy and safety of paliperidone ER in adolescents from 12 to 17 years of age, inclusive, who had a Diagnostic and Statistical Manual of Mental Disorders; 4th Edition (DSM-IV) diagnosis of acute schizophrenia. The study consisted of three phases: an up to 3 weeks screening phase (with a possible overlapping washout period), an 8 Week double-blind acute phase, and an 18 Week double-blind maintenance phase. All subjects active at the end of the 8-week acute phase continued to the 18-week maintenance phase; there was no minimal response needed to continue. The total duration of the study was approximately 29 weeks. Subjects were randomly assigned to 1 of 2 treatment groups (flexible oral doses of paliperidone ER or aripiprazole). Screening and washout were conducted while a subject was an inpatient or an outpatient. Subjects were not supposed to be a danger to themselves or others, and must have had sufficient family support available to be maintained as outpatients after discharge from the hospital.

Number of Subjects (planned and analyzed): Planned: Approximately 228 subjects, 114 subjects in each treatment group, were planned to be enrolled in the study.

Analyzed: A total of 228 subjects were randomized; 227 subjects received at least 1 dose of double-blind study medication (safety analysis set), and 226 subjects received at least 1 dose of double-blind study drug and had both a baseline and at least 1 postbaseline efficacy measurements in the double-blind phase (intent-to-treat [ITT] set).

Diagnosis and Main Criteria for Inclusion:

Males and females, 12 to 17 years of age, inclusive, who met the DSM-IV criteria of schizophrenia (295.10, 295.20, 295.30, 295.60, 295.90). Subjects with acute schizophrenia (PANSS total score of 60 to 120 points) and whose physician believed that the subject was not receiving optimal clinical benefit or the subject was experiencing a problem with safety or tolerability with his/her ongoing antipsychotic medications were enrolled if they met all entry (inclusion) and none of the exclusion criteria.

Test Product, Dose and Mode of Administration, Batch No.: Paliperidone ER, 3 mg and 6 mg capsules. Paliperidone ER was administered at a fixed dose of 6 mg/day during the first week followed by flexible dosing (3, 6, or 9 mg/day) thereafter. (Batch numbers: 3 mg capsules - 11B16/F066, 09E19/F066, 10A18/F066; 6 mg capsules - 09E20/F067, 10A19/F067, 11B17/F067).

Reference Therapy, Dose and Mode of Administration, Batch No.: Aripiprazole 2 mg, 5 mg, and 10 mg capsules. Aripiprazole was titrated from 2 mg/day to 10 mg/day during the first week, followed by flexible dosing (5, 10, or 15 mg/day) thereafter. (Batch numbers: 2 mg capsules - 09L01/G005, 11E23/G005, 09G13/G005, 11C14/G005; 5 mg capsules - 09L01/G008, 11C16/G008, 09G16/G008, 11E23/G008, 11E23/G006, 09G14/G006, 10C15/G006, 11C15/G006; 10 mg capsules - 09L02/G009, 09G17/G009, 11C18/G009, 11E24/G009, 11E24/G007, 09G15/G007, 10C16/G007, 11C17/G007).

Duration of Treatment: The total duration of the study including screening and washout period was approximately 29 weeks.

Criteria for Evaluation:

Efficacy Evaluations: The primary efficacy end point was the change in the PANSS total score from baseline to the Week 8 (Day 56; last observation carried forward [LOCF]) end point.

The secondary efficacy end points were: (1) proportion of subjects maintaining clinical stability at Week 26 (as measured from Week 8 [Day 56]), (2) change from baseline in the PANSS negative symptom factor score (based on Marder factor) at Week 8 (Day 56) and Week 26 (Day 182), (3) change from baseline in the PANSS total score at Week 26, (4) change from baseline in CGI-S score at Week 8 (Day 56) and Week 26 (Day 182), and 5) change from baseline in PSP score at

Week 8 (Day 56) and Week 26 (Day 182). The last post randomization assessment (LOCF) was to be used for all secondary efficacy end points.

Pharmacokinetic Evaluations: A total of 3 blood samples were scheduled to be collected: 2 samples at Visit 4 (1 sample predose and 1 sample at least 2 hours after drug administration) and 1 sample at Visit 6 (at least 2 hours after drug administration). Plasma paliperidone concentrations were analyzed using the population PK model developed before. Data will be reported in a separate report. PK samples obtained from subjects randomized to the aripiprazole treatment group were not analyzed.

Pharmacogenomic Evaluations: A pharmacogenomic blood sample (up to 10 mL) was collected at Visit 2 from subjects who gave separate written informed consent for this part of the study (where local regulations permit). Participation in pharmacogenomic research was optional.

Safety Evaluations: The safety assessments included laboratory measurements (eg, chemistry, hematology, urinalysis, lipid panel, and insulin related tests), body weight, waist circumference, electrocardiograms (ECGs), and physical examination. The Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and Simpson Angus Rating Scale (SARS) were used to assess extrapyramidal symptoms (EPS) and dyskinesia. The Columbia Suicide Severity Rating Scale (C-SSRS) was administered to assess suicidality. Adverse events and vital signs were monitored.

Statistical Methods: The sample size calculation assumed that the standard deviation (SD) of the change from baseline to end point in PANSS total score would be 20 points, which was based on the aripiprazole pediatric studies in schizophrenia. If there were approximately 100 subjects per treatment group who had Week 8 (Day 56; LOCF/end point acute) PANSS total score, the study was expected to have at least 80% power to detect a clinically relevant difference of 8 points between paliperidone ER and aripiprazole in the change from baseline in PANSS total score (with a two sided level of 0.05). With an estimate of approximately 12% of randomized subjects who discontinued before providing post-baseline total PANSS measurements, the number of randomized subjects was adjusted to 114 in each treatment group. Therefore, a total of approximately 228 subjects were to be randomly assigned in this study. This sample size was also adequate to detect a difference of 2.5 points in the change from baseline to end point (8 week LOCF) in negative symptom factor score between paliperidone ER and aripiprazole with approximately 83% power [when a SD=6 was assumed].

Efficacy analyses were conducted using the ITT analysis set. The change from baseline in PANSS total score 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. Treatment effect was estimated based on the difference of the treatment group least-squares (LS) means with a 95% confidence interval.

The proportion of subjects maintaining clinical stability at Week 26 (Day 182; as measured from Week 8 [Day 56]) was analyzed using the Cochran-Mantel-Haenszel test, controlling for country.

The CGI-S score was analyzed using an ANCOVA model on the ranks of the change from baseline to Week 8 (Day 56) and Week 26 (Day 182) end points, with treatment group and country as fixed factors and baseline score as a covariate. Change from baseline to Week 8 (Day 56) and Week 26 (Day 182) end points for the other efficacy variables (PANSS Marder negative factor scores and other factors, PANSS subscales, and PSP scores) were analyzed using an ANCOVA model with treatment group and country as fixed factors and baseline scores as a covariate.

The proportion of symptom responders, defined as those subjects who showed a 20% or more reduction from baseline in PANSS total score at the end of Week 8 (Day 56) and Week 26 (Day 182), was analyzed using the Cochran-Mantel-Haenszel test, controlling for country.

Changes in PANSS total score were also summarized according to the following subgroups: age (12 to 14 years and 15 to 17 years), body weight (<51 kg and ≥51 kg), geographic region, EU versus

non-EU, duration of schizophrenic illness (<3 years and ≥3 years), and number of prior antipsychotic medications (<3 and ≥3).

No formal statistical analyses were conducted for the safety parameters. Descriptive summaries were provided using the safety analysis set.

RESULTS:

STUDY POPULATION:

A total of 228 subjects were included in the all randomized analysis set; 113 subjects in paliperidone ER treatment group and 115 subjects in aripiprazole treatment group. A total of 227 subjects were included in the safety analysis set and 226 evaluable subjects were evaluable in the ITT analysis set (112 subjects with paliperidone ER and 114 subjects with aripiprazole).

One hundred and seventy four subjects (76%) completed the study; 85 subjects (75%) in the paliperidone ER group and 89 subjects (77%) in the aripiprazole group. The most common reason for subject withdrawal was withdrawal of consent (14% of subjects in the paliperidone ER group and 10% of subjects in the aripiprazole group) followed by lack of efficacy (4% of subjects in the paliperidone group and 10% of subjects in the aripiprazole group). Overall 2% of subjects discontinued the study due to an adverse event (4% in the paliperidone ER group and none in the aripiprazole group).

A majority of the subjects were male (66%), White (76%), and between 15 to 17 years of age (72%). The mean age of the subjects was 15.3 years. A majority of the subjects had a diagnosis of paranoid schizophrenia (70%), had moderate (61%) or marked (32%) severity of illness based on the CGI-S score, and had never been hospitalized (39%) or hospitalized only once (33%).

A majority of the subjects in each treatment group remained in the study for ≥180 days (66% of subjects in the paliperidone ER group and 70% in the aripiprazole group). The median mode dose and median final dose was 6 mg in the paliperidone ER group and 15 mg in the aripiprazole group. The percentages of subjects with any protocol deviation were similar in the 2 treatment groups.

EFFICACY RESULTS:

Primary End Point:

Based on the ITT LOCF analysis of the primary efficacy variable (change in PANSS total score from baseline to end point acute [Day 56]), a clinically meaningful improvement was observed in both treatment groups. The mean (SD) change from baseline to end point acute (Day 56; LOCF) in PANSS total score was -19.3 (13.80) in the paliperidone ER group and -19.8 (14.56) in the aripiprazole group. There was no statistically significant difference between the two treatment groups ($p=0.935$).

The longitudinal analysis performed on the observed-case data (mixed models repeated measures) and the worst-rank analysis corroborated the findings from the LOCF analysis.

Secondary End Points:

Based on the ITT LOCF analysis of the change from baseline in PANSS total score at end point (Day 182), improvement was seen in both treatment groups. The mean (SD) change from baseline to end point (Day 182; LOCF) in PANSS total score was -25.6 (16.88) in the paliperidone ER group and -26.8 (18.82) in the aripiprazole group. There was no statistically significant difference between the 2 treatment groups at the Day 182 end point ($p=0.877$).

The percentage of subjects maintaining clinical stability at Day 56 and Day 182 was 51.8% in the paliperidone ER group and 59.6% in the aripiprazole group. The difference between the treatment groups was not statistically significant ($p=0.296$).

No statistically significant differences between paliperidone ER and aripiprazole were observed for any of the other secondary efficacy variables. The mean changes from baseline to end point acute (Day 56) and end point (Day 182) in CGI-S score, PSP score, PANSS Marder negative factor score, other PANSS Marder factors scores, and PANSS subscale scores were similar for the paliperidone ER and aripiprazole treatment groups and indicated improvement for all parameters in both treatment groups. The proportion of subjects achieving a PANSS response (ie, at least a 20% reduction in PANSS total score from baseline) was also similar for the paliperidone ER and aripiprazole treatment groups at the end point acute (Day 56, 67.9% and 76.3%, respectively; p=0.119) and at end point (Day 182, 76.8% and 81.6%; respectively; p=0.444).

Overall, the mean changes in the primary and key secondary variables (see table below) showed that the improvements observed during acute treatment phase were maintained or showed additional improvement during the maintenance period,

Mean (SD) Change^a from Baseline to End Point Acute (Day 56) and End Point (Day 182) in the Primary and Key Secondary Efficacy Variables

	End point	Paliperidone ER (N=112)	Aripiprazole (N=114)	Between-group difference
PANSS total score	Day 56 ^b	-19.3 (13.80)	-19.8 (14.56)	p=0.935
	Day 182	-25.6 (16.88)	-26.8 (18.82)	p=0.877
PANSS Marder Negative factor score	Day 56	-4.3 (4.56)	-4.7 (4.61)	p=0.341
	Day 182	-6.0 (5.51)	-6.2 (5.84)	p=0.723
CGI-S score	Day 56	-1.0 (-4; 0)	-1.0 (-3; 1)	p=0.843
	Day 182	-1.0 (-4; 1)	-1.0 (-4; 1)	p=0.914
PSP score	Day 56	12.2 (11.72)	12.2 (10.17)	p=0.895
	Day 182	17.1 (14.46)	17.1 (14.03)	p=0.705

^a. Except for CGI-S, which is presented as median (range).

^b. Primary end point.

Subgroup analyses of the primary efficacy variable showed the changes in PANSS total score from baseline to end point acute (Day 56) were similar between the paliperidone ER and aripiprazole treatment groups regardless of age group, weight category, region, number of previous antipsychotic medications, and duration of schizophrenic illness, except in the 12 to 14-year age group (between-group difference is >2 points).

PHARMACOKINETIC RESULTS:

The plasma paliperidone ER concentrations were subject to a population PK analysis, the result of which is reported in a separate report. In summary, the PK data from PSZ-3003 confirmed the POP-PK model for adolescents previously generated.

SAFETY RESULTS:

A total of 227 subjects (113 subjects in the paliperidone ER group and 114 subjects in the aripiprazole group) received at least 1 dose of double-blind study medication and were included in the safety analysis set. No deaths were reported in the study. Overall, a higher percentage of subjects in the paliperidone ER group than those in the aripiprazole group experienced TEAEs (77.0% vs 66.7%) and possibly-related TEAEs (61.9% vs 46.5%). Treatment-emergent adverse events leading to study drug withdrawal occurred only in the paliperidone ER group in 5 subjects (4.4%). The TEAEs in the SOC of nervous system disorders occurred in higher percentages of subjects in the paliperidone ER group than the aripiprazole group (48.7% versus 36.0%). Treatment-emergent SAEs occurred in 7 subjects in both groups. Treatment-emergent AEs occurring more frequently in the paliperidone ER group compared to the aripiprazole group (by ≥4%) were headache, vomiting, weight gain, and asthenia. The only TEAE occurring more frequently in the aripiprazole group (by ≥4%) was schizophrenia.

In both treatment groups, the most commonly occurring EPS-related events were those grouped under hyperkinesia, parkinsonism, and tremor. The median change in the AIMS total score and SAS global score was 0 in both treatment groups; and the percentage of subjects with scores of 0 (absent) remained relatively stable from baseline to end point (Day 182) in both treatment groups. Suicidality-related events occurred only in the paliperidone ER treatment group. The events were suicidal ideation in 2 subjects (1.8%) and suicide attempt in 2 subjects (1.8%). The percentage of subjects with glucose-related TEAEs was higher in paliperidone ER group (3.5%) compared to aripiprazole group (0.9%). There was no reported TEAE of neuroleptic malignant syndrome (NMS) in the study. The incidences of TEAEs related to aggression/agitation, somnolence and tachycardia were similar in the 2 treatment groups. Overall, there was a low incidence of potentially prolactin related AEs in the paliperidone ER group, despite the known propensity of paliperidone ER to increase serum prolactin levels. The proportion of subjects with TEAEs related to worsening of psychosis was greater in the aripiprazole group (12.3%) than in the paliperidone ER group (4.4%), while the TEAEs related to and depressed mood was higher in the paliperidone ER group than in the aripiprazole group. Only 1 subject in paliperidone ER group had a TEAE of orthostatic hypotension. For ECG parameters, there were no clinically relevant mean or median changes in heart rate, PR interval, QRS interval, QT interval, RR interval, QTcB, QTcF, QTlc, or QTcLD.

Overall, no new safety signals for paliperidone ER were detected.

STUDY LIMITATIONS:

The study design incorporated an active control, and hence a limitation of the study was a lack of placebo control. In addition, the study was also not powered to demonstrate efficacy for specific subgroups of subjects, such as those of a certain weight, age, or from a particular region.

CONCLUSION(S):

- The study did not meet its primary objective of demonstrating superiority of paliperidone ER over aripiprazole in the acute treatment of adolescent schizophrenia as measured by a change in PANSS total score from baseline to end point acute (Day 56).
- Treatment of adolescents with schizophrenia (age 12 to 17 years, inclusive) with paliperidone ER or aripiprazole led to robust and clinically relevant improvement in PANSS total score at both Week 8 (Day 56) and Week 26 (Day 182) end points. No significant difference in any of the efficacy parameters (primary or secondary) was observed between paliperidone ER and aripiprazole groups indicating that paliperidone ER and aripiprazole had similar treatment effects. Both treatment groups had high study completion rates.
- No new safety findings 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.