# SYNOPSIS

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

* Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Infectious Diseases BVBA; Janssen R&D Ireland; or Janssen Research & Development, LLC. The term "sponsor" is used to represent these various legal entities as identified on the Sponsor List.

**Status:** Approved

**Date:** 12 September 2013

**Prepared by:** Janssen Research & Development, LLC

**Protocol No.:** R076477-SCH-3041

**Title of Study:** Paliperidone Extended Release Tablets for the Prevention of Relapse in Subjects With Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study: Open-Label Extension

**NCT No.:** NCT01662310

**Clinical Registry No.:** CR100427, R076477-SCH-3041

**Coordinating Investigator(s):** [redacted], MD, [redacted], China.

**Study Center(s):** This study was conducted across 18 sites in China.

**Publication (Reference):** 2

Rui Q, Shu L, Liu Y, Wu Y, Wu Q, Nuamah I, Wang Y, Gopal S. Efficacy and Safety of Paliperidone Extended Release in Chinese Patients with Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled Study. Special Congress on Addiction and Mental Health, CINP, Kuala Lumpur Regional Meeting: 2-4 Oct 2013.

Shu L, Zhang H, Wang Y, Rui Q. A Randomized, Double-blind, Placebo-controlled Study on Paliperidone ER Treating Schizophrenia Preventing Relapse. A Chinese publication on Chinese Medical Journal. 2011; 124 Supplement 2.

**Study Period:** 03 June 2011 to 26 April 2013

**Phase of Development: 3**

**Objectives:**

The primary objective of the open-label extension phase of the study was the assessment of the long-term safety and tolerability of paliperidone extended release (ER) 3 to 12 mg/day in subjects diagnosed with schizophrenia. In addition, the long-term efficacy and effect of paliperidone ER on overall symptom improvement, global severity of the illness, and personal and social functioning, were explored.

**Methodology:** Study R076477-SCH-3041 was a randomized, double-blind, placebo controlled, parallel group study to evaluate the efficacy of paliperidone ER compared to placebo in delaying the time to relapse of schizophrenia in Chinese subjects. Study R076477-SCH-3041 design consisted of 5 phases: screening phase of up to 14 days, an 8-week open-label run-in (RI) phase, a 6-week open-label stabilization (ST) phase, a double-blind (DB) phase of variable duration, and a 6-month open-label extension (OLE) phase. Data from the first 4 phases of Study R076477-SCH-3041 were reported previously in a separate study report. Only the data collected from subjects who participated in the 6-month open-label extension phase are included in this study report. However, because certain data collected during the course of Study R076477-SCH-3041 are included in this report, a brief description of the prior phases is provided below:

**Screening phase:** Subjects were evaluated for study eligibility based on prospectively defined inclusion and exclusion criteria during a screening phase of up to 14 days in which their current antipsychotic treatment and any disallowed prestudy medications were discontinued and washed out. Any medication(s) that could not be stopped abruptly were tapered down and washed out. The washout period was shortened to allow a subject to enter the run-in phase as soon as the day after the start of the washout period (with the approval of the sponsor) if the investigator determined that the subject's symptoms were much worse than that prior to the washout. Subjects were admitted to the hospital at any time during screening at the discretion of the investigator. Subjects who met all entry criteria were enrolled in the run-in phase.

**Run-in phase:** During the 8-week run-in phase, eligible subjects were treated with open-label, flexibly-dosed paliperidone ER, administered once daily in a dose range of 3 mg to 12 mg to identify a dose that achieved control of the subjects' acute schizophrenic symptoms. Treatment was initiated with a dose of 6 mg once daily, with increases of 3 mg/day permitted after 5 days and decreases as rapidly as deemed necessary by the investigator for subject safety. The subjects were recommended to be hospitalized for 8 days from the start of this phase. To enter the stabilization phase, subjects had to meet all the following criteria: Positive and Negative Syndrome Scale (PANSS) total score <70; PANSS item P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), P6 (suspiciousness/persecution), P7 (hostility) and G8 (uncooperativeness) scores ≤4; and no change in paliperidone ER dosage in the last week of the run-in phase.

**Stabilization phase:** During the 6-week stabilization phase, subjects continued to receive the fixed dose of paliperidone ER established at the end of the run-in phase. Evaluation visits occurred every 2 weeks. Subjects who maintained a stable dose regimen (dose unchanged) during this phase and met predefined criteria were randomly assigned to the double-blind phase of the study. The predefined criteria to randomize subjects in double-blind phase included: no changes in dose during the entire stabilization phase; no deliberate self-injury or violent behavior resulting in clinically significant injury to the subject, another person, or property damage; no psychiatric hospitalization (involuntary or voluntary admission to a psychiatric hospital for decompensation of the subject's schizophrenic symptoms); PANSS total score <70; and PANSS item P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), P6 (suspiciousness/persecution), P7 (hostility) and G8 (uncooperativeness) score ≤4.

**Double-blind phase:** Subjects who completed the run-in and stabilization phases of the study and met prospectively defined criteria, were randomly assigned in a 1:1 ratio to receive either paliperidone ER or placebo. Subjects were treated until they met either prospectively defined criteria for relapse or predefined study conclusion criteria. Relapse was defined as any one of the following: psychiatric hospitalization (involuntary or voluntary admission); deliberate self-injury or violent behavior resulting in clinically significant injury to the subject, another person, or property damage; suicidal or homicidal ideation; and aggressive behavior that was clinically significant (in frequency and severity) in the investigator's judgment; increase of 25% in the total PANSS score from randomization, if the score at randomization was >40, or a 10-point increase in the total PANSS score from randomization, if the score at randomization was ≤40; for PANSS items P1 (delusions), P2 (conceptual disorganization),

P3 (hallucinatory behavior), P6 (suspiciousness/persecution), P7 (hostility) or G8 (uncooperativeness), a score ≥5 after randomization on any of the above PANSS items if the maximum score for the above PANSS items was ≤3 at randomization, or a score ≥6 after randomization on any of the above PANSS items if the maximum score for the above PANSS items was 4 at randomization. The double-blind phase (of variable duration) was to be completed after 86 relapse events were observed or if the study was positive at the interim analysis. If the result of the interim analysis was statistically significant, the main part of the study (the run-in, stabilization and double-blind phases) was to be terminated and paliperidone ER was declared superior to placebo in delaying time to relapse. Otherwise, the study was continued until a total of 86 relapse events were obtained, at which time a final analysis was to be performed.

The double-blind phase was terminated and enrollment ceased when the results of the interim analysis (when 61 relapse events had been obtained) determined paliperidone ER to be superior to placebo in delaying relapse. Subjects who were in the run-in or stabilization phase at that time were to enter the open-label extension phase; however, no such subjects entered the open-label extension phase since all enrolled subjects had either been randomized to the double-blind phase or had withdrawn during the run-in and stabilization phases.

**Open-label Extension phase:** Subjects were treated with flexibly-dosed paliperidone ER ranging from 3 to 12 mg/day during the open-label extension phase. For subjects who experienced a relapse and subjects who remained relapse free in the double-blind phase when the main part (ie, run-in, stabilization, and double-blind phases) of the study was terminated, a starting dose of 6 mg was given. The dose could be adjusted up or down in 3 mg increments as judged by investigators. Subjects, who were still in the run-in or stabilization phase when the main-part of the study was terminated, were to continue with the same dose as at the study termination, and dose adjustments between 3 to 12 mg/day were permitted. Study visits occurred weekly for the first 4 weeks and every 4 weeks thereafter until Week 24. A subject was considered to have completed the open-label treatment phase of the study if he or she completed all 24 weeks of the open-label extension phase and had assessments at Week 24. Subjects who withdrew early from the open-label extension phase had the end-of-extension (EOEx)/early withdrawal visit procedures performed.

**Number of Subjects (planned and analyzed):** Planned: Approximately 360 subjects were planned to be enrolled in the run-in phase of Study R076477-SCH-3041 and continue throughout subsequent phases per protocol or withdraw early appropriately from a particular phase.

Analyzed: A total of 106 subjects were enrolled in the open-label extension phase of Study R076477-SCH-3041, including 59 subjects who received placebo (Pla/Pali) and 47 subjects who received fixed-dose paliperidone ER 3 to 12 mg/day (Pali/Pali) in the double-blind phase of the study. Prior to the open-label extension phase, of the 201 subjects enrolled in the run-in phase, 161 (80%) subjects entered the stabilization phase, and 136 (68%) subjects were randomized (1:1) to paliperidone ER (3-12mg, n=65) or placebo (n=71) during the double-blind phase.

**Diagnosis and Main Criteria for Inclusion:** Men and women 18 years of age and older and met the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV-TR) criteria for schizophrenia and experienced an acute episode (PANSS score between 70 and 120, inclusive) were eligible for enrollment in Study R076477-SCH-3041. There were no specific inclusion criteria for the open label extension phase. Subjects who experienced a relapse, who remained relapse-free in the double-blind phase, and subjects who were in the run-in/stabilization phases when the main part (ie, run-in, stabilization, double-blind phases) of the study was terminated were eligible to enter the 6-month, open-label extension phase of Study R076477-SCH 3041.

**Test Product, Dose and Mode of Administration, Batch No.:** The oral flexible dosage of paliperidone ER ranged between 3 mg and 12 mg once a day (3, 6, 9, or 12 mg per day). Paliperidone ER was administered at a starting dose of 6 mg for subjects who entered the open-label extension phase from the double-blind phase or the same as the last dose in the previous phase if the subjects entered the open-label extension phase from either the run-in or stabilization phase. The dose could be increased by 3 mg/day up to the maximum (12 mg/day) and decreased as deemed necessary by the investigator for the subject's safety.

Batch/formulation numbers for 3 mg tablets: 9KD1190/F066 (expiry date: July 2012) and OMD2611-X/F039 (expiry date: November 2013). Batch/formulation numbers for 6 mg tablets: 9JD1089/F067 (expiry date: July 2012) and OMD2605-X/F040 (expiry date: November 2013).

**Reference Therapy, Dose and Mode of Administration, Batch No.:** No reference therapy was used in the open-label extension phase of the study.

**Duration of Treatment:** Study medication was administered for 6 months during the open-label extension phase of the study.

**Criteria for Evaluation:**

Efficacy: The changes from OLE baseline to OLE endpoint in PANSS total score, Clinical Global Impression Scale-Severity (CGI-S) scale, and Personal and Social Performance (PSP) scale were evaluated.

Pharmacokinetic: Pharmacokinetic analyses were not conducted in the open-label extension phase of the study.

Pharmacogenomic: Pharmacogenomic analyses were not conducted in the open-label extension phase of the study.

Safety: Safety evaluations in the OLE phase included adverse event (AE) monitoring, clinical laboratory evaluations (hematology, serum chemistry, urinalysis, and serum and urine pregnancy tests [for females of child bearing potential]), vital sign measurements, physical examinations, and 12-lead electrocardiograms (ECGs). Serum concentrations of prolactin were also determined. The Columbia Suicide Severity Rating Scale (C-SSRS) was administered to monitor suicidal ideation and behavior.

**Statistical Methods:**

The intent-to-treat (ITT) (OLE) analysis set, denoted as 'ITT (OLE)', included all subjects who received at least one dose of open-label extension medication as recorded on the electronic case report form (eCRF). The ITT (OLE) analysis set was used for efficacy and safety analysis in the open-label extension phase.

The analysis of data in the open-label extension phase was presented by the total group. In addition, subjects were placed in groups according to the treatment they received prior to entering the open-label extension phase, if any. The 3 treatment groups were:

- Pali (paliperidone ER) (no DB)/Pali (this group of subjects refers to the subjects who were not randomized during the double-blind phase but entered the open-label extension phase directly from run-in/stabilization phases)
- Pla (placebo)/Pali (this group of subjects refers to the subjects who were randomized to the placebo during the double-blind phase and subsequently entered the open-label extension phase)

- Pali/Pali (this group of subjects refers to the subjects who were randomized to the Pali during the double-blind phase and subsequently entered the open-label extension phase).

No subjects entered the open-label extension phase directly from run-in/stabilization phases without being randomized to the double-blind phase of the study.

Efficacy Analyses:

**Positive and Negative Syndrome Scale for Schizophrenia**

For each assessment time point for both observed case and last observation carried forward (LOCF), descriptive statistics including N, mean, and standard deviation (SD) were produced on the score and change from OLE baseline to OLE end point. Descriptive summaries for the change from OLE baseline over time were presented.

**Clinical Global Impression – Severity**

The change in the CGI-S from OLE baseline was calculated. At each assessment time point and end point, frequency counts of scores (and LOCF values) by severity label were produced. Descriptive statistics of the raw and change from OLE baseline scores were presented.

**Personal and Social Performance Scale**

The change in PSP score from OLE baseline to OLE end point was also summarized. Descriptive summaries for the change from OLE baseline over time were presented.

Safety Analyses:

Safety and tolerability profile during the open-label extension phase was summarized using descriptive statistics. A treatment-emergent flag was created to identify the AEs that occurred in the open-label extension phase. Serious adverse events (SAEs) and AEs that lead to study discontinuation were summarized separately by treatment group, system organ class (SOC) and preferred term. Data listings were generated for deaths, SAEs, AEs with outcome of death, and discontinuations due to AEs. Treatment-emergent adverse events (TEAEs) that were related to EPS and potentially prolactin-related were summarized by treatment group as AEs of clinical interest. Potentially suicide-related AEs were categorized by the investigator using the C-SSRS.

Descriptive statistics (mean [SD], median [range]) were provided for the clinical laboratory tests at each on-study determination and endpoint in the OLE phase. Continuous variables such as orthostatic changes in vital sign measures, heart rate (HR), blood pressure, and change from OLE baseline were calculated for each position, at each assessment time point and at endpoint during the OLE phase. Descriptive statistics such as mean (SD) and median (range) were presented at each assessment point and at endpoint during the OLE phase.

The change from run-in baseline (ie, average pre-dose) for various ECG parameters was calculated for each subject at each time point and endpoint. The frequency of treatment-emergent abnormalities were tabulated and presented by treatment group.

**RESULTS:**

STUDY POPULATION:

Of the 201 subjects who were enrolled into the run-in phase of Study R076477-SCH-3041, 106 subjects entered the open-label extension phase. These included 59 subjects who received placebo (Pla/Pali group) and 47 subjects who received paliperidone ER 3, 6, 9, or 12 mg/day (Pali/Pali group) in the double-blind

phase of the study. No subjects entered the open-label extension phase directly from either the run-in or stabilization phase without being randomized to the double-blind phase of the study. Therefore, no subjects were included in the Pali (no DB)/Pali group and consequently this treatment group is not presented in the tables from the data analysis. A majority of subjects were females (59%), with a mean (SD) age of 30.7 (10.49) years at run-in enrollment. At OLE baseline, based on the BMI, 62% of the subjects were classified as having normal body weight. The mean (SD) OLE baseline body weight was 65.8 (15.00) and the mean (SD) OLE baseline BMI was 24.45 (4.262). Based on CGI-S score, subjects' psychotic condition at OLE baseline consisted of 'not ill' (1%), 'very mild' (15%), 'mild' (31%), 'moderate' (36%), 'marked' (12%) or 'severe' (5%) scores. The mean (SD) PANSS total score, CGI-S score, and PSP score at open-label extension baseline was 62.4 (15.58), 3.6 (1.07), and 63.4 (15.81), respectively, in the total group.

Of the 106 OLE enrolled subjects, 85 subjects (80%) completed the 6-month open-label extension phase and 21 subjects (20%) discontinued the study prematurely. The most frequent reason for discontinuation was withdrawal of consent (8%). Three subjects (3%) discontinued during the open-label extension phase due to AEs, which had onset dates prior to the start of the open-label extension phase.

EFFICACY RESULTS:

Substantial improvements in symptom control were observed from the open-label extension baseline to open-label extension end point based on the mean change in PANSS total score (mean change [SD], -10.4 [13.20]) in the total group. A decrease (ie, improvement) in the global severity of clinical impairment (median change in CGI-S rating, -1.0 point) was observed in the Pla/Pali group, whereas CGI-S score was maintained in the Pali/Pali group (0.0 point). An increase (ie, improvement) in PSP scores from open-label extension baseline to open-label extension end point was observed in the total group (mean [SD] change 7.4 [13.24]). Improvement was also observed in all PANSS subscale and factor scores.

PHARMACOKINETIC RESULTS:

No PK analyses were performed during the open-label extension phase.

PHARMACOGENOMIC RESULTS:

No genes were genotyped during the open-label extension phase.

SAFETY RESULTS:

Overall, one or more TEAEs were reported for 33% of the subjects during the open-label extension phase. The most frequently reported TEAEs during this phase were akathisia, somnolence, nasopharyngitis, and constipation (each reported in 3.8% of subjects). One subject died in the Pali/Pali group due to the event of completed suicide by jumping from her balcony on the twelfth floor. Treatment-emergent SAEs occurred in 2 subjects (1.9%, one with completed suicide and the other with schizophrenia) in the total group. No AEs with onset dates during the open-label extension phase (treatment-emergent during OLE phase) led to discontinuation. Extrapyramidal symptom-related TEAEs were reported in 8 (7.5%) of the 106 subjects. Based on AE reports, orthostatic changes in vital signs and elevations in serum prolactin were of limited clinical relevance.

For most laboratory analytes, the incidence of treatment-emergent markedly abnormal (TEMA) laboratory findings was low in both treatment groups. Increased prolactin levels were not commonly associated with reported TEAEs. A small percentage of subjects (4%) had an increase in standing pulse rate ≥15 and value ≥100. Also, only 1% of subjects observed the supine pulse rate increase ≥15 and value of ≥100. Similarly, the percentage of subjects who had a decrease in supine pulse rate ≥15 and value ≤50 was low (1%) in the total group. There were no subjects with standing pulse rate increase ≥15 and

value ≤50. A small percentage of subjects (3%) had a decrease in standing SBP ≥20 and value ≤90. Also, only 3% of subjects observed the SBP decrease ≥20 and value ≤90. There were no subjects with standing SBP increase ≥20 and value ≥180, standing DBP decrease ≥15 and value ≤50, standing DBP increase ≥15 and value ≥105, supine DBP decrease ≥15 and value ≤50, and supine DBP increase ≥15 and value ≥105. One subject (0.9%) was reported to have sinus bradycardia and 1 subject (0.9%) was reported with nodal arrhythmia in the total group. The incidence of TEAEs of weight increased, which represents subjects with clinically significant weight gain as assessed by the investigators was low (2 subjects [1.9%]). The incidence of TEAEs of weight decreased and weight loss was also low (2 subjects [1.9%]) in the total group. The incidence of treatment-emergent abnormalities in recorded ECG parameters was low during the open-label extension phase and showed no clinically relevant differences between both groups. A majority of subjects had normal linear-derived QT correction (QTcLD) values during the study. Electrocardiogram abnormal was reported as a TEAE in 1 subject (0.9%) in the total group, which was not an SAE or AE leading to study discontinuation.

STUDY LIMITATIONS: The Study R076477-SCH-3041 was limited to subjects in China; hence, extrapolations to other populations might be difficult. The results shown in this CSR are about the open-label extension phase of the Study R076477-SCH-3041; therefore, all data interpretations are subject to the results from phases prior to it.

CONCLUSION(S):

In this 6-month open-label extension phase of the study, flexibly-dosed paliperidone ER 3 mg to 12 mg/day was safe and well-tolerated in Chinese subjects with schizophrenia. The safety profile was generally consistent with that observed in subjects after short-term use in the double-blind studies and was consistent with the known pharmacologic properties of paliperidone ER. No new or unexpected safety findings related to long-term exposure emerged during the open-label extension phase of the study. Findings using rating instruments to assess long-term effectiveness showed further improvements in the severity of symptoms associated with schizophrenia (PANSS), personal and social functioning (PSP), and global severity of illness (CGI-S) during the open-label extension phase and were consistent with the known profile of paliperidone ER in long-term global studies. Since the main use for paliperidone ER in China will be in the long-term treatment of schizophrenia, these findings are particularly relevant and provide valuable guidance for practicing clinicians.

Overall, the findings from this open-label extension phase of the study provide strong support for the long-term treatment with paliperidone ER in Chinese subjects with schizophrenia.