# SYNOPSIS

**Issue Date:** 14 FEBRUARY 2013

| | |
|---|---|
| Name of Sponsor/Company | Janssen Pharmaceutical K. K. |
| Name of Finished Product | Paliperidone palmitate |
| Name of Active Ingredient(s) | Paliperidone |

**Protocol No.:** PALM-JPN-5

**Title of Study:** A Long-Term, Open-Label Study of Flexibly Dosed Paliperidone Palmitate Long-Acting Intramuscular Injection in Japanese Subjects With Schizophrenia

**NCT No.:** NCT01258920

**Clinical Registry No.:** CR017077

**Coordinating Investigator(s):** Teruhiko Higuchi, MD, PhD - National Center of Neurology and Psychiatry, Tokyo, Japan, Yoshio Hirayasu, MD, PhD - Department of Psychiatry, Graduate School of Medicine, Yokohama City University, Kanagawa, Japan, Koichiro Watanabe, MD, PhD - Department of Neuropsychiatry, School of Medicine, Keio University, Tokyo, Japan

**Study Center(s):** The study was conducted at 33 sites in Japan

**Publication (Reference):** None

**Study Period:** 27 September 2010 to 07 November 2012 Database lock date: 22 November 2012 **Phase of Development:** Phase 3

**Objectives:**

Primary Objective: The primary objective of this study was to evaluate the long-term safety and tolerability of paliperidone palmitate administered intramuscularly (im) as an initial loading dose of 150 mg eq. on treatment Day 1 and 100 mg eq. 1 week later (Day 8) in the deltoid muscle, followed by flexible doses of 25 to 150 mg eq. at 4-week intervals either in the deltoid or gluteal muscle, for a total of 11 injections in Japanese subjects with schizophrenia.

Secondary Objectives: Secondary objectives of this study were to:

- Explore the efficacy of paliperidone palmitate on treatment of symptoms of schizophrenia and the maintenance of treatment effect;
- Explore the pharmacokinetics of paliperidone palmitate through sparse pharmacokinetic sampling.

**Methodology:** This was an open-label, flexible-dose, multicenter study of paliperidone palmitate in Japanese subjects with schizophrenia. Men and women, aged 20 years or older, who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-Text Revision (DSM-IV-TR) criteria for schizophrenia for at least 1 year before screening and had a Positive and Negative Syndrome Scale (PANSS) total score of 60 to 120 were eligible for the study. The study consisted of 3 periods: an up to 2-week preobservation (screening) period, an observation period from Day 1 (baseline) to the Week 49 (end-of-observation-period) assessment, and a postobservation period after the Week 49 (end-ofobservation-period) assessment up to Week 57.

Subjects who were currently taking another antipsychotic and who had demonstrated tolerability in the past to risperidone or paliperidone continued their current antipsychotic until Day -1. There was no washout period.

Subjects without prior demonstrated tolerability to risperidone or paliperidone discontinued their current antipsychotic and started oral tolerability testing during the screening period. Subjects were given oral risperidone 2 mg/day or more or paliperidone Extended Release (ER) 6 mg/day or more for at least 4 days between the day of informed consent and the day before baseline. Only subjects who demonstrated an ability to tolerate the drug, as judged by the investigator, were eligible to enter the study.

Eligible subjects were administered an initial loading dose of paliperidone palmitate 150 mg eq. im on Day 1 and 100 mg eq. 1 week later in the deltoid muscle. The study drug was administered in a flexibledose range of 25 to 150 mg eq. from Week 5 at 4-week intervals for a total of 11 injections in either the deltoid or gluteal muscle. A dose of 75 mg eq. was recommended from Week 5 until Week 45. Based on individual subjects' tolerability and/or efficacy, doses were increased or decreased to 25 mg eq., 50 mg eq., 75 mg eq., 100 mg eq., or 150 mg eq. at the discretion of the investigator. For subjects who discontinued the study before the last assessment in Week 49, the postobservation period started after the discontinuation-from-observation-period assessment, followed by visits at 4, 8, and 12 weeks after the last injection. The total duration of the study was 57 weeks, including the observation and postobservation periods.

Safety was evaluated periodically throughout the study. Samples for pharmacokinetic evaluation were collected and efficacy evaluations were performed at designated time points. An optional 10 mL pharmacogenomic blood sample was collected from subjects who provided a separate written informed consent for this part of the study. Approximately 160 mL of whole blood were collected in this study for pharmacokinetic and clinical laboratory evaluations.



**Number of Subjects (planned and analyzed):** Approximately 200 subjects were planned to be enrolled to ensure 100 subjects received paliperidone palmitate for 1 year. A total of 201 subjects received at least 1 dose of paliperidone palmitate (safety analysis set), and 198 subjects had baseline and at least 1 postbaseline efficacy measurements (full analysis set). Pharmacokinetic analyses were based on 198 subjects who had at least 1 plasma paliperidone concentration after drug administration, which was available for the evaluation of pharmacokinetics (pharmacokinetic analysis set). Of the 201 subjects, 119 subjects completed the observation period and 180 subjects completed the postobservation period.

**Diagnosis and Main Criteria for Inclusion:** Men and women, 20 years of age or older, who met the DSM-IV-TR criteria of schizophrenia for at least 1 year before screening and had a PANSS total score of 60 to 120 at screening and baseline were enrolled in the study. Subjects who had a primary active Axis I disorder other than schizophrenia were excluded.

**Test Product, Dose and Mode of Administration, Batch No.:** Paliperidone palmitate was supplied as a 25 mg eq. (Batch No. 9JB7V/F013, AJB6N/F013), 50 mg eq. (Batch No. 9JB7W/F013, AJB6P/F013), 75 mg eq. (Batch No. 9HB5W/F013, AJB6Q/F013), 100 mg eq. (Batch No. 9HB5K/F013, AJB6R/F013), and 150 mg eq. (Batch No. 9JB7X/F013, AJB6S/F013) injectable suspension. Paliperidone palmitate was administered im as an initial loading dose of 150 mg eq. on treatment Day 1 and 100 mg eq. 1 week later in the deltoid muscle. Thereafter, the study drug was administered in a flexible-dose range of 25 to 150 mg eq. from Week 5 at 4-week intervals for a total of 11 injections in either the deltoid or gluteal muscle.

**Reference Therapy, Dose and Mode of Administration, Batch No.:** Not applicable.

**Duration of Treatment:** The study consisted of 3 periods: an up to 2-week preobservation (screening) period, an observation period from Day 1 (baseline) to the Week 49 (end-of-observation-period)

assessment, and a postobservation period starting after the Week 49 (end-of-observation-period) assessment up to Week 57.

**Criteria for Evaluation:**

Pharmacokinetic Evaluations: Blood samples were collected before each study drug injection at Day 1, Weeks 1, 5, 9, 13, 21, 25, 37, and 45, and at Weeks 47 and 49 or early discontinuation from the observation period to study the paliperidone concentration-time profiles. Plasma paliperidone concentration-time data were to be used for a population pharmacokinetic analysis.

Efficacy Evaluations: All efficacy analyses done for this study were exploratory. The efficacy criteria were the changes in PANSS total score and Clinical Global Impression-Severity (CGI-S) score from Day 1 (baseline) to Week 49 or early discontinuation from the observation period.

Safety Evaluations: Safety was monitored by the evaluation of adverse events (AEs), Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS), clinical laboratory test results, vital sign measurements, electrocardiogram (ECG) parameters, and weight, body mass index (BMI), and waist circumference measurements. The tolerability of injections was assessed by the investigator (who evaluated injection site reactions) and by the subject (who evaluated the pain of the injection) using a Visual Analog Scale (VAS). The Columbia-Suicide Severity Rating Scale (C-SSRS) was administered to monitor suicidality.

**Statistical Methods:** Based on the results of a completed international long-term study, 50% of enrolled subjects were assumed to complete the 1-year study. The targeted number of subjects was 200, so that at least 100 subjects would complete this 1-year study.

Pharmacokinetic Analyses: All enrolled subjects who received at least 1 injection of study drug and had at least 1 plasma paliperidone concentration after drug administration, which was available for the evaluation of pharmacokinetics, were included in the analysis set. Descriptive statistics were calculated for the plasma concentrations of paliperidone at each scheduled time point using the following 2 dose groups:

- Dose at the last administration before each blood sampling (25, 50, 75, 100, 150 mg eq.);
- Doses from Day 1 to Day 64 (150/100/25/25, 150/100/50/50, 150/100/75/75, 150/100/100/100, 150/100/150/150 mg eq.).

For the first dose group above, descriptive statistics were also calculated for the following subgroups:

- By injection site at the last administration before each blood sampling (deltoid, gluteal);
- By baseline BMI (<25 kg/m$^2$, 25 to <30 kg/m$^2$, 30 kg/m$^2$) for plasma concentrations before Day 260;
- By BMI at Day 176 (<25 kg/m$^2$, 25 to <30 kg/m$^2$, 30 kg/m$^2$) for plasma concentrations on or after Day 260.

Actual plasma paliperidone concentrations were graphically displayed for each pharmacokinetic visit, in order to explore dose proportionality and achievement of steady state.

An exploratory population pharmacokinetic analysis is conducted separately.

Efficacy Analyses: The efficacy analyses were based on the full analysis set population, which included all subjects who received at least 1 dose of study injection and had baseline and at least 1 postbaseline

efficacy measurements. The primary parameter was the change in the imputed PANSS total score from baseline to end point; ie, the last postbaseline observation in the observation period.

Descriptive statistics were calculated for the change from baseline (Day 1) to each scheduled visit in PANSS total score, PANSS factor scores, PANSS subscales, and CGI-S. Descriptive statistics were also produced for the primary parameter by subgroup (BMI, final dose of study drug, and mode dose of study drug).

Safety Analyses: All subjects who received at least 1 injection of study drug were included for safety analyses. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 14.1. The number and the percentage of subjects with treatment-emergent adverse events (TEAEs) were calculated. Descriptive statistics were calculated for the change from baseline to each scheduled visit in DIEPSS, clinical laboratory test results, vital sign assessments, ECG parameters, and weight, BMI, and waist circumference measurements. The number and the percentage of subjects with injection site reactions were calculated and the VAS of injection pain was analyzed descriptively. For CSSRS, the number and the percentage of subjects with a suicide-related outcome were summarized.

**RESULTS:**

The results described in this Final Clinical Study Report are based on the final dataset that was produced after completion of the study. An Interim Clinical Study Report was issued separately on 6 August 2012, based on the cutoff dataset that was produced when all subjects enrolled in the study reached the Day 176 (Week 25) assessment or discontinued the study before Day 176 (Week 25).



STUDY POPULATION:

Eligible subjects (N=201) from 33 sites in Japan were enrolled in the study. Among these, 119 (59.2%) subjects completed the observation period, and 180 (89.6%) subjects completed the postobservation period.

Of the 201 enrolled subjects, 198 (98.5%) subjects had baseline and at least 1 postbaseline efficacy measurement and were included in the full analysis set. All enrolled subjects received at least 1 dose of paliperidone palmitate and were included in the safety analysis set.

In the safety analysis set, the number of subjects was balanced between males (51.7%) and females (48.3%). Ages of subjects ranged from 20 to 79 years with a mean (SD) age of 45.5 (12.56) years, and 7.5% of subjects were older than 65 years. The mean (SD) BMI was 24.89 (4.503) kg/m$^2$, and 12.9% of subjects were obese (BMI 30 kg/m$^2$). All subjects had a diagnosis of schizophrenia for at least 1 year according to the DSM-IV-TR criteria. More than half (59.2%) of the subjects were diagnosed with paranoid schizophrenia. In the full analysis set, the subjects' PANSS total score at baseline ranged from 60 to 120 as per the protocol, with a mean (SD) of 81.1 (13.89).

Of the 201 subjects in the safety analysis set, 119 (59.2%) subjects received all 13 doses of study drug. The mean (SD) duration of exposure to paliperidone palmitate was 238.7 (137.66) days, with a range from 4 to 358 days. All paliperidone palmitate doses ranged from 25 to 150 mg eq., and the most frequent dose was 75 mg eq. through the third to 13th injections.

PHARMACOKINETIC RESULTS:

During the first 2 injections of paliperidone palmitate (ie, 150 mg eq. on Day 1 and 100 mg eq. on Day 8), the mean (median) plasma paliperidone concentrations at predose were similar between Day 8 and Day 36 (21.3 [17.1] ng/mL on Day 8 and 23.0 [19.7] ng/mL on Day 36).

For the third injection and thereafter, the mean, median, and individual trough plasma paliperidone concentrations on Day 64 and later and those at the end of the observation period (Day 344) remained fairly constant in the subjects receiving 75 mg eq. The mean (median) plasma concentrations were comparable to those on Day 8 and Day 36.

On Day 148 and thereafter, plasma paliperidone concentrations increased with increasing dose at the last administration before each blood sampling.

On Days 8 and 36, the median plasma paliperidone concentration in subjects with BMI of 30 $kg/m^2$ (obese) was lower compared to that in subjects with BMI of <25 $kg/m^2$ (normal) or 25 to <30 $kg/m^2$ (overweight). However, plasma concentrations obtained from each subject with BMI of 30 $kg/m^2$ were within the range of the plasma concentrations in subjects with BMI of <25 $kg/m^2$ and 25 to <30 $kg/m^2$.

On Day 64 and later, in the subjects administered paliperidone palmitate with 75 mg eq. at the last administration before blood sampling, the distribution range of plasma paliperidone concentrations overlapped between the 2 injection sites (deltoid or gluteal). Therefore, it seemed that the injection site had no significant effect on plasma paliperidone concentrations while approaching to and remaining at the steady state.

EFFICACY RESULTS:

In Japanese subjects who had schizophrenia for at least 1 year before screening and had a PANSS total score of 60 to 120 at baseline, neuropsychiatric symptoms improved with a paliperidone palmitate flexible-dose regimen of 25 to 150 mg eq. in the observation period. Based on the last-observationcarried-forward (LOCF) analysis, the PANSS total score decreased from baseline to end point with a mean (SD) change of -3.6 (16.26). The score decreased until Day 92 and essentially remained stabilized thereafter, indicating that the improvement was maintained throughout the observation period. Based on the observed case analysis without imputation of missing data, the PANSS total score decreased on a continuous basis over time, with a mean (SD) change of -10.7 (12.37) from baseline to Day 344 as the time point of final evaluation.

The result obtained for PANSS total score was supported by PANSS factor scores and subscales and by CGI-S. The scores for 4 of 5 PANSS Marder factors improved slightly from baseline to end point, with mean changes ranging from -1.6 to -0.5. The subjects' overall clinical condition, as evaluated by CGI-S, remained stable without any change in the median CGI-S score.

With respect to the BMI subgroups, the mean (SD) changes in PANSS total score from baseline to end point in subjects with BMI of <25 $kg/m^2$, 25 to <30 $kg/m^2$, and 30 $kg/m^2$ were -3.9 (16.02), -5.4 (14.78), and 2.0 (19.78), respectively.

The neuropsychiatric symptoms of schizophrenia improved or maintained during the observation period in all of the mode dose subgroups.

SAFETY RESULTS:

One subject died due to completed suicide and another subject died from asphyxia. Both events were of doubtful relationship to the study drug, based on the investigator's assessment. During the observation period, 12.9% of subjects experienced serious adverse events (SAEs) and 19.9% of subjects discontinued study treatment due to AEs. Psychiatric symptom, which is likely to occur in association with the underlying schizophrenia, accounted for the majority of the events that were serious or led to study drug discontinuation.

AEs were reported in 91.5% and 28.9% of subjects during the observation and postobservation periods, respectively, and were generally mild or moderate in severity. The most frequently reported ( 5%) events during the observation period were blood prolactin increased, nasopharyngitis, psychiatric symptom, injection site pain, injection site induration, weight increased, insomnia, akathisia, and constipation. The frequency of AEs decreased with time. The type and incidence of AEs were not affected by age and BMI.

Suicidality was reported in a small number of subjects, which was consistent with C-SSRS results indicating that treatment-emergent suicide-related events were infrequent (5.9% for suicidal ideation without serious events).

There were no reports of hypersomnia, lethargy, sedation, or seizures during the observation period. Five subjects reported mild somnolence, and the dose of study drug was reduced for 1 of 5 subjects. One subject experienced 3 episodes of severe convulsion, of which 2 were judged serious. The study drug was withdrawn for this subject after the third episode. Another subject also developed 2 episodes of nonserious convulsion.

Extrapyramidal symptom (EPS)-related AEs were reported in 18.4% of subjects during the observation period. The most frequently reported events were akathisia, tremor, and extrapyramidal disorder. The majority of the events were mild or moderate in severity. None of the EPS-related events was serious, but 3 subjects discontinued study treatment due to EPS-related AEs including akathisia and postural reflex impairment. Antiparkinsonian medications were conditionally allowed according to the protocol, and were taken by about one-third (35.8%) of the subjects. The severity of EPS, evaluated by DIEPSS, remained stable throughout the observation period.



As a cardiovascular system-related AE suggestive of cardiac arrhythmias, 1 subject experienced mild, non-serious electrocardiogram QT prolonged and study treatment was discontinued. The subject also experienced mild supraventricular extrasystoles, but both events were confirmed to have resolved. Besides the above, cardiac arrhythmias (ie, ventricular extrasystoles, bradycardia, arrhythmia, and bundle branch block right) were reported in 5 subjects, and AEs suggestive of orthostatic hypotension (ie, dizziness postural and orthostatic hypotension) were reported in 2 subjects, during the observation period. All of these events were mild or moderate in severity, non-serious, and did not result in study drug discontinuation.

Glucose-related AEs occurred in 2.5% of subjects during the observation period. The events included diabetes mellitus, blood glucose increased, and glucose urine present. All of them were mild, non-serious, and did not result in study drug discontinuation.

Overall, local injection site tolerability was good. Most injection site-related AEs were mild in severity, and assessments by investigators and by subjects indicated that injection pain decreased over time or did not worsen during the observation period.

Increases in serum prolactin level were observed, and the change was generally larger for females than males. However, the incidence of potentially prolactin-related AEs, excluding blood prolactin increased, was low. For other laboratory tests, no treatment-related pattern was apparent for the mean changes from baseline to each time point and end point.

For vital sign measurements, weight, waist circumference, and BMI, the mean changes from baseline to each time point and end point were small and not clinically relevant. Weight increases of 7% or greater from baseline were reported in 35 (17.4%) subjects at end point.

When ECG data were assessed for prolongation of corrected QT (QTc) intervals, 2 subjects had a maximum QTcLD (linear derived) value of >480 msec and 5 subjects had a maximum QTcLD increase

of >60 msec, during the observation period. However, QT prolongation was reported as an AE in only 1 subject who had no QTcLD of >450 msec during observation period.

STUDY LIMITATIONS:

No notable study limitations were identified by the sponsor.

CONCLUSION(S):

In Japanese subjects with schizophrenia, long-term im injections of paliperidone palmitate in a flexibledose range of 25 to 150 mg eq. were generally safe and well tolerated. No new safety signals were detected in this study. Based on the neuropsychiatric symptoms as assessed by PANSS and subjects' overall clinical condition as assessed by CGI-S, paliperidone palmitate was effective and efficacy was maintained throughout the long-term treatment period up to 1 year, without any reduction or loss of efficacy.

***Disclaimer***

*Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.*