SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Finished Product	Paliperidone palmitate
Name of Active Ingredient(s)	R092670 (paliperidone palmitate)

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Status: Approved

Date: 2 September 2014

Prepared by: Janssen Research & Development, LLC

Protocol No.: R092670PSY3012

Title of Study: A Randomized, Multicenter, Double-Blind, Relapse Prevention Study of Paliperidone Palmitate 3-Month Formulation for the Treatment of Subjects with Schizophrenia

EudraCT Number: 2011-004676-11

NCT No.: NCT01529515

Clinical Registry No.: CR100717

Coordinating Investigator: Natalia Maruta, MD - Institute of Neurology, Psychiatry and Narcology of the Academy of Medical Science of Ukraine, [redacted], Ukraine.

Study Centers: Colombia (5 sites), Malaysia (3 sites), Mexico (5 sites), Romania (5 sites), South Korea (3 sites), Turkey (2 sites), United States (14 sites), Ukraine (27 sites).

Publication (Reference): None

Study Period: 26 April 2012 to 09 April 2014

Phase of Development: Phase 3

Objectives:

Primary Objectives

The primary objective of this study was to evaluate the efficacy of paliperidone palmitate 3-month formulation (PP3M) compared with placebo in delaying the time to first occurrence of relapse of the symptoms of schizophrenia.

Secondary Objectives

The secondary objectives of the study were to:

- Evaluate the improvement in the symptoms of schizophrenia as measured by the Positive and Negative Syndrome Scale (PANSS) associated with the use of PP3M compared with placebo.
- Assess the change in the severity of illness associated with the use of PP3M as measured by the change in Clinical Global Impression-Severity (CGI-S) scale compared with placebo.

- Assess the change in functional status with the use of PP3M as measured by the change in Personal and Social Performance (PSP) scale compared to placebo.
- Assess the safety and tolerability of PP3M compared to placebo.
- Assess the pharmacokinetics (PK) of PP3M including its relationship with demographic and dose-related variables.

Exploratory Objectives

- Assess the medication preferences of subjects for PP3M relative to prior oral and/or long-acting injectable (LAI) antipsychotics using the Medication Preference Questionnaire (MPQ).
- Explore the consequences of the subject's illness on the designated caregiver when the subject was treated with PP3M relative to oral and/or LAI antipsychotics using the Involvement Evaluation Questionnaire (IEQ; 31-item version).
- Explore the convergent or divergent validity of the concepts in IEQ by comparing like concepts in the 12-item Short Form Health Survey (SF-12®) (reporting of the SF-12 results will be conducted separately from this study).
- Assess physician and patient trade-off preferences for choice of formulation and key benefit and harm outcomes associated with schizophrenia treatment, using stated-choice conjoint analysis surveys (Patient and Physician Stated-choice Preference Surveys). Compare benefit and risk between PP3M and paliperidone palmitate 1-month formulation (PP1M) using weights based on these preferences and outcome rates (reporting of the survey results will be conducted separately from this study).
- Compare hospitalization and healthcare utilization rates prior to study entry to hospitalization and healthcare utilization rates during the study using the Healthcare Resource Utilization Questionnaire (HRUQ) (the economic analyses and reporting will be conducted separately from this study).
- Evaluate changes in level of healthcare utilization and intervention (eg, increased need for benzodiazepines, emergency room visits, additional clinic visits, initiation of day treatment, etc.) of PP3M compared to placebo (the economic analyses and reporting was to be conducted separately from this study).
- Measure serum biomarkers that could predict (1) impending symptom exacerbation and/or relapse, (2) symptom stability, or (3) correlations with systemic drug exposure of paliperidone during the Maintenance and Double-blind (DB) Phases of the study.

Methodology:

This was a randomized, double-blind, parallel-group, placebo-controlled, multicenter study designed to determine the efficacy and safety of PP3M in the prevention of relapse of schizophrenia. The study consisted of 4 phases: a Screening Phase (up to 3 weeks); a 17-week, flexible dose, open label Transition Phase; a 12-week, fixed dose, open-label Maintenance Phase; and a randomized, double-blind, fixed dose, placebo-controlled relapse prevention phase (referred to as the Double-blind Phase) of variable duration. There were 3 treatment phases: the Transition Phase, the Maintenance Phase, and the Double-blind Phase. Study phases and critical study events and evaluations are described below.

Screening Phase: Subjects with schizophrenia, who were either stable with safety or tolerability problems with their current medications or were in a state of acute exacerbation and who met all entry criteria at screening, were enrolled in this phase, which was up to 3 weeks. If necessary, subjects had their current disallowed psychotropic medications tapered and discontinued (ie, washout) during the Screening Phase. In addition, for subjects with no documented history of exposure to oral or LAI formulations of risperidone or paliperidone, an oral tolerability test was required. All washout procedures and/or

tolerability testing had to be completed on or before Day -1. Screening, washout, and tolerability testing could be conducted while a subject was an inpatient or an outpatient.

Transition Phase: In the 17-week Transition Phase, all subjects except for those switching from other LAI antipsychotics and those who were already on PP1M prior to study entry received PP1M for 120 days. These subjects received the first injection of PP1M (150 milligram equivalents [mg eq.]) on Day 1 and the second injection of PP1M (100 mg eq.) on Day 8 of the study, both in the deltoid muscle. For stable subjects who continued on PP1M at study entry or subjects who switched from other LAIs, a full injection cycle must have elapsed between the time of the last depot injection and the first dose of PP1M was administered on Day 8. Injections on Day 36 and on Day 64 were given in either the deltoid or gluteal muscle and were flexibly dosed (50, 75, 100, or 150 mg eq.). On Day 92, subjects received the dose of PP1M that was administered on Day 64. Those subjects who completed the Transition Phase and who met the prospectively defined criteria entered the Maintenance Phase.

Maintenance Phase: At the start of the 12-week Maintenance Phase (Day 120/Week 17), subjects received a single injection of PP3M (using a 3.5 fold multiple of the PP1M dose received on Day 92 during the Transition Phase). Subjects who met specific stabilization criteria entered the Double-blind Phase at Week 29.

The Transition Phase and Maintenance Phase together are referred to as 'Open-label Phase' for reporting of the analysis results.

Double-blind Phase: At the start of the Double-blind Phase (Day 204/Week 29), subjects were randomly assigned, in a 1:1 ratio, to receive either a fixed dose of PP3M or placebo. Subjects assigned to PP3M received the same dose of study agent that was administered on Day 120 of the Maintenance Phase; the dose was to remain fixed throughout the Double-blind Phase. The study design used in this phase (ie, randomized withdrawal of treatment) was intended to evaluate treatment effects and to assess whether, after symptom stabilization with PP1M for 17 weeks in the Transition Phase and with PP3M for 12-weeks in the Maintenance Phase, continuation with PP3M in the Double-Blind Phase resulted in longer time to relapse compared with placebo treatment. The length of the Double-blind Phase was variable in duration. Subjects remained in the Double blind Phase until they experienced a relapse event (based on prospectively defined criteria), they met one or more of the study discontinuation/withdrawal criteria, or the study was terminated by the sponsor based on positive results of the interim analysis or because 70 relapse events had occurred when interim analysis is not positive.

Number of Subjects (planned and analyzed):

Planned: Approximately 392 subjects were to be enrolled in the study, with a maximum of up to 500 subjects.

Analyzed: Of the 506 subjects who received at least 1 dose of the study agent in the Transition Phase, 379 subjects (75%) entered the Maintenance Phase, and 305 subjects (60%) were randomized to double-blind treatment (Placebo, n=145; PP3M, n=160).

The ITT (DB) analysis set for the interim analysis included 283 subjects (Placebo, n=135; PP3M, n=148) (which was considered primary analysis). The ITT (DB) analysis set for the final analysis included 305 subjects (Placebo, n=145; PP3M, n=160).

Diagnosis and Main Criteria for Inclusion:

Men or women between 18 and 70 years of age (inclusive) who met the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV-TR) criteria of schizophrenia for at least 1 year before screening and had a PANSS total score of <120 at screening and baseline (Day 1) were eligible for enrollment in this study. Subjects, who attempted suicide within 12 months before screening or at an imminent risk of suicide or violent behavior, or who had a primary active DSM-IV-TR Axis I diagnosis

other than schizophrenia, or who with a history of neuroleptic malignant syndrome (NMS) or tardive dyskinesia or any malignancy within the previous 5 years, were excluded from the study.

Test Product, Dose and Mode of Administration, Batch No.:

During the Transition Phase, all subjects received injections of PP1M. Subjects could be flexibly dosed (50, 75, 100, or 150 mg eq.) on Days 36 and 64. At Day 92, subjects were to receive the dose of PP1M that was administered at the Day 64 visit. During the 12-week Maintenance Phase, subjects received a dose of PP3M that was a 3.5-fold multiple of the final PP1M dose administered on Day 92. During the Double-blind Phase, subjects received injections of either PP3M or placebo (20% Intralipid solution) every 3 months. The doses of PP3M were 175, 263, 350, or 525 mg eq. Subjects assigned to the PP3M group in the Double-blind Phase received the same dose of study drug that was administered on Day 120 of the Maintenance Phase; the dose was to remain fixed throughout the Double-blind Phase.

Subjects who were taking another depot antipsychotic were permitted to enter the study as long as all other criteria are met. If a subject was currently stable on PP1M, 4 weeks were to elapse from the time of the last injection to the Day 8 injection of PP1M. Such subjects could then receive the next PP1M injection on Day 36. For subjects who were switching from another LAI antipsychotic, including Risperdal CONSTA, the timing of the first dose of PP1M occurred on Day 8, such that one injection cycle passed from the time of the last prior depot injection before the first injection of PP1M. The second dose of PP1M was administered on Day 36. (Bulk lot numbers/packaged lot numbers for Paliperidone ER OROS 6mg: 0MD2605-X/365851, 366123. Bulk lot numbers/packaged lot numbers for OL Paliperidone Palmitate 50mg: BEB9B/365852, BHB6B/366226, and DBB5W/4367689. Bulk lot numbers/packaged lot numbers for OL Paliperidone Palmitate 75mg: BEB9C/365853, BIB78/366227, and CHB6C/4367688. Bulk lot numbers/packaged lot numbers for OL Paliperidone Palmitate 100mg: BFB7R/365854, BIB76/366228, and CHB6E/4367547. Bulk lot numbers/packaged lot numbers for OL Paliperidone Palmitate 150mg: BFB7S/365855, BIB77/366229, and CHB6F/4367548. Bulk lot numbers/packaged lot numbers for OL Paliperidone Palmitate 175mg: 11J26/F015/366040, 12A04/F015/366333, and 12F18/F015/4367107. Bulk lot numbers/packaged lot numbers for OL Paliperidone Palmitate 263mg: 11J26/F015/366041, 12A04/F015/366334, and 12F18/F015/4367106. Bulk lot numbers/packaged lot numbers for OL Paliperidone Palmitate 350mg: 11J26/F015/366042, 12A04/F015/366335. Bulk lot numbers/packaged lot numbers for OL Paliperidone Palmitate 525mg: 11J26/F015/366043, 12A04/F015/366336, and 12F18/F015/4367108. Bulk lot numbers/packaged lot numbers for DB Paliperidone Palmitate 175mg: 12C07/F015/366284, 13A16/F015/4367102, 13C11/F015/4367893, 13E13/F015/4367938, and DJB6V00/4367985. Bulk lot numbers/packaged lot numbers for DB Paliperidone Palmitate 263mg: 12C07/F015/366285, 366285/4367103, 4367103/4367894, 13E13/F015/4367939, and DJB6M00/4368160. Bulk lot numbers/packaged lot numbers for DB Paliperidone Palmitate 350mg: 12C07/F015/366286, 13A16/F015/4367104, 13C11/F015/4367895, 13E13/F015/4368040, and DJB6L00/4368161. Bulk lot numbers/packaged lot numbers for DB Paliperidone Palmitate 525mg: 12C07/F015/366287, 13A16/F015/4367105, 13C11/F015/4367896, and 13E13/F015/4368041.

Reference Therapy, Dose and Mode of Administration, Batch No.:

During the Double-blind Phase, subjects assigned to placebo received placebo injections matching PP3M administered every 3 months (Bulk lot numbers/packaged lot numbers for DB Placebo 175mg: 12D02/F000/366284; 12J25/F000/4367102; 13H19/F000/4367893; 13H19/F000/4367938; and 13H19/F000/4367985. Bulk lot numbers/packaged lot numbers for DB Placebo 350mg: 12D02/F000/366286; 12J25/F000/4367104; 13H19/F000/4367895; 13H19/F000/4368040; and 13H19/F000/4368161. Bulk lot numbers/packaged lot numbers for DB Placebo 525mg: 12D02/F000/366287; 12J25/F000/4367105; 13H19/F000/4367896; and 13H19/F000/4368041).

Duration of Treatment:

Study agent was administered for 17 weeks during the Transition Phase; 12 weeks during the Maintenance Phase; and a variable length of time during the Double-blind Phase (until they experienced a relapse event, met discontinuation/withdrawal criteria, or pre-defined study conclusion criteria were reached.

Criteria for Evaluation:

Efficacy: The primary efficacy end point was the time from randomization to first relapse event in the Double-blind Phase. The date of relapse was the date of the first assessment for symptoms of relapse. Secondary efficacy end points included the change from baseline to end point in PANSS (total and subscales), CGI-S, and PSP during the Double-blind Phase.

Pharmacokinetic: A single venous blood sample (4 mL) was collected for the determination of plasma concentration of paliperidone. An unscheduled PK sample could be collected at the discretion of the investigator or sponsor for cases of severe or serious adverse events (AEs) that could be potentially related to unexpected increases in plasma concentrations of study drug. If deemed necessary to explain the study results, drug concentrations for paliperidone enantiomers, paliperidone palmitate or other antipsychotics including risperidone could be determined.

Pharmacogenomic: An optional 10 mL pharmacogenomic blood sample was collected on Day 1 from subjects who provided a separate written informed consent to allow for pharmacogenomic research (where local regulations permit). The effect of genes/genotypes that could be related to efficacy or tolerability of PP1M or PP3M was assessed.

Safety: Assessments of safety included laboratory measurements (chemistry, hematology, lipid assessments, fasting insulin and glucose, and urine drug screens), body weight and height, waist circumference, vital signs, electrocardiograms (ECGs), physical examination, and monitoring of AEs. Serious adverse events (SAEs) were collected for a minimum period either up to the End-of-Study (EOS) Visit, or for 3 months after the last dose of study drug, whichever was later. Extrapyramidal symptoms (EPS) were assessed using the AIMS, BARS, and SAS scales. The Columbia Suicide Severity Rating Scale (C-SSRS) was administered to monitor suicidal ideation and behavior. At the end of study, the homeostatic model assessment (HOMA) was conducted to estimate changes in beta-cell function and insulin sensitivity.

For local tolerability, there was an assessment of injection pain by the subject within 30 minutes after the injection using a visual analog scale (VAS). This subject assessment was done independently and in a blinded fashion. The investigator or sub-investigator was to assess redness, induration and swelling within 30 minutes of the injection. All injection site AEs with objective findings (eg, swelling, redness, and induration) and a severity assessment of “moderate” or “severe” were to be photographed along with a metric ruler for later review.

Exploratory: Other assessments included a MPQ (assessing preference for oral vs. injectable drugs, 1-month vs. 3-month injections, and injection site preferences), an IEQ, the SF-12, a HRUQ, and Patient and Physician Stated-choice Preference Surveys.

An Independent Data Monitoring Committee (IDMC) was established to review the blinded efficacy and safety data on an ongoing basis. In addition, the IDMC was to meet and review the results of the interim analysis and provide recommendation to the sponsor on whether to continue the study or to terminate the study.

An interim analysis was to be conducted by the IDMC after at least 42 relapse events had occurred. If interim analysis using 2-sided log-rank test was to show a statistically significant difference ($p<0.0101$ for exactly 42 relapse events in the interim ITT [DB] analysis set) between PP3M and placebo in the time to

relapse, the study was to be terminated. The interim analysis would then be considered as the primary analysis and the final analysis, performed after study termination, would be reported as confirmative results. If interim analysis failed to show a significant difference, the study was to continue until 70 relapse events had been obtained, and the final analysis, now considered primary analysis was to be performed at a significance level of 0.0464.

Statistical Methods: Unless otherwise specified, a two-sided significance level of 5% was to be used. There was 1 interim efficacy analysis for superiority. The interim analysis was performed at a significance level of 0.0101 and, if study was not terminated due to nonsignificant results, the final analysis was to be performed at the 0.0464 significance level.

Sample Size Determination

It was assumed that the 12-month relapse rates for PP3M and placebo would be 20% and 40%, respectively, resulting in a relative risk of 0.44. Approximately, 196 subjects were expected to be randomized in the Double-blind Phase in a 1:1 ratio to either PP3M or placebo in order to obtain 70 relapse events to show that PP3M was significantly different from placebo at the 2-sided significance level of 0.05, with 90% power to detect a relative risk of 0.44 (ie, hazard rate of PP3M/ hazard rate of Placebo=0.44).

A 2-stage group sequential design with 1 interim analysis was to be implemented to allow for early stopping if there was significant evidence of efficacy based upon the interim analysis after 60% (ie, 42 events) of the projected relapse events had occurred. The O'Brien-Fleming boundary (corresponding to the Wang and Tsiatis power boundary with shape parameter 0) was to be used for sequential monitoring.

It was assumed that at least 50% of subjects who entered the Transition Phase would discontinue the study or not meet the criteria for randomization in the Double-blind Phase. To meet the expected number of 196 subjects (98 per treatment group) to be randomized in the Double-blind Phase, a total of at least 392 subjects were expected to be enrolled. The total number of subjects enrolled would depend on the time that it took to obtain 70 relapse events. Blinded surveillance of the total number of events in the Double-blind Phase was to be performed during the study to assess the appropriateness of the 50% dropout assumption and the time necessary to obtain 70 relapse events. The total number of subjects enrolled could be increased up to approximately 500.

For data analysis purposes, the Transition and the Maintenance Phase data were combined and collectively referred to as Open-label Phase. The intent-to-treat (ITT) (OL) analysis set included all subjects who received at least 1 dose of open-label study agent. This analysis set was used to summarize all efficacy and safety data for the Open-label Phase. The ITT (MA) analysis set included all subjects who received at least 1 dose of study agent during the Maintenance Phase. All Randomized analysis set included all subjects who were randomized to treatment during the Double-blind Phase. The ITT (DB) analysis set included all subjects who were randomly assigned to treatment during the Double-blind Phase and received at least 1 dose of Double-blind study agent. The safety analysis set included all subjects who were randomly assigned to treatment during the Double-blind Phase and received at least 1 dose of double-blind study agent, and by definition was identical to the ITT (DB) analysis set. The ITT (DB) analysis set (safety analysis set) was used to summarize the completion and withdrawal information and all efficacy and safety analyses for the final analysis of Double-blind Phase data (ie, after the study was terminated and applied to data collected up to final database lock). The interim ITT (DB) analysis set included all subjects who were randomly assigned to treatment during the Double-blind Phase and received at least 1 dose of Double-blind study agent at the time of interim cut-off (ie, when 42 relapse events were obtained).

In the event that the study was terminated because of the significant results of the interim analysis, the interim analysis was considered the primary analysis as prespecified in the statistical analysis plan (SAP).

The final analysis of data, including events subsequent to interim analysis data cutoff on 24 January 2014, which are the cumulative data in the whole trial up to the date of study completion on 09 April 2014, was considered confirmatory. The corresponding analysis populations used for the interim analysis are defined similarly in the IDMC SAP. The treatment groups were labeled based on the phase for which data were summarized. Only 1 treatment group 'Pali Palmitate' was used for the summaries of data from the Open-label Phase.

Two treatment groups were used for the presentation of results for the Double-blind Phase:

- PP3M (this treatment group referred to subjects who were randomized into PP3M treatment group during the Double-blind Phase).
- Placebo (this treatment group referred to subjects who were randomized into Placebo group during the Double-blind Phase).

Pharmacokinetics: A separate PK analysis plan was developed for non-compartmental PK analysis. Further details of the non-compartmental PK analysis will be provided in a separate report. Population PK analysis of plasma concentration-time data for paliperidone was to be performed using nonlinear mixed effects modeling. The results of the population PK analysis will be provided in a separate report.

Pharmacogenomics: No pharmacogenomic parameters were calculated or derived.

Efficacy: The primary analysis for efficacy was carried out on the intent-to-treat (ITT) population, defined as all subjects who receive at least 1 dose of Double-blind medication during the Double-blind Phase. The primary efficacy end point for this study was the time between subject randomization into the Double-blind Phase and the first documentation of a relapse event. Subjects who met at least 1 of the criteria for relapse while on Double-blind treatment at the time of study completion for the primary analysis were considered to have had a relapse event. All other subjects without a relapse at the end of study (end of Double-blind Phase) were considered censored. Treatment comparison between PP3M and Placebo in the changes from baseline to end point of PANSS total score, PSP, and CGI-S during the Double-blind Phase was performed using an analysis of covariance (ANCOVA) model with treatment and country as factors and baseline (Double-blind Phase) value as a covariate. Least-squares estimates of the treatment differences and 95% confidence intervals were presented.

Safety: For safety, the incidence of AEs was summarized for each treatment group by system organ class (SOC) and PTs. Changes from baseline in clinical laboratory values and vital signs measurements were presented descriptively. The effects on cardiovascular measurements were evaluated using descriptive statistics and frequency tabulations. All clinically significant abnormalities from the ECG readings were listed. Weight, waist circumference, body mass index (BMI), extrapyramidal symptom scales (AIMS, BARS, SAS), and the subjective and objective injection site evaluations were summarized using descriptive statistics. For C-SSRS, the percentage of subjects with a suicide-related outcome was summarized.

Exploratory: Descriptive statistics were provided for the MPQ, IEQ, Short Form Health Survey (SF-12), and the Healthcare Resource Utilization Questionnaire (HRUQ). The descriptive statistics for the IEQ only applied to those subjects who had a designated caregiver during the study. Additionally, demographic characteristics of the caregiver and caregiving arrangements were summarized for the ITT (OL) and ITT (DB) analysis sets. Any other detailed analysis of these end points is presented in a separate analysis plan. A separate plan is provided for the Patient and Physician Stated-choice Preference Surveys. The health outcome report of this study will be presented in a separate report.

A separate statistical analysis plan was developed for the biomarker analysis before the samples were analyzed. The biomarker results from this study are presented in a separate report.

RESULTS:

STUDY POPULATION:

Overall, 506 subjects with schizophrenia were enrolled into and dosed in the Open-label Phase and 305 subjects with schizophrenia were randomized into in the Double-blind Phase, as of 09 April 2014, the date of study completion. Of the 506 ITT (OL) subjects, 379 subjects (75%) completed the Transition Phase and continued to the Maintenance Phase. The most common reason for discontinuation from the study during the Transition Phase was withdrawal of consent for 51 subjects (10%). Of the 379 subjects who entered the Maintenance Phase, 305 subjects (80%) continued into the Double-blind Phase, and a total of 74 subjects (20%) discontinued from the study at this stage; the most common reason (≥4%) being withdrawal of consent (15 subjects [4%]). Of the 305 randomized subjects, 145 subjects were in the Placebo group and 160 subjects were in the PP3M group. A total of 270 subjects (89%) completed the study, while 35 subjects (11%) discontinued from the Double-blind Phase. The most common reasons (≥5%) to discontinue this phase of the study in any treatment group were withdrawal of consent (10 subjects [7%] in the Placebo group, 7 subjects [4%] in the PP3M group), and other reasons (8 subjects [6%] in the Placebo group, 2 subjects [1%] in the PP3M group).

At Open-label baseline, more male (75%) than female (25%) subjects were enrolled in the study. A majority of subjects were white (59%), with a mean standard deviation (SD) age of 38.4 (11.15) years (range: 18 to 68 years). Based on BMI, 44% of subjects were classified as having normal body weight; 33% of subjects were overweight, and 24% were obese. At Double-blind baseline, demographic and baseline characteristics data was similar between the Placebo and PP3M groups. At Open-label baseline, the mean (SD) PANSS total score was 74.0 (15.43) (range: 33 to 114).

PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS: The results of the PK analysis are described in a separate report and are added to the clinical study report (CSR) as an attachment.

BIOMARKERS:

The biomarker analysis will be completed later and reported separately.

PHARMACOGENOMIC RESULTS:

No pharmacogenomic analyses have been conducted for this study at the time of the writing of this CSR. These samples may potentially be analyzed at a later time and reported separately.

EFFICACY RESULTS

During the 29-week Open-label treatment, substantial improvements in the symptoms of schizophrenia were observed for subjects in the ITT (OL) analysis set based on the decrease in the PANSS total score from Open-label baseline in the Transition and Maintenance Phases. Analyses of other secondary efficacy variables were consistent with this observation. The global severity of the subjects' clinical impairment, as reflected in CGI-S scores, was improved from the Open-label baseline. Improvement was observed with regard to the change from Open-label baseline in all 3 subscales scores and 5 PANSS factor scores. The PSP scores obtained at the end of the Open-label treatment period indicated improvement in personal and social performance. Overall, these results indicate that by the end of the Open-label Phase, most subjects had achieved control of their acute schizophrenic symptoms.

In the Double-blind Phase, PP3M was superior to placebo in delaying relapse of symptoms of schizophrenia in subjects who had achieved satisfactory symptom control during the 29-week Open-label treatment. Based on the preplanned interim analysis, conducted by an IDMC after the 42nd relapse event, there was a statistically significant difference between the 2 treatment groups in the time to relapse of symptoms of schizophrenia in favor of PP3M. The 25% quantile of time to relapse (the estimated time point at which 25% of subjects have experienced a relapse event) was 140 days in the Placebo group and not estimable in the PP3M, based on the Kaplan-Meier estimates.

Since the preplanned interim analysis of time to relapse was statistically significant in favor of PP3M over placebo, this interim analysis was considered as the primary analysis, and the final analysis of data was considered confirmatory.

The final analysis of the relapse data confirmed the findings of the interim analysis. There was a statistically significant difference between the 2 treatment groups in the time to relapse with a longer time to relapse in subjects assigned to PP3M ($p<0.0001$). Three times as many subjects in the Placebo group (29.0%) as in the PP3M group (8.8%) experienced a relapse event. The median estimated time to relapse was 395 days for subjects in Placebo group and not estimable for PP3M group. The 25% quantile of time to relapse was 141 days in the Placebo group and not estimable in the PP3M group, based on the Kaplan-Meier estimates. The instantaneous risk (Hazard Ratio) for relapse of schizophrenia symptoms was 3.81 (95% CI: 2.08, 6.99), ie, a subject switching to placebo was 3.81 times more likely to experience a relapse than a subject continuing to receive PP3M in the final analysis. This indicates that there was a 74% decrease in relapse risk with continued PP3M treatment. The most common reasons for relapse were increase in PANSS total score and psychiatric hospitalization.

Analyses of the efficacy of PP3M compared with placebo with regards to time to relapse of symptoms of schizophrenia was consistent after adjusting for age, sex, race, BMI or region (US, Europe, and rest of the world [ROW]).

Analyses of secondary efficacy variables provided further evidence of the efficacy of PP3M in the maintenance treatment of subjects with schizophrenia.

For subjects in the PP3M group, the mean PANSS total score remained stable over time, whereas in the placebo-treated subjects, there was an overall deterioration in symptom control. PP3M was also statistically significantly more effective than placebo in maintaining the symptomatic and global improvements achieved during the 29-week Open-label treatment.

The mean PANSS subscale and Marder factor scores decreased from Double-blind baseline to Double-blind end point in the PP3M group for all subscale and factor scores, except for "anxiety/depression factor", which showed a numerical increase at Double-blind end point; while subjects who received placebo experienced an increase (ie, worsening) in these scores.

At Double-blind baseline, disease severity based on CGI-S score for the majority of subjects in both groups was rated by the investigators as ‘mild’, ‘very mild’ or ‘moderate’. At Double-blind end point, the proportion of subjects with a CGI-S rating of ‘marked’ or ‘severe’ was approximately 4 times higher in the Placebo group than in the PP3M group (11.3% vs. 2.5%). The mean (SD) change in the CGI-S score from Double-blind baseline to Double-blind end point in the Placebo group was statistically greater than that in the PP3M group (Placebo group: 0.4 [0.87]; PP3M group: 0.1 [0.6]; $p<0.001$).

A statistically significant advantage over Placebo was observed for the PP3M group with regard to the mean change from Double-blind baseline to Double-blind end point in PSP score, indicating that continued treatment with PP3M prevented deterioration in personal and social functioning in schizophrenic subjects.

Taken together, the results of the efficacy evaluations indicate that Open-label treatment with PP1M/PP3M during the Transition and Maintenance phases led to a considerable improvement in the symptoms and severity of schizophrenia based on all efficacy evaluations. Double-blind treatment with PP3M in those subjects who had achieved satisfactory control of acute symptoms during the Transition and Maintenance phases was associated with a statistically significantly longer time to relapse of the symptoms of schizophrenia and with a lower incidence of relapse of events compared with subjects who switched to receive placebo in the Double-blind Phase.

SAFETY RESULTS:

PP3M at fixed doses of 175, 263, 350 or 525 mg eq. was generally well tolerated in subjects with schizophrenia. Subjects received fixed doses of PP3M that was a 3.5 fold multiple of the final PP1M dose administered on Day 92 of the 17-week Transition Phase.

There was 1 death (subject treated with PP1M) during the Open-label phase of the study due to the treatment-emergent adverse event (TEAE) of megacolon, which was considered not related to study agent by investigator. No deaths were reported during the Double-blind Phase of the study.

The incidence of TEAEs leading to permanent discontinuation of study drug during the Open-label Phase (Transition Phase and Maintenance Phase) was 5.1% and mainly related to psychiatric disorders (3.4%). During the Maintenance Phase only, 2.6% of TEAEs lead to study discontinuation and were also mainly observed in the psychiatric disorders SOC (2.1%). During the Double-blind Phase a single subject (0.7%) in the Placebo group discontinued the study agent due to the TEAE of transaminases increased.

The most common TEAE (>5% of the subjects) reported in the Open-label Phase was weight increased (10.1%), insomnia (9.9%), anxiety and injection site pain (each 8.7%), and headache (6.5%). The most frequently reported TEAE during the Maintenance Phase only was anxiety (5.8%). The TEAEs that occurred more frequently in the PP3M group than in the Placebo group in the Double-blind Phase were nasopharyngitis (5.6% vs. 1.4%), weight increased (8.8% vs. 3.4%), and headache (8.8% vs. 4.1%).

Overall, TEAEs were reported in 65.2% of the 506 subjects during the Open-label Phase. During the Double-blind Phase, TEAEs occurred at a numerically higher rate in the PP3M group compared with the Placebo group (61.9% vs. 57.9%). Treatment-emergent SAEs occurred in 6.5% of subjects during the Open-label Phase. Treatment-emergent SAEs in the Placebo group (10.3%) were reported with an incidence more than 4 times the incidence of treatment-emergent SAEs in the PP3M group (2.5%) during the Double-blind Phase. As in the Open-label Phase, treatment-emergent SAEs in the Double-blind Phase were mainly observed in the psychiatric disorders SOC, suggesting that they were most likely related to the worsening of symptoms (acute exacerbations or relapses) associated with the underlying psychotic disorder. The only SAE reported at the incidence of 5% or more during the Double-blind Phase was schizophrenia in the Placebo group.

Treatment-emergent EPS-related AEs were reported in 10.3% of the 506 subjects during the Open-label Phase. The most commonly occurring treatment-emergent EPS-related AEs during the Open-label Phase (reported by at least 2% of all subjects) included akathisia and tremor. During the Double-blind Phase, the incidence of EPS-related AEs was higher in the PP3M group than in the Placebo group (8.1% vs. 3.4%); akathisia being the most commonly reported AE (4.4% in PP3M and 0.7% in Placebo). One subject each discontinued the study drug during the Open-label Phase for the TEAEs of restlessness and Parkinsonism. None of the EPS-related AEs were reported as SAEs or resulted in study drug discontinuation during the Double-blind Phase. Results of the EPS rating scales did not reveal important changes from pre-treatment assessment, consistent with the frequency and intensity of EPS-related AEs. One subject reported an EPS-related TEAE of dyskinesia during the Open-label Phase and 3 subjects reported TEAEs of dyskinesia in the Double-blind Phase (Placebo 2 subjects, PP3M 1 subject).

Treatment-emergent diabetes mellitus and hyperglycemia-related AEs were uncommon (0.6%; 3 of 506 subjects) during the Open-label Phase. During the Double-blind Phase, 5.5% of Placebo-treated subjects and 2.5% of PP3M treated subjects experienced diabetes mellitus and hyperglycemia-related AEs, consistent with the absence of TEMA glucose levels and the absence of clinically meaningful changes from baseline in mean glucose levels. The effect of PP3M on glucose metabolism as assessed by the HOMA-IR and HOMA-%B revealed that PP3M had no significant negative impact on beta-cell functioning and insulin resistance.

During the Open-Label Phase, 4.7% subjects experienced treatment-emergent potentially prolactin-related AEs. During the Double-blind Phase, 1 of 42 female subjects (2.4%) in the PP3M group experienced a

TEAE of amenorrhea, while no TEAEs were noted in the Placebo group. Like other drugs that block dopamine D2 receptors, treatment with PP3M is associated with increases in plasma prolactin levels. Increases in median prolactin levels from Open-label baseline were observed during the Open-label Phase in both male and female subjects. Increases in median prolactin levels were observed throughout the Transition and Maintenance Phases to Double-blind baseline. During the Double-blind Phase, median prolactin levels for both male and female subjects in the Placebo group showed a decrease from Double-blind baseline levels. For male subjects who continued to receive PP3M, the median prolactin levels were stable throughout the Double-blind Phase. For female subjects who continued to receive PP3M, median prolactin levels remained stable during the first 6 months of the Double-blind Phase, followed by a further median increase observed across a small number of subjects remaining in the Double-blind Phase beyond Week 24. Since the majority of subjects with elevated prolactin levels had no treatment-emergent potentially prolactin-related AEs, this suggests that the increases in median prolactin levels are likely of limited clinical relevance.

No subject had TEAEs related to seizures and convulsions, ischemia, rhabdomyolysis, or overdose during the Open-label and Double-blind Phases of the study. There was no reported TEAE of NMS in the study. Suicidality-related TEAEs occurred in 3.0% of subjects in the Open-label Phase. Similarly, in the Double-blind Phase, the incidence of suicidality-related TEAEs was low (Placebo group 2.1% and PP3M group 1.3%). During the Open-label Phase, an overall shift from the categories of suicidal ideation and suicidal behavior to no event category was observed for most of the subjects from screening to Open-label postbaseline. During the Double-blind Phase, a higher percentage of subjects in the PP3M group than the Placebo group shifted from the categories of suicidal ideation and suicidal behavior to the category of no event from screening to Double-blind postbaseline, thus indicating no worsening in suicidal ideation or behavior.

The incidence of orthostatic hypotension was low for ITT (OL) subjects in the Open-label Phase (1% subjects) and for ITT (DB) subjects in Double-blind Phase (only Placebo group 0.7%), suggesting that these findings were of limited clinical relevance.

A total of 13.0% of ITT (OL) subjects in the Open-label Phase had TEAEs related to injection site reaction, while only 3.8% of ITT (DB) subjects in the PP3M group had TEAEs related to injection site reaction in the Double-blind Phase.

With regard to laboratory evaluations, there were no noteworthy mean changes from baseline to end point for most analytes during either Open-label or Double-blind Phases. Across study phases, the low incidences of TEMA laboratory analyte values for most analytes were consistent with the low incidence of TEAEs related to abnormal laboratory findings.

During the Open-label Phase, abnormal increases in supine and standing pulse rate were noted in 3.2% and 14.0% of ITT (OL) subjects, respectively. The TEAE of tachycardia was reported in 1.6% of the subjects during the Open-label Phase. Abnormal decreases in supine and standing systolic blood pressure measurements were observed in 1.2% and 1.6% of subjects, respectively. Other abnormal changes (decrease in supine and standing pulse rate, supine and standing DBP, supine and standing SBP, and increase in supine and standing DBP) were reported in less than 2% of subjects.

During the Double-blind Phase, a higher percentage of subjects in the PP3M group than in the Placebo group were found to have an increase in standing pulse rate (PP3M group 7.5% and Placebo group 4.1%) and increase in standing DBP (1.9% vs. 1.4%). The incidence of treatment-emergent abnormal vital sign values for increase in supine pulse rate, decrease in supine SBP, decrease in standing SBP, and decrease in standing DBP was numerically higher in the Placebo group than in the PP3M group. However, the difference between the 2 treatment groups was $\leq$1%.

The incidence of TEAEs of weight increased, which represents subjects with clinically significant weight gain as assessed by the investigators, was 10.1% in the Open-label Phase, compared to 3.4% in the

Placebo group and 8.8% in the PP3M group during the Double-blind Phase. The mean (SD) increases in body weight from Open-label baseline to Double-blind end point were 0.55 kg and 2.38 kg for Placebo and PP3M groups, respectively. None of the weight abnormalities were reported as SAEs or resulted in study drug discontinuation. Eighteen subjects (13%) in the Placebo group and 16 subjects (10%) in the PP3M group experienced an abnormal decrease in body weight (≥7%) from Open-label baseline to Double-blind end point. Twenty-five subjects (18%) in the Placebo group and 38 subjects (24%) in the PP3M group experienced an abnormal increase in body weight (≥7%) from Open-label baseline to Double-blind end point.

The incidences of treatment-emergent abnormalities in recorded or derived ECG parameters (HR, PR interval, QRS duration, QT interval, RR interval, and corrected QT [QTc] intervals) were low during the course of the study and showed no clinically relevant differences between treatments during the Open-label and Double-blind Phases. Based on ECG recordings, the incidence of abnormally high HR occurred in 6% of the ITT (OL) subjects during the Open-label Phase, and was higher in the Placebo group compared with the PP3M group (7% vs. 2%) for ITT (DB) subjects during the Double-blind Phase; these findings are consistent with the pulse rate data. The majority of subjects had normal QTcLD values during the Open-label and Double-blind Phases of the study. Of the 465 subjects with normal average predose QTcLD interval, 6 subjects had maximum QTcLD values >450 msec during the Open-label Phase. Five subjects and 1 subject had maximum QTcB value >480 msec and >500 msec, respectively. During the Double-blind Phase, 2 subjects in the Placebo group and 1 subject in the PP3M group had maximum QTcLD values >450 msec and none of the subjects had maximum QTcLD values >480 msec. Clinically significant instances of QTc interval prolongation were to be reported as TEAEs. The TEAE of electrocardiogram QT prolonged resulted in study discontinuation in 1 subject in the Open-label Phase. No cases of QTc interval prolongation or other ECG abnormalities were reported as SAEs during the Open-label and Double-blind Phases.

STUDY LIMITATIONS:

- The relapse prevention design was based on the principle of enrichment; ie, criteria of clinical stability were applied prior to entry into the Maintenance Phase and Double-blind Phase. Hence, the ITT (DB) analysis set does not reflect the overall sample of subjects who were initially enrolled in Study PSY3012 for treatment with PP1M/PP3M. Therefore results may not reflect true efficacy for prevention of relapses in the overall population.
- In addition, the fixed doses evaluated during the Double-blind Phase were not directly informative of any changes in the dose of PP3M that could occur during long-term treatment in clinical practice.
- Conversely, the fixed doses in the Double-blind Phase cannot inform the dose response of PP3M for use as maintenance therapy, as dosing was flexible during the acute Open-label Phase; ie, subjects were not randomly assigned to distinct dose levels of PP1M/PP3M.
- Because of variable length in the Double-blind Phase for different subjects, effects overtime in this phase for secondary efficacy and safety end points should be interpreted with caution.

CONCLUSION(S):

In this long-term study, after treatment with PP1M for at least 4 months, PP3M (175, 263, 350, or 525 mg eq.) was generally well tolerated by subjects with schizophrenia and significantly delayed time to relapse of symptoms in subjects with schizophrenia compared to Placebo. The final analysis of the primary efficacy end point was consistent with the results from the interim analysis. A significant difference ($p<0.001$ based on the log-rank test) between the PP3M and Placebo groups in the time to relapse was observed in favor of PP3M. The instantaneous risk (Hazard ratio) of relapse of schizophrenia symptoms was 3.81 (95% CI: 2.08, 6.99) times higher for a subject switching to Placebo than for a subject continuing to receive PP3M in the final analysis, indicating that there was a 74% decrease in relapse risk

with continued PP3M treatment. The null hypothesis that the survival distributions of the two treatment groups were the same in time to relapse was rejected.

During the Double-blind Phase, PP3M treatment maintained symptom control as measured by the efficacy scales including PANSS, CGI-S, and PSP.

The safety and tolerability profile of PP3M, observed over the course of the 12-week Maintenance Phase and the subsequent Double-blind Phase of variable duration, was consistent with that observed in other clinical trials with paliperidone palmitate. No new safety signals emerged during this trial.