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

Protocol R092670PSY3012; Phase 3

AMENDMENT INT-4

R092670 (paliperidone palmitate)

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	American Diabetes Association
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BARS	Barnes Akathisia Rating Scale
BMI	body mass index
C_{max}	maximum plasma concentration
CGI-S	Clinical Global Impression – Severity
C-SSRS	Columbia Suicide Severity Rating Scale
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision
ECG	electrocardiogram
eCRF	electronic case report form
EPS	extrapyramidal symptoms
IDMC	independent data monitoring committee
i.m.	intramuscular
ITT	intent-to-treat
LAI	long-acting injectable
LC-MS/MS	liquid chromatography/dual mass spectrometry
MAOI	monoamine oxidase inhibitor
mg eq.	milligram equivalent
NMS	neuroleptic malignant syndrome
PANSS	Positive and Negative Syndrome Scale
PP1M	paliperidone palmitate 1 month formulation
PP3M	paliperidone palmitate 3 month formulation
PSP	Personal and Social Performance Scale
SAE	serious adverse event
SAS	Simpson-Angus Scale
SCI-PANSS	Structured Clinical Interview-PANSS
t1/2	half-life
TEAE	treatment-emergent adverse event
VAS	Visual Analog Scale

PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	7 December 2011
Amendment INT-1	27 February 2012
Amendment INT-2	2 July 2012
Amendment INT-3	13 May 2013
Amendment INT-4	25 July 2013

Amendments are listed beginning with the most recent amendment.

Amendment INT-4 (25 July 2013)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union in that it does not significantly impact the safety or physical/mental integrity of patients, nor the scientific value of the study.

The overall reason for the amendment: This amendment is needed primarily to specify the countries that will participate in the biomarker component of the study. Other minor clarifications are included in the amendment.

Applicable Section(s)	Description of Change(s)
Rationale: Due to business reasons, only sites in specified countries will participate in the biomarker component of the study.	
Synopsis; Time and Events Schedule; 9.5. Exploratory Evaluations; Attachment 6	Specified that only sites located in the United States, Ukraine, Romania, and Mexico will participate in the biomarker component of the study, whereas sites located in Turkey, Colombia, Korea, and Malaysia will not take part in the biomarker component.
Rationale: To clarify where urine drug screen is to be performed.	
Time and Events Schedule for Clinical Laboratory Tests	Clarified that at Visit 2 urine drug screen must be performed on site whereas at other specified visits a urine sample must be sent to the central laboratory for drug screen.
Rationale: To clarify procedures for serum biomarker sample handling.	
Attachment 6	Clarified procedures for serum biomarker sample collection and shipment.
Rationale: Minor formatting and edits are made for consistency.	
Throughout the protocol	Minor formatting and edits were made for consistency and clarity.

Amendment INT-3 (13 May 2013)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: This amendment is needed primarily to incorporate a new biomarker component into the study to measure serum biomarkers that may 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 Phases of the study. Other minor clarifications are included in the amendment.

Applicable Section(s)	Description of Change(s)
Rationale: To specify the exploratory objectives of the biomarker component of the study.	
Synopsis; 2. Objectives and Hypothesis.	Provided the objectives of the biomarker component of the study.
Rationale: To provide specific procedures for the biomarker component of the study.	
Synopsis; Time & Events Schedule; 3.2.2.General Design Elements; 4.1. Inclusion Criteria 9.1. Overview; 9.5. Exploratory Evaluations; 10.2. Withdrawal from the Study; 11.5. Exploratory Analyses; 16.2.3. Informed Consent; Attachment 6.	• Specified the inclusion criteria for participating in the biomarker component of the study; • Provided a list of potential biomarkers to be measured and analyses to be carried out that may help predict symptom stability, symptom worsening, or illness relapse; • Specified the time points for blood sample collection and additional blood volumes to be collected; • Stated that a separate statistical plan will be developed for the biomarker analysis before the samples are analyzed; • Provided procedures for biomarker sample destruction upon withdrawal of consent for future biomarker research; • Provided detailed instructions for blood sampling and shipment for the biomarker component of the study; • Added serum biomarker sample collection and shipment procedure.
Rationale: To specify when a full PANSS assessment should be completed to evaluate potential impending relapses.	
Time and Events Schedule; 9.2.2.2. PANSS Scale	Specified situations in which a full PANSS assessment is required to assess potential relapses.
Rationale: To clarify the time points and personnel responsible for the evaluation of injection site reaction.	
Time and Events Schedule; 9.6. Safety Evaluations	Clarified that Investigators or sub-investigators will assess injection site reaction within 30 min of each drug injection.
Rationale: To state that use of prohibited antipsychotics will lead to study withdrawal.	
10.2. Withdrawal from the Study	Specified that use of prohibited antipsychotics as detected by PK analysis showing a clinically relevant exposure will lead to study withdrawal.
Rationale: To Specify that a pharmacokinetics/pharmacodynamics analysis may be conducted to help elucidate potential correlations between systemic exposure of paliperidone and biomarker, efficacy, and safety parameters.	

11.4. Pharmacokinetics Analyses	Stated that a PK/PD analysis may be conducted if deemed useful and will be reported separately from the main CSR after the study is completed.

Rationale: To specify the needle size to be used in study drug injection.

6. Dosage Administration	Clarified that for deltoid injections it is required that a 1.5 inch needle be used for patients ≥200 lb (90 kg). For patients <200 lb (90 kg), a 1 inch needle is to be used.

Rationale: To provide instructions for calculating % change of PANSS total score for relapses.

9.2.2.2. Relapse Criteria; Attachment 7	Provided detailed instructions for calculating changes in PANSS total score as a criterion of relapse.

Rationale: To clarify the sequence of study procedures to be performed.

Time and Events Schedule	Stated in the footnote that study medication injection must not be given before PK sample collection, and should occur only after all efficacy and safety assessments are completed. It is also recommended that vital sign and ECG assessments be completed before any blood samples are collected.

Rationale: To Clarify the timing of ECG assessments before the first dose of study drug.

Time and Events Schedule; 9.6. Safety Evaluation	Removed the phrase "and up to 72 hours before Visit 2" from the sentence describing the timing of the ECG assessment during the Screening Phase.

Rationale: To clarify the informed consent for the optional pharmacogenomic research and to state DSM-5 diagnostic criteria of schizophrenia will be collected in the eCRF when DSM-5 is released.

9.1.2. Screening Phase; 16.2.3. Informed Consent	• Removed "or refusal" from the text related to the informed consent for pharmacogenomic research for clarity; • Stated that DSM-5 diagnostic criteria of schizophrenia will be collected in the eCRF for each patient when DSM-5 is released in May 2013.

Rationale: Add references related to the biomarker component of the study.

3.2.2. General Design Elements; References	Included references for some reported biomarkers.

Rationale: Minor formatting and edits are made for consistency.

Throughout the protocol	Minor formatting and edits were made for consistency and clarity.

Amendment INT-2 (2 July 2012)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: This amendment is needed primarily to incorporate feedback from the US FDA, resulting in an increase in the number of relapse events at interim analysis and the use of a more stringent error spending function based on the O'Brien-Fleming method. Additionally, telephone contacts between visits are added to monitor for potential impending relapses during the Double-blind Phase per Independent Ethics Committee and/or investigators' feedback. Furthermore, some changes in Exclusion Criteria are made for practical reasons or clarifications. Other minor clarifications will be included in the amendment.

Applicable Section(s)	Description of Change(s)
Rationale: To increase the percentage of relapse events from 50% to 60% (ie, from 35 to 42 relapse events) of the projected target with a critical p value of 0.0101 at the Interim Analysis.	
Synopsis; 3.1. Overview of Study Design; 6. Sample Size Determination; 11.7 Interim Analysis	• Increased the number of relapse events at Interim Analysis from 35 to 42 (ie, increased the corresponding percentage of relapse events from 50% to 60% of the projected 70 relapse events); • The significance level to terminate the study at the Interim Analysis was changed from p=0.0106 to p=0.0101 based on the modified number of relapse events (from 35 to 42) and a more stringent error spending function.
Rationale: To address possible safety concerns and monitor for potential impending relapse events during the Double-blind Phase	
Time & Events Schedule; 3.2.2 General Design Elements; 9.1.5 Double-blind Relapse Prevention Phase	Added telephone contact with patients once every 2 weeks or as needed to monitor for potential impending relapse events during the Double-blind Phase.
Rationale: Text is included to ensure post-study follow-up contact for the surveillance of serious adverse events (SAEs).	
12.3.1 Adverse Events	Added telephone contact to monitor for SAEs after the End-of-Study Visit.
Rationale: To remove wording that is too restrictive or to clarify certain criteria.	
4.2 Exclusion Criteria	• Criterion 3: removed wording related to suicide attempt that is too restrictive; • Criterion 4: Clarified status of patients involuntarily committed to hospital for the current acute episode; • Criterion 23: Clarified the criterion for patients with heart rate less than 50 beats per minute.

Applicable Section(s)	Description of Change(s)
Rationale: To provide more guidance on enrollment of patients who miss a dose of 1-month paliperidone palmitate long-acting injectable (PPIM).	
6. Dosage and Administration	Stated that for a patient who misses a dose of PP1M prior to screening, she/he may still be eligible to enroll in the study, provided the patient is restabilized on the monthly regimen prior to screening and all other inclusion/exclusion criteria are met.
Rationale: To avoid protocol deviations in countries where other dose strengths of tablets of oral lorazepam and insomnia medications may be available.	
8.1 Allowed Concomitant Medication	• Deleted strengths of oral lorazepam tablets; • Deleted strengths of zolpidem, zaleplon, and zopiclone.
Rationale: To clarify the number and timing of and conditions for Patient Stated-choice Preference Survey.	
Time & Events Schedule; 9.5 Exploratory Evaluations	• T & E Schedule, footnote m: stated the number and when Patient stated-choice preference survey should be conducted. • 9.5: clarified when and in what situations the survey should or should not be conducted.
Rationale: As Visit 2 is the first time insulin and C-peptide are measured, their cross-reference to footnote a is not applicable.	
Time & Events Schedule for Clinical Laboratory Test	Removed cross-reference to footnote a from insulin and C-peptide.
Rationale: Clarification so that investigators know that the test is done at a CRO.	
Time & Events Schedule for Clinical Laboratory Test	Clarified urine macro panel in footnote d.
Rationale: To clarify re-initiation of PP1M or other LAI after last injection of study drug.	
10.3 Antipsychotic Therapy After Study Discontinuation or Completion	Stated that PP1M or other LAI antipsychotics should not be reinitiated within 90 days after last study drug injection.
Rationale: To include injection guidelines to guide proper drug administration.	
Attachment 1	• Added Injection Site Guidelines as Attachment 1; • Renumbered other attachments accordingly.
Rationale: To correct errors and clarify instructions**.**	
Attachments 2 and 3 (Attachments 1 and 2, respectively, in INT-1)	Edits and corrections were made.
Rationale: Minor formatting and spelling errors were noted.	
Throughout the protocol	Minor formatting and spelling changes were made.

Amendment INT-1 (27 February 2012)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: This amendment is needed primarily for clarification of how to initiate study drug administration in patients currently on other depot antipsychotics prior to enrollment. Other minor clarifications will be included in the amendment.

Applicable Section(s)	Description of Change(s)
Rationale: To include explicit instructions and clarification for continuation of stable patients receiving the paliperidone palmitate 1-month formulation (PP1M) and for switching from various dose levels of Risperdal CONSTA® and other depot antipsychotics.	
Synopsis; Time and Events Schedule, Footnote e; 3.1. Overview of Study Design; 6. Dosage and Administration	The Day 1 injection of PP1M does not apply to patients who are being switched from another depot antipsychotic or stable patient who are continuing on current treatment with PP1M. Elaborated and clarified recommendations for patients receiving other depot antipsychotics (including PP1M and Risperdal CONSTA) prior to study entry. Added footnote to Table 3 referring to Tables 1 and 2 for stable patients on PP1M and patients who switch from other depot antipsychotics.
Rationale: Because of the dosing instructions for switching included with this amendment, criteria for eligibility of patients receiving a depot antipsychotic prior to the study and for continued treatment of patients after the study were changed.	
3.2.2. General Design Elements; 4.1. Inclusion Criteria	Patients who are taking another LAI antipsychotic prior to study entry must be symptomatically stable in the judgment of the investigator.
4.2. Exclusion Criteria	Deleted criteria "Receiving injection of paliperidone palmitate at the time of current acute episode or within 4 weeks prior to screening" and "LAI antipsychotic within 4 weeks before screening"; stated that patients who are currently unstable with PP1M treatment are not allowed to be enrolled; and stated that other oral antipsychotics should be tapered if necessary. Due to lack of a corresponding dose of PP1M in the stabilization phase, patients currently receiving PP1M doses below 50 mg eq. or above 150 mg eq. will not be eligible for enrollment. Likewise, due to lack of a corresponding dose of PP1M in the stabilization phase, as well as to off-label dosing of Risperdal CONSTA, patients currently receiving Risperdal CONSTA at doses below 25 mg or above 50 mg will not be eligible. Additionally those patients receiving PP1M or Risperdal CONSTA with a nonstandard injection cycle will not be eligible to enroll in the study.
Time and Events Schedule, Footnote s; 8.3. Disallowed Concomitant Medications and Substances; 9.1.2. Screening Phase	Revised rules for disallowed LAI antipsychotics and for washout of prohibited medications.
10.3. Antipsychotic Therapy after Study Discontinuation or Completion	Added guidance on resuming antipsychotic treatment after patients leave the study.

Applicable Section(s)	Description of Change(s)
16.1. Study-specific Design Considerations	Clarified that only patients with a valid reason to discontinue current antipsychotic therapy, including preference for injectable medications with a longer injection interval, are eligible for the study.
Rationale: To exclude patients with dementia-related psychosis from the study, based on Institutional Review Board feedback.	
4.2. Exclusion Criteria	Added dementia-related psychosis as an exclusion criterion.
Rationale: To include double-barrier method as a standard contraceptive measure, and to state that use of contraceptive measures should be in compliance with local regulations.	
4.1. Inclusion Criteria	Revised inclusion criteria related to contraception.
Rationale: Since Visits 6 and 7 are only 1 week apart, the window for Visit 7 should be less than 7 days	
Time and Events Schedule	Changed window for Visit 7 to ±3 days.
Rationale: To add Patient Stated-choice Preference Survey to the Time and Events Schedule as it is one of the clinical assessments**.** To provide more information on the stated-choice preference surveys.	
Synopsis, Exploratory Objectives and Other Evaluations; Time and Events Schedule; 3.2.2. General Design Elements; 9.5. Exploratory Evaluations; 11.5 Exploratory Analysis; 15. Study-specific Materials; 17.6. Data Quality Assurance/Quality Control	Added Patient Stated-choice Preference Survey to Time and Events Schedule. Added more information on how the surveys will be conducted. Added details on how the survey data will be used and analyzed.
Rationale: To correct error in criteria for randomization to double-blind phase.	
4.3.2. Criteria for Randomization to Double-blind Phase	Stated that patients must meet criteria at Visits 9, 10, and 11 to proceed to double-blind phase.
Rationale: To correct error in number of blood samples collected per patient	
9.1.1. Overview, Table 6	Total of 15 samples will be collected per patient for pharmacokinetic analysis and for measurement of prohibited antipsychotics
Rationale: To address logistical difficulties in implementing analyte in a global study.	
Time and Events Schedule for Clinical Laboratory Tests	Removed blood type Rh factor.
Rationale: Investigators will be supplied with materials for urine drug screening.	
15. Study-specific Materials	Added urine drug screen test strip.

Applicable Section(s)	Description of Change(s)
Rationale: T**o a**dd sampling and handling instructions for samples for analysis of prohibited antipsychotics	
Attachment 1; Attachment 2	Revised instructions for collection, handling, and shipping of samples for pharmacokinetic analysis and for screening of prohibited antipsychotics.
Rationale: To clearly indicate that data will only be collected with the IEQ from those patients who have a designated caregiver, to clarify the nature of the caregiver, and to clarify that only designated caregiver data will be analyzed. To provide justification for use of the SF-12®.	
Synopsis, Exploratory Objectives; 2.1. Objectives; 3.2.2. General Design Elements; 4.1. Inclusion Criteria; 9.5. Exploratory Evaluations; 11.5. Exploratory Analyses	Clarified definition of 'designated caregiver' and 'identified support person' for the IEQ. Added statement that descriptive statistics for IEQ will only apply to patients who have designated caregiver. Added statement that SF-12 is included to explore the validity of the IEQ.
Rationale: To clarify that HRUQ data from the study will be provided in a later report.	
2.1. Objectives; 9.5. Exploratory Evaluations; 11.5. Exploratory Analyses; 17.11. Use of Information and Publication	Clarified that reporting of economic analyses will be conducted separately from the study. Removed HRUQ from list of questionnaires for which descriptive statistics will be provided in the Clinical Study Report.
Rationale: To clarify task of study drug administrator.	
5. Treatment Allocation and Blinding	Stated that there will be no restrictions for the study drug administrator to perform other tasks.
Rationale: To include a statement on concomitant therapy with regard to compliance with more restrictive local regulations, where applicable.	
8. Concomitant Therapy	Clarified that concomitant medications should be used that are consistent with local regulations.
Rationale: Revisions made according to updates to protocol template	
16.2.2. Independent Ethics Committee or Institutional Review Board; 17.3. Patient Identification, Enrollment, and Screening Logs; 17.5. Case Report Form Completion	Revised 'Annual Study Report' to 'Development Safety Update Report.' Changed 'assigned number' to 'patient ID and date of birth,' and added that, in cases where the patient is not enrolled in the study, the date seen and date of birth will be used. Revised language to state that all subjective measurements are to be completed by the same individual.
Rationale: Minor formatting and spelling errors were noted.	
Throughout the protocol	Minor formatting and spelling changes were made.

1. OBJECTIVES

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

The secondary objectives of the study are to:

- Evaluate the improvement in the symptoms of schizophrenia as measured by 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 scale (PSP) 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

2. STUDY DESIGN

This is a randomized, double-blind, parallel group, placebo-controlled, multicenter study, designed to determine the efficacy and safety of PP3M, in adults 18 to 70 years of age, who have a Diagnostic and Statistical Manual of Mental Disorders; 4th Edition, Text Revision (DSM-IV-TR) diagnosis of schizophrenia (295.10, 295.20, 295.30, 295.60, and 295.90). Approximately 392 patients are planned to be enrolled in the study, with a maximum of up to 500 patients.

The study consists 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). The double-blind phase will be of variable duration, patients may remain in the study for as long as they are clinically stable. Patients with schizophrenia, who are either stable with safety or tolerability problems with their current medications or are in a state of acute exacerbation and who meet all entry criteria at screening will be enrolled. If necessary,

patients will have their current disallowed psychotropic medications tapered and discontinued during the screening phase.

Screening, washout, and tolerability testing may be conducted while a patient is an inpatient or an outpatient. Patients must not be a danger to themselves or others and symptoms must be sufficiently controlled to be maintained as outpatients after discharge from the hospital.

After enrollment, there will be 3 treatment phases: the Transition Phase, the Maintenance Phase and the Double-blind Phase. In the transition phase, all patients will receive PP1M for 92 days. Patients who are not switching from other LAI antipsychotics will receive the first injection of 150 mg eq. on Day 1 and the second injection of 100 mg eq. on Day 8, both in the deltoid muscle. The injection on Day 36 and on Day 64 may be given in either the deltoid or gluteal muscle and will be flexibly dosed (50, 75, 100, or 150 mg eq.). At Day 92, patients will receive the dose of PP1M that was administered at Day 64. A change in dose from Day 64 to Day 92 will lead to withdrawal from the study. Those patients who complete the transition phase and who meet the prospectively defined criteria will enter the maintenance phase. On Day 120 (Week 17), patients will receive a single injection of PP3M [using a 3.5-fold multiple of the dose received on Day 92]. Patients who meet specific stabilization criteria will enter the double-blind phase at Week 29. Patients will be randomly assigned, in a 1:1 ratio, to receive either a fixed dose of PP3M or placebo. Patients assigned to PP3M in the double-blind phase will receive the same dose of study drug that was administered on Day 120 of the maintenance phase; the dose will remain fixed throughout the double-blind phase. The randomized withdrawal of treatment design used in this phase is intended to evaluate treatment effects and assess whether, after symptom stabilization with PP1M and continuation with PP3M, a difference in the course of the disease is engendered by discontinuation of treatment with paliperidone palmitate. Patients will remain in the double-blind phase until they experience a relapse event (based on prospectively defined criteria), meet discontinuation/withdrawal criteria, or predefined study conclusion criteria are reached.

A group sequential design will be utilized in this study with one interim analysis for efficacy. The interim analysis is planned when at least 42 relapse events are obtained in the Relapse Prevention phase. An independent data monitoring committee (IDMC) will be utilized to

independently review the blinded efficacy and safety data. The IDMC will 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. Based upon the recommendation from the IDMC, the sponsor may decide to terminate the study and PP3M will be declared superior to placebo in delaying relapse. Otherwise the study will continue until a total of 70 relapse events are obtained, at which time the study will be terminated and a final analysis will be performed. All patients will be discontinued from the study at the time of study termination and referred to the routine care of their personal physician.

Blood samples will be collected from all patients enrolled for population PK analysis to further explore the PK of PP3M. The total approximate volume of blood to be drawn for laboratory evaluations, and PK sampling throughout this study is approximately 290 mL for each patient.

A diagram of the study design is provided in Figure 1.

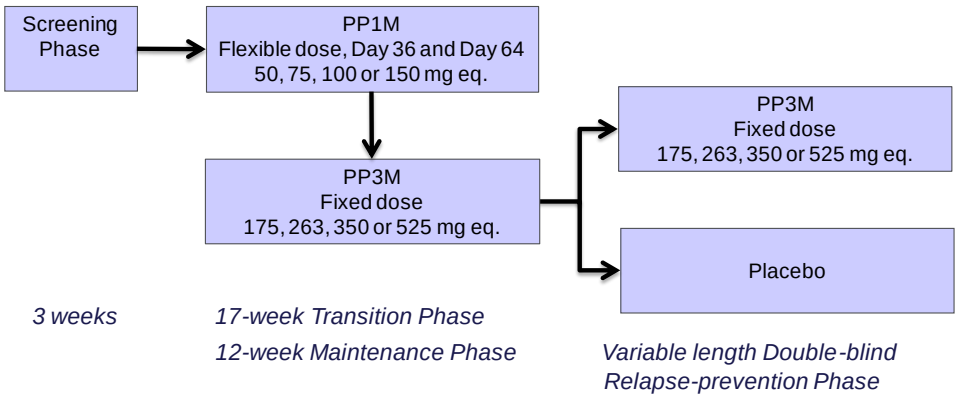

Figure 1: Study flowchart

3. PATIENT SELECTION

The inclusion and exclusion criteria for enrolling patients in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the appropriate sponsor representative before enrolling a patient in the study.

Patients who have met the inclusion and exclusion criteria will be enrolled in this study (planned enrollment of 392 patients, with a maximum of up to 500 patients).

3.1. Inclusion Criteria

Each potential patient must satisfy all of the following criteria to be enrolled in the study:

1. Men or Women 18 (or the legal age of consent in the jurisdiction in which the study is taking place) to 70 years of age, inclusive

2. Must have a valid reason to discontinue current antipsychotic therapy (including insufficient efficacy with current therapy, safety or tolerability issues, or patient preference for injectable medications)

3. Women patients must be postmenopausal for at least 2 years, surgically sterile, or practicing or agree to practice an effective method of birth control if they are sexually active before entry and throughout the study. Effective methods of birth control include intrauterine devices (coils), depot injection of gestagen, subdermal implantation, hormonal vaginal ring, transdermal depot patches, and double-barrier method (eg, condom, diaphragm, or cervical cap, with spermicidal foam, cream, gel, or suppository). Oral contraceptives should contain at least 20 μg of estrogen and should not be used as the only method of birth control. Women of childbearing potential must have a negative serum pregnancy test result at screening, and have a negative urine pregnancy test result at baseline, before receiving the first dose of study drug. Women of child-bearing potential included in the study must continue to use one of the above-mentioned contraceptive methods for a minimum of 6 months after her last injection of study medication. Contraceptive measures should be used that are consistent with local regulations regarding use of birth control methods for patients participating in clinical studies

4. Men patients must agree to use a double-barrier method of birth control (eg, condom, diaphragm, or cervical cap, with spermicidal foam, cream, gel, or suppository) and to not donate sperm during the study and for 6 months after receiving the last dose of study drug

5. Signed an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study. Note: It is acceptable to have additional signatures if required by local regulations

6. Fluent in the language of the investigator and study staff (including raters)

7. Able and willing to meet or perform study requirements (eg, answer self-administered questionnaires). If a patient is unable to read the questions, study personnel may read documents and the patient may then mark his/her choice

8. Have an identified support person (eg, family member, social worker, caseworker, or nurse) considered reliable by the investigator in providing support to the patient to ensure compliance with study treatment, outpatient visits, and protocol procedures, including alerting trial staff to any signs of impending relapse

9. Met diagnostic criteria for schizophrenia according to DSM-IV-TR (disorganized type [295.10], catatonic type [295.20], paranoid type [295.30], residual type [295.60], or undifferentiated type [295.90]) for at least 1 year before screening

10. Have a total PANSS score of <120 at screening and baseline (Day 1)

11. Body mass index (BMI) (weight/height^2 [kg/m^2]) of $\geq$ 17.0 at screening

12. Must have a stable place of residence for the previous 3 months prior to screening and for the foreseeable future

13. Be medically stable on the basis of a physical examination at baseline, and medical history, vital signs, and 12 lead electrocardiogram (ECG) performed at screening

14. Be medically stable on the basis of clinical laboratory tests performed at screening. If the results of the clinical laboratory tests are outside the normal reference ranges, the patient may be included only if deemed clinically not significant by the investigator. This determination must be recorded in the patient's source documents

15. Patients who are taking another LAI antipsychotic (including PP1M or Risperdal CONSTA) prior to study entry must be symptomatically stable in the judgment of the investigator.

3.2. Exclusion Criteria

Any potential patient who meets any of the following criteria will be excluded from participating in the study:

1. A primary, active DSM-IV-TR Axis I diagnosis other than schizophrenia, eg, dissociative disorder, bipolar disorder, major depressive disorder, schizoaffective disorder, schizophreniform disorder, autistic disorder, primary substance-induced psychotic disorder

2. A DSM-IV-TR diagnosis of active substance dependence within 6 months before screening (nicotine and caffeine dependence are not exclusionary)

3. Attempted suicide within 12 months before screening or are at imminent risk of suicide or violent behavior as clinically assessed by the investigator.

4. Involuntarily committed to psychiatric hospitalization at the time of screening. If a patient was involuntarily committed to hospital for the current acute episode, the status of the patient must no longer require involuntary hospitalization and he/she must have agreed to voluntary hospitalization for at least 48 hours before screening.

5. Relevant history or current presence of any significant or unstable cardiovascular, respiratory, neurological (including seizures or significant cerebrovascular), renal, hepatic, hematologic, endocrine (including uncontrolled or insulin dependent diabetes mellitus), morbid obesity (BMI >40 kg/m^2), immunologic or other systemic disease, encephalopathic syndrome, mental retardation, risk factors for prolonged QT interval, torsade de pointes or sudden cardiac death

6. Biochemistry, hematology, ECG or urinalysis results that are not within the laboratory's normal reference range and are deemed to be clinically significant by the investigator

7. History or evidence of clinically significant hepatic disease [including aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2 times the upper limit of normal] at screening

8. History of neuroleptic malignant syndrome (NMS) or tardive dyskinesia

9. For women, pregnancy, breast-feeding, or planning to become pregnant while enrolled in this study or within 6 months after her last injection of study medication

10. History of any malignancy within the previous 5 years, with the exception of basal cell carcinomas

11. History of treatment resistance as defined by failure to respond to 2 adequate trials with adequate doses of different antipsychotic medications (an adequate trial is defined as a minimum of 4 weeks at a maximum dosage)

12. Clozapine use in the last 2 months for treatment resistant or treatment refractory disease

13. Exposure to an experimental drug, experimental biologic, or experimental medical device within 30 days before screening OR participation in 2 or more interventional clinical trials (where trial medication was dispensed) in the year prior to screening

14. Known or suspected hypersensitivity or intolerance to risperidone, paliperidone, 20% Intralipid, or any of their excipients (eg, soybean oil, egg yolks, phospholipids, and glycerol)

15. History of life-threatening allergic reaction to any drug

16. Patients with known or suspected Stevens Johnson Syndrome after exposure to phenytoin, carbamazepine, barbiturates, or lamotrigine

17. For patients requiring oral tolerability testing: history of any severe pre-existing gastrointestinal narrowing (pathologic or iatrogenic) or inability to swallow oral paliperidone ER tablets whole with the aid of water

18. History of disallowed therapies:

    - Electroconvulsive therapy (ECT) with 60 days before screening
    - Nonselective/irreversible monoamine oxidase inhibitors (MAOI) antidepressants within 30 days before screening
    - Other antidepressants unless at a stable dosage for 30 days before screening (If the dosage has been stable for less than 30 days and the patient does not require the

antidepressant, it can be washed out by the baseline visit; if the dosage has been stable for less than 30 days and the patient requires antidepressant treatment, the patient should not be included in this study)

- Other oral antipsychotics (including oral tolerability testing) should be tapered if necessary and washed out during screening. Washout must be arranged so that the last dose of antipsychotic is given by Day -1
- Mood stabilizers, including lithium, valproic acid, topiramate, carbamazepine, and lamotrigine, should be tapered and washed out during screening. Washout must be arranged so that the last dose is given by Day -1
- Other prescription, over-the-counter, or herbal agents with psychoactive properties should be tapered and washed out such that the last dose is given by Day -1
- Patients receiving PP1M at doses <50 mg eq. or >150mg eq.
- Patients receiving PP1M with a nonstandard injection cycle (3 weeks, 5 weeks, etc)
- Patients receiving Risperdal CONSTA at doses <25 mg or >50 mg
- Patients receiving Risperdal CONSTA with a nonstandard injection cycle (1 week, 3 weeks, etc)

19. Unable to provide their own consent

20. Previously participated in this study

21. Employees of the investigator or study center, with direct involvement in the proposed study or other studies under the direction of that investigator or study center, as well as family members of the employees or the investigator

22. History or presence of circumstances that may increase the risk of the occurrence of torsade de pointes or sudden death in association with the use of drugs that prolong the QTc interval, including

    - Heart rate <50 beats per minute, based on at least 2 measurements of supine pulse at screening or baseline. (Resting heart rate should be measured for a full minute.)

- Demonstration of repeated prolonged QTc Fridericia interval >450ms, as measured on more than one ECG (either during screening, or from prior medical record)
- The following cardiac conditions: sick sinus syndrome, complete atrioventricular block, congestive heart failure, polymorphic ventricular tachycardia
- Clinically relevant hypocalcemia, hypokalemia or hypomagnesemia
- Concomitant use of drugs that prolong the QTc interval (including Class IA (eg, quinidine, procainamide) or Class III (eg, amiodarone, sotalol) antiarrhythmic medications)
- Presence of congenital prolongation of the QT interval (Romano-Ward Syndrome, Jervell and Lange-Nielsen syndrome)

23. Patients with a history of no response to risperidone or paliperidone when psychotic or acutely psychotic. Lack of response is defined as patients who have had (at least twice) a documented medical history of no clinical response, despite adequate doses and durations of treatment, or the inability to tolerate effective doses

24. A diagnosis of dementia-related psychosis

25. Currently unstable with recent or current treatment with PP1M.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a patient's status changes (including laboratory results) after screening but before first dose of study drug is given such that they now no longer meet all the criteria, they should be excluded from participation in the study.

3.3. Criteria for Maintenance and Double-blind Phases

Patients who do not meet the predetermined criteria as defined below will be discontinued from the study, undergo End-of-Study/Early Withdrawal visit procedures, and treated according to an accepted standard of care.

3.3.1. Criteria to Enter Maintenance Phase

After treatment with open-label paliperidone palmitate (PP1M) during the transition phase, patients must have a PANSS total score <70 at Visit 8 (Week 17) to enter the maintenance phase.

3.3.2. Criteria for Randomization to Double-blind Phase

Each potential patient must satisfy all of the following clinical stability criteria to be randomized into the double-blind phase of the study:

- A score of <70 in the PANSS total score
- Scores of ≤4 for PANSS items P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), P6 suspiciousness/persecution), P7 (hostility), G8 (uncooperativeness) and G14 (poor impulse control).

Patients must meet each of the criteria at Visits 9, 10, and 11 (Weeks 21 through 29) to proceed to the double-blind phase.

4. DOSAGE AND ADMINISTRATION

For the tolerability testing, oral tablets will be given to patients, who will self-administer the medication if they are outpatients at the time of tolerability testing. The oral tablets will be administered by study staff to patients if they are inpatients. The study drug administrator will administer the injectable study drug at the study site.

4.1. Paliperidone Tolerability Test

For those patients without documented tolerability to oral or injectable risperidone or paliperidone, paliperidone ER 6 mg tablets will be administered for 4 to 6 consecutive days. Tolerability testing will occur during the screening phase (the last dose to be taken by Day -1) and may be concurrent with any required washout.

Patients must be instructed not to chew, divide, dissolve, or crush the study medication (as this may affect the release profile).

The oral tolerability test will allow the investigator to rule out problems with tolerability and allergic or hypersensitivity reactions that may be related to paliperidone. Examples of problems that would lead to exclusion of the patient would include intolerable sedation, clinically symptomatic orthostatic hypotension, torticollis or other severe extrapyramidal side effects, or evidence of an allergic reaction.

Documentation of oral tolerability may include medical or pharmacy records, a letter from a previous provider, or a written statement by the investigator of a credible report from the patient, patient's identified support person that must be documented in the source documents.

4.2. Patients Receiving Other Depot Antipsychotics Prior to Study Entry

Patients who are taking another depot antipsychotic will be permitted to enter this study as long as all other criteria are met. Although it is not the intent of this study to remove stable patients from a therapeutic medication regimen solely for the purposes of entering this study, patients receiving current or recent treatment with PP1M will be allowed to enter the study as described below (Table 1). If a patient is currently stable on PP1M, 4 weeks should elapse from the time of the last injection to the Day 8 injection of PP1M. Such patients would then receive the next PP1M injection on Day 36. Patients receiving PP1M who are symptomatically unstable would normally require a dose adjustment or a switch to a different medication regimen, and should not be enrolled.

In patients who are switching to PP1M from oral antipsychotics, the normal method for switching involves a 2-dose initiation sequence. This 2-dose initiation sequence is not recommended for patients who are switching from another LAI antipsychotic, including Risperdal CONSTA. For such patients, a full injection cycle must elapse between the time of the last depot injection and the first dose of PP1M. Therefore, the first dose of PP1M for patients who are switching from a LAI antipsychotic will be given on Day 8. The second dose of PP1M should be administered on Day 36. Details of the dosing administration schedule during the open-label transition phase for patients on other LAI antipsychotics at enrollment are described below and summarized in Table 2.

4.2.1. Stable Patients Continuing on PP1M at Study Entry

If a patient is receiving PP1M (injection cycle of 4 weeks), then 4 weeks should elapse from the time of the last PP1M injection (on Day -21) to the Day 8 injection of PP1M. Patients currently stable on PP1M at study entry may receive their first injection of PP1M (at Day 8) in either the deltoid or gluteal muscle. Such patients would then receive the next PP1M injection on study Day 36 (skipping the Day 1 dose of PP1M). Note that only clinically stable patients currently treated with PP1M 50, 75, 100, or 150 mg eq. every 4 weeks may be enrolled in the study. If a

patient is clinically unstable while receiving current or recent treatment with PP1M, the patient should not be enrolled in the study. Patients currently receiving PP1M doses of < 50 mg eq. or > 150 mg eq. will not be eligible for enrollment in the study due to lack of a corresponding PP1M dose in the stabilization phase. Additionally, those patients receiving PP1M with a nonstandard injection cycle (3 weeks, 5 weeks, etc) will not be eligible to enroll in the study. If a dose of PP1M is missed prior to screening, it may still be possible to enroll the patient in the study, provided that the patient is restabilized on the monthly regimen prior to screening, and all other inclusion/exclusion criteria are met.

Table 1 provides a guide for patients continuing on PP1M at a prestudy stable dose during the open-label transition phase of the study.

Table 1. Medication Administration Schedule During Open-Label Phase for Stable Patients Continuing on PP1M at Study Entry

Visit	1	2	3	4	5	6
Study Day	-21	1	8	36	64	92
	Last dose of PP1M					
	PP1M 50 mg eq.	Skip	PP1M 50 mg eq. (D/G)	PP1M 50-150 mg eq. (D/G)	PP1M 50-150 mg eq. (D/G)	Same as Visit 5 (Week 9)
	PP1M 75 mg eq.	Skip	PP1M 75 mg eq. (D/G)	PP1M 50-150 mg eq. (D/G)	PP1M 50-150 mg eq. (D/G)	Same as Visit 5 (Week 9)
	PP1M 100 mg eq.	Skip	PP1M 100 mg eq. (D/G)	PP1M 50-150 mg eq. (D/G)	PP1M 50-150 mg eq. (D/G)	Same as Visit 5 (Week 9)
	PP1M 150 mg eq.	Skip	PP1M 150 mg eq. (D/G)	PP1M 50-150 mg eq. (D/G)	PP1M 50-150 mg eq. (D/G)	Same as Visit 5 (Week 9)

D/G denotes deltoid or gluteal muscle. PP1M denotes paliperidone palmitate 1 month formulation.

4.2.2. Patients Switching from Risperdal CONSTA

If a patient is receiving Risperdal CONSTA (injection cycle of 2 weeks), then 2 weeks should elapse from the time of the last Risperdal CONSTA injection (on Day -7) to the Day 8 injection of PP1M. This patient would then receive the next PP1M injection on study Day 36 (skipping the Day 1 dose of PP1M). Note that only clinically stable patients currently treated with Risperdal CONSTA 25 mg, 37.5 mg, or 50 mg every 2 weeks may be enrolled in the study. If a patient is clinically unstable while currently receiving Risperdal CONSTA, the patient should not be enrolled in the study.

Table 2 provides a guide for switching from Risperdal CONSTA to PP1M during the open-label transition phase of the study. Patients currently receiving Risperdal CONSTA doses of <25 mg or >50 mg will not be eligible for enrollment in the study due to lack of a corresponding PP1M dose in the stabilization phase. Additionally, those patients receiving Risperdal CONSTA with a nonstandard injection cycle (1 week, 3 weeks, etc) will not be eligible to enroll in the study.

4.2.3. Patients Switching from Other LAI Depots

For patients switching from other LAIs, a full injection cycle must elapse before receiving the first dose of PP1M. For example, a patient receiving a LAI with a 4-week cycle (eg, haloperidol decanoate) should have 4 weeks elapse from the time of the last prior depot injection to the Day 8 injection of PP1M. For patients switching from depot antipsychotics other than Risperdal CONSTA, the Day 8 injection of PP1M will be an initiation dose of 150 mg eq. This patient would then receive the next PP1M injection on study Day 36 (skipping the Day 1 dose of PP1M). Table 2 provides details on switching from other antipsychotics to PP1M during the open-label transition phase of the study.

Table 2. Medication Administration Schedule During Open-Label Phase for Patients Switching from Other LAIs, Including Risperdal CONSTA

4-Week Injection Cycle						
Visit	1	2	3	4	5	6
Study Day	-21	1	8	36	64	92
	Last dose of previous LAI	Skip	PP1M 150 mg eq. (D)	PP1M 50-150 mg eq. (D/G)	PP1M 50-150 mg eq. (D/G)	Same as Visit 5 (Week 9)
3-Week Injection Cycle						
Study Day	-14	1	8	36	64	92
	Last dose of previous LAI	Skip	PP1M 150 mg eq. (D)	PP1M 50-150 mg eq. (D/G)	PP1M 50-150 mg eq. (D/G)	Same as Visit 5 (Week 9)
Risperdal CONSTA (2 Week Injection Cycle)						
Study Day	-7	1	8	36	64	92
Risperdal CONSTA 25 mg	RC 25 mg	Skip	PP1M 50 mg eq. (D)	PP1M 50-150 mg eq. (D/G)	PP1M 50-150 mg eq. (D/G)	Same as Visit 5 (Week 9)
Risperdal CONSTA 37.5 mg	RC 37.5 mg	Skip	PP1M 75 mg eq. (D)	PP1M 50-150 mg eq. (D/G)	PP1M 50-150 mg eq. (D/G)	Same as Visit 5 (Week 9)
Risperdal CONSTA 50 mg	RC 50 mg	Skip	PP1M 100 mg eq. (D)	PP1M 50-150 mg eq. (D/G)	PP1M 50-150 mg eq. (D/G)	Same as Visit 5 (Week 9)
Other LAIs (2 Week Injection Cycle)						
Study Day	-7	1	8	36	64	92
	Last dose of previous LAI	Skip	PP1M 150 mg eq. (D)	PP1M 50-150 mg eq. (D/G)	PP1M 50-150 mg eq. (D/G)	Same as Visit 5 (Week 9)
1-Week Injection Cycle						
Study Day		1	8	36	64	92
		Last dose of previous LAI	PP1M 150 mg eq. (D)	PP1M 50-150 mg eq. (D/G)	PP1M 50-150 mg eq. (D/G)	Same as Visit 5 (Week 9)

D denotes deltoid muscle. D/G denotes deltoid or gluteal muscle. LAI denotes long-acting injectable. PP1M denotes paliperidone palmitate 1 month formulation. RC denotes Risperdal CONSTA.

4.3. Overview of Study Drug Administration

An overview of the dosing administration schedule in the transition, maintenance and double-blind phases of the study is provided in Table 3.

Table 3. Dosing Administration Schedule

	Transition Phase					Maintenance Phase			Double-blind Phase			
Visit	2	3	4	5	6	8	9	10	11	12	13	Every
Day	1*	8*	36	64	92	120	148	176	204	232	260	12 weeks
PP1M Dose	150 mg eq.	100 mg eq.	50-150 mg eq.	50-150 mg eq.	50-150 mg eq.	--	--	--	--	--	--	--
Muscle	D	D	D or G	D or G	D or G	D or G			D or G			D or G
Flexible or Fixed	Fixed	Fixed	Flexible	Flexible	Fixed†	Fixed‡	--	--	Fixed‡	--	--	Fixed‡
PP3M/ Placebo Dose	--	--	--	--	--	X	--	--	X	--	--	X

*Refer to Table 1& 2 respectively, for patients who are stable on PP1M at study entry and for patients who are switching from other depot antipsychotics
†Dose on this visit should be the same as given on Visit 5 (Day 64)
‡The dose of PP3M given will be a 3.5-fold multiple of the PP1M dose given on Visit 6 (Day 92)
D denotes deltoid muscle. G denotes gluteal muscle. PP1M denotes=paliperidone palmitate 1 month formulation. PP3M denotes paliperidone palmitate 3 month formulation.

4.3.1. Dose during Transition Phase

During the transition phase, all patients will receive PP1M injections. All patients who are not switching from other depot antipsychotics will receive the first injection of 150 mg eq. on Day 1 and the second injection of 100 mg eq. on Day 8, both in the deltoid muscle. Patients may be flexibly dosed on Days 36 and 64 with doses of 50, 75, 100, or 150 mg eq. At Day 92, patients are to receive the dose of PP1M that was administered at Day 64. The choice of the dose to be administered at Days 36 and 64 will be based on the severity of the patient's symptoms, safety and tolerability issues, and previous dose levels of antipsychotic medication needed to keep symptoms under control. After injection of PP1M on Days 1 and 8, subsequent doses can be administered in either the deltoid or gluteal muscle.

4.3.2. Dose during Maintenance Phase

During the 12-week maintenance phase, patients will receive a dose of PP3M that is a 3.5-fold multiple of the final PP1M dose administered on Day 92. During this phase, a single dose of PP3M will be administered on Day 120. The dosing conversion between PP1M and PP3M doses should be based upon that provided in Table 4.

Table 4. Conversion Between PP1M Dose and PP3M Doses Using 3.5-Fold Multiple

PP1M Dose (mg paliperidone palmitate)	PP1M Dose (mg eq. paliperidone)	PP3M Dose (mg paliperidone palmitate)	PP3M Dose (mg eq. paliperidone)
78 mg	50 mg eq.	273 mg	175 mg eq.
117 mg	75 mg eq.	410 mg	263 mg eq.
156 mg	100 mg eq.	546 mg	350 mg eq.
234 mg	150 mg eq.	819 mg	525 mg eq.

PP1M denotes paliperidone palmitate 1 month formulation. PP3M denotes paliperidone palmitate 3 month formulation.

4.3.3. Dose during Double-blind Relapse Prevention Phase

During the double-blind phase, patients will receive fixed dose injections of either PP3M or placebo (20% Intralipid solution) every 3 months. The dose range for PP3M will be 175, 263, 350, or 525 mg eq. Patients assigned to PP3M in the double-blind phase will receive the same dose of study drug that was administered on Day 120 of the maintenance phase. Dosing during the double-blind phase will be fixed. Changing of the dose during the double-blind phase will not be allowed. Supplementation with oral antipsychotics will also not be allowed. The selected muscle for injection will alternate between the left and the right sides. The injection site may be changed (between deltoid and gluteal muscles) at the investigator's discretion if needed to mitigate local tolerability concerns.

Injection Guidelines

It is critical to shake the syringe vigorously for 15 seconds before administration.

Needle Size

For deltoid injections, it is required that a 1.5 inch needle be used for patients ≥200 lb (90 kg). For patients <200 lb (90 kg), a 1 inch needle is to be used.

For gluteal injections all injections should be administered with a 1.5 inch needle (regardless of a patient's weight).

4.4. Concomitant therapy

All medications (prescriptions, over-the-counter, herbal remedies) continued at the start of the study or started during the study and different from the study drug must be documented in the Concomitant Drug/Therapy section of the eCRF.

The medical monitor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

For any concomitant medication given as a treatment for a new or worsening condition, the condition must be documented in the Adverse Event (AE) section of the eCRF.

Concomitant medications should be used that are consistent with local regulations regarding use of concomitant therapy for patients participating in clinical studies.

4.4.1. Allowed Concomitant Medication

The following psychotropic medications and pain medications are allowed during this study:

- Medications for general medical conditions if not listed under "Disallowed and Discouraged Concomitant Medications and Substances" below
- It is recommended that anti-parkinsonian medication be tapered to discontinuation during the screening phase. If extrapyramidal symptoms (EPS) emerge or worsen during the study, the investigator may initiate anti-parkinsonian treatment. The antiparkinsonian medications that are allowed are: trihexyphenidyl, benztropine, biperidin, or other antihistamines with anticholinergic properties. At each subsequent visit, the investigator should determine whether continuation of anti-parkinsonian therapy is required
- It is recommended that beta-blocker treatment for akathisia be tapered to discontinuation during the Screening Phase. If akathisia emerges or worsens during the study, the investigator may initiate treatment with a beta-blocker. At each subsequent visit, the investigator should determine whether continuation of the beta-blocker is required
- Up to 6 mg/day oral lorazepam may be used for agitation or anxiety. This is the preferred benzodiazepine due to its low potential for drug-drug interactions and relatively short half-life. If lorazepam is unavailable, another equivalent benzodiazepine may be used (prespecified). Investigators are encouraged to use the lowest dose of benzodiazepine

clinically necessary. If clinically needed, an injectable (i.m. or i.v.) dose of lorazepam may be given through Week 4.

Use of benzodiazepine doses higher than those prespecified must be approved by the medical monitor prior to dose increase. Use of benzodiazepine is prohibited within 8 hours of a scheduled efficacy assessment or rating scale.

- For insomnia or sleep related difficulties, zolpidem, zaleplon, or zopiclone may be used. The frequency of dosing should not exceed once daily and should not be given for more than 10 consecutive days without reassessment. Use of any of these hyponotic agents is discouraged within 8 hours of a scheduled efficacy assessment or rating scale.
- Antidepressant use (except nonselective/irreversible MAOIs) will be allowed during the study if the patient has been taking a stable dosage for 30 days before entering the study. Changes in the dosage or initiation of antidepressant medication should be minimized during the study and any action should be discussed with the medical monitor.

4.4.2. Allowed Psychotherapy/Psychoeducation

All forms of psychosocial therapy and education are allowed. However, individual psychotherapy should not be performed by clinicians administering any study procedures.

4.4.3. Disallowed Concomitant Medications and Substances

All of the following medications are prohibited during the study. They must be tapered and washed out during the screening phase and the washout arranged so that the last dose is administered by Day -1.

- All oral antipsychotics (including paliperidone ER tablets given for oral tolerability) may be given only through Day -1
- All LAI antipsychotics are prohibited during the study, with the exception of those for patients switching from a LAI antipsychotic with a 1-week cycle, as described in Table 2. These patients will be allowed to receive an LAI injection on Visit 2 (Day 1) only, and any further administration of LAI antipsychotics thereafter is prohibited

- Mood stabilizers including lithium, valproate, carbamazepine, phenytoin, gabapentin, and other antiepileptics
- Antidepressants not taken at a stable dosage for 30 days before screening, and all nonselective/irreversible MAOIs
- Any prescription, herbal, or over-the-counter agents with psychotropic actions, including any substances with stimulant and cognitive-enhancing properties

4.4.4. Discouraged Concomitant Medications and Substances

- Alcohol and illicit substances

5. STUDY EVALUATIONS

5.1. Study Procedures

The time and events schedules summarize the frequency and timing of the various PK, efficacy, safety, and other measurements. Study procedures should be done in the following sequence: ECG, vital signs, PK sample collection, clinical laboratory sample collection, safety and efficacy assessments, and study medication injection.

Since the double-blind phase for this study is of variable duration, it is not possible to calculate an exact total for the volume of blood to be collected during the study. The approximate volume of blood collected for each type of sample is listed in table 5. Blood samples are collected in the double-blind phase every 12 weeks. For every 3 additional months in the double-blind phase, an extra 73 ml of blood will be collected.

Table 5. Volume of Blood to be Collected From Each Patient

Type of Sample	Volume per Sample (mL)	No. of Samples per Patient	Total Volume of Blood (mL)*
Safety (including screening and posttreatment assessments			
Hematology and serum chemistry	19	4	76
Serum β-hCG pregnancy tests	2	1	2
Pharmacokinetic samples	4	15	60
Blood samples for screening of prohibited antipsychotics	4	15	52
Total			190

*Calculated as number of samples multiplied by amount of blood per sample and assuming the patient participates in the double-blind Phase for 6 months; β-hCG=human beta chorionic gonadotropin

5.1.1. Screening Phase

Up to 3 weeks before entry into the transition phase, all patients will undergo screening procedures. Eligibility will be evaluated using informed consent, medical and psychiatric history (including smoking history), clinical and safety assessments (including electrocardiogram (ECGs), Positive and Negative Syndrome Scale (PANSS), EPS scales, vital signs, and clinical laboratory testing), and review of the inclusion/exclusion criteria. If necessary, patients will undergo tapering and washout of disallowed concomitant medication, tolerability testing, or both during this period. Patients not requiring a washout or oral tolerability testing with paliperidone ER may enter directly into the transition phase once all screening procedures are complete and the inclusion/exclusion criteria have been met.

After signed informed consent has been obtained, the inclusion and exclusion criteria will be reviewed to verify the patients' eligibility.

For patients who are outpatients, a screening phase of up to 3 weeks is allowed for completion of all assessments, tapering and discontinuation of prohibited medications, and oral tolerability testing. Hospitalization during screening is allowed if the clinical condition of the prospective patients, in the opinion of the investigator, warrants hospitalization. For inpatients, it is expected that the screening phase will not exceed 10 days, during which time all screening procedures will be conducted. Some patients will also require a washout of psychotropic medication, an oral tolerability test, or both.

Washout Period

Use of any psychotropic medication other than antidepressants at stable dosage and allowed concomitant medication should be tapered and discontinued as clinically indicated, and the patient begun on a washout period which should run concurrently with the screening phase. The final dose of prohibited medications should be given by Day -1, with the exception of patients switching from a LAI antipsychotic as described in Table 2.

Oral Tolerability Test

Before entry into the transition phase, all patients must have source documentation of previous treatment with oral or injectable risperidone or paliperidone. If a patient does not have documented evidence (source documents, medical or pharmacy records, a letter from a previous provider, or a statement in the source documents by the investigator of a credible report from the patient or patient's identified support person), he or she will undergo an oral tolerability test. All details of the oral tolerability testing must be documented in the electronic case report form (eCRF). (Also refer section 4.1).

In addition to a detailed psychiatric history, information regarding DSM-5 diagnostic criteria for schizophrenia will be collected in the eCRF for each patient once the DSM-5 Criteria are released in May 2013.

5.1.2. Transition Phase

At the beginning of the 17-week, open-label transition phase (on Day 1), each patient will have a review of the inclusion/exclusion criteria to confirm eligibility. Safety, efficacy, and other study assessments will be performed as outlined in the Time and Events Schedule-Table 6. Results for all screening assessments performed must be available to the investigator before the first injection of study treatment on Day 1.

Open-label i.m. injections of PP1M will be administered at Day 1, Day 8, Week 5, Week 9, and Week 13.

5.1.3. Maintenance Phase

Patients eligible for the maintenance phase will begin this phase with the Week 17 visit. Safety, efficacy and other assessments will be performed as described in the Time and Events Schedule. An open-label i.m. injection of PP3M will be administered on Day 120. Before use, shake

syringe vigorously for 15 seconds in order to ensure that investigational product is uniformly distributed in the suspension. Patients not meeting the criteria for continuation will discontinue study treatment and have End-of-Study/Early Withdrawal assessments performed as outlined in the Time and Events Schedule.

5.1.4. Double-blind Relapse Prevention Phase

Stable patients who complete the maintenance phase of the study and who meet prospectively defined criteria will be randomized on a 1:1 ratio to receive either a fixed dose of i.m. PP3M or matching placebo. The double-blind phase will begin at Week 29 once patients have received their assigned injection. Patients not meeting the criteria for continuation will discontinue study treatment and have End-of-Study/ Early Withdrawal assessments performed as outlined in the Time and Events Schedule.

Patient visits will be scheduled every 4 weeks beginning with Week 29. Assessments will be completed as indicated in the Time and Events Schedule. In addition, for the purposes of monitoring for impending relapse after Week 29, telephone contacts are recommended between the site and the patient at intervals of every 2 weeks (14 days +/- 4 days) or as needed after the patient's last visit. The study site will keep a record of telephone contacts in the source documents. If a relapse event is suspected, the patient should be fully evaluated (with efficacy assessments documented in the eCRF), and managed accordingly.

Patients with early signs of deterioration will be closely monitored (this may include use of PANSS to assess relapse). If they meet the relapse criteria, they will be considered to have completed the double-blind phase and will complete the End-of-Study visit.

5.2 Efficacy Evaluations

5.2.1. Qualified Rater

Only a qualified rater may administer the PANSS, CGI-S, and PSP scores. If possible, for a given patient, the same rater should administer the scale at all visits.

A qualified rater must be locally licensed to practice, alone or under supervision, in one of the following disciplines:

- Psychiatry (eg, MD, DO), or

- Senior Psychiatry Resident (eg, MD, DO) who fulfills the other requirements, or
- Psychology (eg, Ph.D.), or
- Clinical specialty (at least a Master's degree, eg, MS or Ph.D.) where patient care is a central component (eg, social work, counseling, psychology, nurse practitioner) and the practitioner is independently licensed

In addition, the qualified rater must have had:

- Recent experience in performing PANSS ratings in psychiatry clinical studies
- At least 3 years' experience in evaluating patients with schizophrenia in an inpatient or outpatient setting
- Qualification training in performing PANSS and CGI-S assessments. Raters must be certified by the sponsor to perform the PANSS; and trained by the sponsor to perform the CGI-S
- The sponsor's rater training

5.2.2. Positive and Negative Syndrome Scale for Schizophrenia

The neuropsychiatric symptoms of schizophrenia will be assessed using the 30-item PANSS scale, which provides a total score (sum of the scores of all 30 items) and scores for 3 subscales, the positive subscale (7 items), the negative subscale (7 items), and the general psychopathology subscale (16 items). Each scale is rated 1 (absent) to 7 (extreme). The PANSS assessment should be administered by a qualified and certified rater as previously defined. If possible, for a given patient, the same rater should administer this scale at all visits. The Structured Clinical Interview-PANSS (SCI-PANSS) is mandatory for all assessments and should be maintained in the source documents.

The mini-PANSS consists of items required for assessment of relapse: P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), P6 (suspiciousness/persecution), P7 (hostility) and G8 (uncooperativeness). The mini-PANSS will be administered on scheduled visit days in which the full PANSS is not being administered to assess for potential relapse. The mini-PANSS should also be administered by a qualified rater as previously defined. In instances

when the mini-PANSS meets item score criteria for relapse, the relapse must be confirmed with a full PANSS assessment 3-7 days later. In instances when the mini-PANSS does not meet criteria for relapse, but a relapse is suspected, an unscheduled full PANSS assessment should be completed on the same day. If the full PANSS assessment meets criteria for relapse, the relapse must be confirmed 3-7 days later.

5.2.3. Clinical Global Impression–Severity

The CGI-S rating scale is used to rate the severity of a patient's overall clinical condition on a 7-point scale ranging from 1 (not ill) to 7 (extremely severe). This scale permits a global evaluation of the patient's condition at a given time. The CGI-S assessment should be administered by a qualified rater as previously defined. The individual administering the PANSS should also score the CGI-S.

5.2.4. Personal and Social Performance Scale

The PSP scale assesses the degree of difficulty a patient exhibits over a 7-day period within 4 domains of behavior: a) socially useful activities, b) personal and social relationships, c) self-care, and d) disturbing and aggressive behavior. The results of assessment are converted to a numerical score following the PSP scoring guidelines. The PSP assessment should be administered by a qualified rater as previously defined. Individual domain items of the PSP will be collected and recorded in the eCRF. If possible, for a given patient, the same person should administer this scale each time it is administered.

5.3. Efficacy Endpoints

5.3.1. Primary Efficacy Endpoint

The primary efficacy endpoint will be the time to first relapse event in the double-blind phase. For the primary analysis, time to relapse is defined as the time between randomization to treatment in the double-blind phase and the first documentation of a relapse.

5.3.2. Relapse Criteria

The specific relapse criteria will be defined as 1 or more of the following:

- Psychiatric hospitalization (involuntary or voluntary admission to a psychiatric hospital for decompensation of the patient's schizophrenic symptoms), or
- For PANSS
  - The patient has an increase of 25% in total PANSS score from randomization for 2 consecutive assessments separated by 3 to 7 days if the score at randomization was >40, or
  - The patient has a 10 point increase in the total PANSS score from randomization for 2 consecutive assessments separated by 3 to 7 days if the score at randomization was ≤40, or
- The patient inflicts deliberate self-injury or exhibits violent behavior resulting in suicide, clinically significant injury to him/herself or another person, or significant property damage, or
- The patient has suicidal or homicidal ideation and aggressive behavior that is clinically significant (in frequency and severity) in the investigator's judgment, or
- For PANSS items P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), P6 (suspiciousness/persecution), P7 (hostility), and G8 (uncooperativeness):
  - The patient has a score of ≥5 after randomization for 2 consecutive assessments separated by 3 to 7 days on any of the above items if the maximum score for the above PANSS items was ≤3 at randomization, or
  - The patient has a score of ≥6 after randomization for 2 consecutive assessments separated by 3 to 7 days on any of the above items if the maximum score for the above PANSS items was 4 at randomization.

The date of the relapse will be the date of the first assessment for symptoms of relapse (not the date of confirmation).

5.3.3. Secondary Efficacy Endpoints

Secondary efficacy endpoints will include the change from baseline to endpoint during the double-blind phase in PANSS (total and subscales), CGI-S, and PSP.

5.4. Pharmacokinetics

5.4.1. Evaluations

Venous blood samples of 4 mL, to obtain approximately 2 mL of plasma, will be collected for the determination of plasma concentration of paliperidone.

5.4.2. Analytical Procedures

Plasma samples will be analyzed to determine paliperidone concentrations using a validated, specific, and sensitive (eg, liquid chromatography/dual mass spectrometry [LC-MS/MS]) method by or under the supervision of the sponsor. If deemed necessary to explain the study results, drug concentrations for paliperidone enantiomers, paliperidone palmitate, or other antipsychotics including risperidone may be determined.

5.4.3. Pharmacokinetic Parameters

For patients who completed the trial in the maintenance and double-blind phases, based on the individual plasma concentration-time data using the actual sampling times, the following PK parameters of paliperidone will be estimated for the last PP3M cycle, using non-compartmental analysis:

- $C_{predose}$: plasma concentration measured immediately before the last i.m. injection
- C_{max}: observed maximum plasma concentration after the last i.m. injection
- t_{max}: time to reach the maximum plasma concentration after last the i.m. injection
- AUC_{τ}: area under the plasma concentration-time curve after the last i.m. injection
- $C_{avg, \tau}$: average plasma concentration, calculated as the AUC_{τ} divided by the actual dosing interval
- Peak-to-trough ratio: ratio between the peak and trough plasma concentration after the second and eighth i.m. injection, as defined by ($C_{max}/C_{predose}$).

Other PK parameters (eg, apparent clearance) may be calculated as needed to characterize the PK of PP3M.

Corresponding PK parameters will be calculated for PP1M administered during the transition phase.

5.5. Safety Evaluations

The study will include the following evaluations of safety and tolerability according to the time points provided in the Time and Events Schedule. These evaluations may be done at other times at the discretion of the investigator to assess possible AEs.

Adverse Events

The AEs will be reported from the time a signed and dated informed consent form is obtained until completion of the patient's last study related procedure. The investigator will follow any clinically significant abnormalities persisting at the end of the study until resolution or until a clinically stable endpoint is reached.

Unscheduled Pharmacokinetic Samples for Adverse Events of Special Interest

Since paliperidone from the PP3M product is meant to be delivered over a 3-month period, several AEs would be of concern if instant release of paliperidone from its palmitate ester were to occur. It is recommended that investigators who observe serious or severe AEs of this nature in patients within 72 hours after an injection of study medication collect an unscheduled PK sample for later analysis:

- sedation/somnolence,
- EPS,
- QTc prolongation,
- coma,
- seizure, or
- orthostatic hypotension

Events with a severity rating of "mild" or "moderate" or those AEs that do not meet the criteria for an SAE do not require collection of an unscheduled PK sample. To preserve the treatment blind, the results of this PK sample will not be revealed to the investigator, but will be used by the sponsor in the final safety analysis after database lock.

Clinical Laboratory Tests

Clinical laboratory tests for serum chemistry, metabolic chemistry, hematology, and urinalysis will be collected according to the Time and Events Schedule for Clinical Laboratory Tests. The investigator must review the laboratory report, this review must be documented, and any

clinically relevant changes occurring during the study must be recorded in the AE section of the eCRF. Please refer to the Time and Events Schedule for specific tests to be obtained at each time point. Prolactin levels will not be available to the investigators or the sponsor during the study because knowledge of these levels could cause breaking of the study blind.

Electrocardiograms

The ECGs will be recorded at the times specified in the Time and Events Schedule. Before the first dose of the study drug, a total of 3 ECG tracings will be obtained. Two of these ECGs should be obtained at any time during the screening phase, at least 24 hours apart but the second of these should be before Visit 2. The third ECG should be obtained at the baseline visit (Visit 2). The ECGs throughout the study should be recorded at approximately the same time each day (preferably in a fasted state in the morning).

The 12-lead ECGs will be recorded electronically and intervals measured by a central reader. In addition to ECG interpretation and morphology, other ECG variables to be obtained and recorded are: heart rate (or RR), PR interval, QRS interval, QT interval, QTc intervals, ST wave depression and elevation, T wave, conduction, rhythm, and technical findings. A printout of the ECG recording must be filed in the source document. Any clinically relevant changes that occur during the study must be recorded on the AE form of the eCRF.

Vital Signs

Orthostatic blood pressure and heart rate will be recorded at screening, baseline (Day 1), and as indicated in the Time and Events Schedule.

Physical Examination

Physical examinations will be completed at baseline, Visit 11, and at the End-of-Study visit or upon early study withdrawal. Oral temperature will be measured at each physical examination. Height will be measured at screening only. Body weight and waist circumference will be measured at screening, baseline, and at other times as specified in the Time and Events Schedule.

Pregnancy Tests

A serum human beta chorionic gonadotropin (β-HCG) pregnancy test will be performed for women of childbearing potential at screening, at the End-of-Study visit, or upon early withdrawal from the study. A urine pregnancy test will be performed at the visits indicated on the Time and Events Schedule for Clinical Laboratory Tests.

Abnormal Involuntary Movement Scale

Dyskinesia will be rated according to the Abnormal Involuntary Movement Scale (AIMS). Measurements using AIMS will be performed at screening, baseline, and at all other times indicated in the Time and Events Schedule.

Barnes Akathisia Rating Scale

The Barnes Akathisia Rating Scale (BARS) will be used to detect akathisia. Measurements using BARS will be performed at screening, baseline, and at all other times indicated in the Time and Events Schedule.

Simpson-Angus Rating Scale

Extrapyramidal side effects, in particular parkinsonian symptoms, will be evaluated using the Simpson-Angus Rating Scale (SAS). A measurement using SAS will be performed at screening, baseline, and at all other times indicated in the Time and Events Schedule.

Columbia Suicide Severity Rating Scale

The Columbia Suicide Severity Rating Scale (C-SSRS) is a low-burden measure of the spectrum of suicidal ideation. It can also be used during treatment to monitor for clinical worsening. The C-SSRS will be assessed as indicated in the Time and Events Schedule.

Note: AIMS, BARS, SAS, and C-SSRS assessments may be performed by any trained clinician including physicians, nurse practitioners, and physician's assistants.

Evaluation of the Injection Site and Patient's Assessment of Injection Site Pain

Investigator or sub-investigator will evaluate the site(s) of injection for redness, swelling, and induration, within 30 minutes of each injection and will evaluate the site of the last injection at

the End-of-Study Visit, or upon early withdrawal from the study. The evaluation (0=absent; 1=mild; 2=moderate; 3=severe) will be recorded on the eCRF. Every effort should be made to have the same individual perform all injection site evaluations for a particular patient. All injection site AEs with objective findings (eg, swelling, redness, induration) and a severity assessment of "moderate" or "severe" will be photographed along with a metric ruler for later review. Follow-up photographs should be taken until the AE resolves or until the severity assessment is "mild."

Patients with an AE related to the injection site that involves:

- Suspected cellulitis or abscess should be referred to a dermatologist or surgeon for consideration of incision and drainage procedure along with tissue microbiological samples.
- Nodule, fibroma, furuncle or other non-infectious reaction with a severity assessment of either "moderate" or "severe," should be referred to a dermatologist or surgeon for consideration of fine needle aspiration and/or tissue biopsy.

The investigator will follow any clinically significant abnormalities persisting at the end of the study until resolution or until reaching a clinically stable endpoint.

For local tolerability, there will be an assessment of injection pain by the patient within 30 minutes after each injection using a visual analog scale (VAS) (0 to 100 mm). This patient assessment will be done independently and in a blinded fashion so that the primary investigator is not aware of the assessment.

Table 6. Time and Events Schedule

Period	**Screening**	**Transition**						**Maintenance**			**Double-Blind**									
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	Visits every 4 weeks[a]	Visits every 8 weeks[a]	Visits every 12 weeks[a]	Week 54 PK	Week 55 PK	EOS/ Early WD Visit
Week	-3 to -1		1	5	9	13	14	17	21	25	29	33	37	41						
Day	-21 to -1	1	8	36	64	92	99	120	148	176	204	232	260	288						
Window (days)		NA	± 3	± 7	± 7	± 7	± 3	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	NA
Screening/Administrative Procedures																				
Informed consent	X																			
Psychiatric evaluation	X																			
History [b]	X																			
Inclusion/exclusion criteria	X	X																		
Physical examination		X									X									X
Randomization											X									
Tolerability test [c]	X																			
Study drug administration																				
Administer study medication		X[d,e]	X	X	X	X		X			X			X			X			
Pharmacokinetic Procedures																				
PK Sample collection [f]		X			X	X	X	X	X	X	X	X	X	X	X			X[g]	X[g]	X
Efficacy Procedures																				
PANSS [h]	X	X		X	X	X		X	X	X	X	X	X	X	X					X
Mini PANSS [i]							X											X	X	
CGI-S [h]		X		X	X	X		X	X	X	X	X	X	X	X					X
PSP		X			X			X			X			X			X			X
Healthcare Resource Utilization Questionnaire		X						X			X			X			X			X

Table 6. Time and Events Schedule

Period	Screening	Transition						Maintenance			Double-Blind									
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	Visits every 4 weeks[a]	Visits every 8 weeks[a]	Visits every 12 weeks[a]	Week 54 PK	Week 55 PK	EOS/ Early WD Visit
Week	-3 to -1		1	5	9	13	14	17	21	25	29	33	37	41						
Day	-21 to -1	1	8	36	64	92	99	120	148	176	204	232	260	288						
Window (days)		NA	± 3	± 7	± 7	± 7	± 3	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	NA
Safety Assessments																				
Vital signs[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X
Height	X																			
Temperature		X									X									X
Body weight	X	X				X			X		X			X			X			X
Waist circumference	X	X				X			X		X			X			X			X
Electrocardiogram (ECG)[k]	X	X				X			X					X			X			X
Patient Injection Site Ratings VAS[l]		X	X	X	X	X		X			X			X			X			
Investigator Injection Site Ratings[l]		X	X	X	X	X		X			X			X			X			X
AIMS/BARS/SAS	X	X						X	X	X	X		X			X				X
Clinical Laboratory Tests	X	X									X						X			
Adverse Events[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X
Concomitant Medication	X[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X
Telephone Contact[o]											Every two weeks between Visits (14 days +/- 4 days) or as needed.									

[a] After Visit 14 (Week 41), visits will take place every 4 weeks. Assessments listed for every 12 weeks will be performed at Week 41, Week 53, Week 65, etc. Assessments listed for every 8 weeks will be performed at Week 37, Week 45, Week 53, Week 61, etc. The assessments in these columns will be performed mutually inclusive of each other.
[b] Medical, psychiatric, and medication histories. Smoking history will also be recorded.
[c] Paliperidone ER 6 mg tablets will be given for 4 to 6 consecutive days (last dose must be given by Day –1) to test for paliperidone tolerability in patients without a written, documented history of previous use or exposure to oral risperidone, oral paliperidone, paliperidone palmitate, or 1 dose of i.m. Risperdal CONSTA.

[d] Before the first injection of study medication on Day 1, the results of all screening assessments must be available to the Investigator and washout of prohibited concomitant medication as well as oral tolerability testing must be completed. Before use, shake syringe vigorously for 15 seconds. Please refer to Table 2 & 3 in the protocol for details of study drug administration.
[e] Day 1 injection of PP1M does not apply to patients who are being switched from another depot antipsychotic (including Risperdal CONSTA), or stable patients who are continuing on current treatment with PP1M at enrollment.
[f] Venous samples of 4 mL should be obtained prior to dose administration on each PK day. Unscheduled PK samples may be obtained at the Investigator's discretion for cases of severe or serious adverse events that may be potentially related to unexpected increases in plasma concentrations of study drug.
[g] PK samples should be obtained 10 days (Week 54) and 20 days (Week 55) after study drug injection at Week 53.
[h] In addition to indicated visits, the PANSS and CGI-S should be administered whenever the investigator thinks a patient may be experiencing a relapse event. Note: If any of the PANSS criteria for relapse are exceeded on a given day, the PANSS assessments must be repeated 3-7 days later to confirm a relapse event.
[i] A mini-PANSS consists of items P1, P2, P3, P6, P7, G8, and will be used as screening for potential relapse at the prespecified time points. In instances when the mini-PANSS meets one or more of the item scores criteria for relapse, the relapse must be confirmed with a full PANSS assessment 3-7 days later. In instances when the mini-PANSS does not meet criteria for relapse, but a relapse is suspected, an unscheduled full PANSS assessment should be completed on the same day.
[j] Blood pressure and heart rate will be measured after the patient is supine for 5 minutes and again after the patient is standing for 2 minutes.
[k] A total of 3 ECG tracings will be obtained before the first dose of the study drug. Two of these ECGs should be obtained during the Screening Phase, at least 24 hours apart. The second ECG during the Screening Phase should be scheduled in a timely manner to ensure the cardiologist-read report is available before Visit 2. The third ECG should be obtained at the baseline visit (Visit 2). The ECGs throughout the study should be recorded at approximately the same time each day (preferably in a fasted state in the morning).
[l] To be obtained within 30 minutes of injection. At the EOS, the investigator will rate the site of the final injection.
[m] Adverse events will be collected from the time informed consent is signed until the patient's last study related procedure.
[n] Oral antipsychotics and other disallowed medications should be tapered during the screening period
[o] During the Double-blind Phase of the study, regular telephone contact with the patient and/or identified support person is recommended in between regularly scheduled visits. The optimal timing of the telephone contacts is up to the discretion of the investigator, but is recommended at least once every two weeks.
NOTE: Study medication injection must not be given before PK sample collection, and should occur only after all efficacy and safety assessments are completed. It is also recommended that vital sign and ECG assessments be completed before any blood samples are collected. AIMS denote Abnormal Involuntary Movement Scale. BARS denotes Barnes Akathisia Rating Scale. CGI-S denotes Clinical Global Impression-Severity scale. ; ECG denotes electrocardiogram; EOS denotes end-of-study. NA denotes not applicable. PANSS denotes Positive and Negative Syndrome Scale.PK denotes pharmacokinetic. PSP denotes Personal and Social Performance Scale. SAS denotes Simpson Angus Scale. SF12 denotes Short Form Health Survey; VAS denotes Visual Analog Scale. WD denotes withdrawal.

6. DISCONTINUATION OF TREATMENT

A patient will be withdrawn from the study:

- The investigator believes that for safety reasons (eg, AE) it is in the best interest of the patient to stop treatment
- The patient becomes pregnant
- The patient fails to meet criteria for continuing into the maintenance and double-blind phases (see Section 3.3)
- PK assessment for prohibited antipsychotics indicates a clinically relevant exposure to prohibited medications.
- The investigator believes there is lack of efficacy (transition and maintenance phases only)
- The blind is broken by the investigator
- The patient is lost to follow-up
- The patient withdraws consent
- The sponsor terminates the study

If the patient requires a change in dose from Day 64 to Day 92 of the open-label phase, the patient will be withdrawn from the study.

If a patient is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the patient and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

When a patient withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. End-of-Study/Early Withdrawal visit procedures should be performed. Study drug assigned to the withdrawn patient may not be assigned to another patient. Patients who withdraw will not be replaced.

7. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

7.1. Patient Information

The primary population for efficacy consists of intent-to-treat (ITT) patients for the double-blind phase. For the interim analysis, the ITT population consists of all patients who received at least 1 dose of double-blind study medication at the time of database lock for the interim analysis. If the double-blind phase is not stopped early for efficacy based upon the interim analysis, the ITT population for the final analysis will be defined as all patients who receive at least 1 dose of double-blind study medication during the double-blind phase. All data for patients who receive study medication during the transition and maintenance phases but not during the double-blind phase will be summarized separately.

The primary population for safety consists of all patients who receive at least 1 dose of double-blind medication during the double-blind phase. For the transition and maintenance phases all patients who receive at least one dose of study medication in that phase will be included in the summary of all safety assessments.

7.2. Sample Size Determination

It is assumed that the 12-month relapse rates for PP3M and placebo will be 20% and 40%, respectively, resulting in a relative risk of 0.44. Approximately 196 patients are 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 is significantly different from placebo at the 2-sided significance level of 0.05, with 90% power to detect a relative risk of 0.44. A 2-stage group sequential design with 1 interim analysis will be implemented to allow for early stopping if there is significant evidence of efficacy based upon the interim analysis after 60% (ie, 42 events) of the projected relapse events have occurred. The O'Brien-Fleming boundary (corresponding to the Wang and Tsiatis power boundary with shape parameter 0) will be used for sequential monitoring.

It is assumed that at least 50% of patients who enter the transition phase would either withdraw or not meet the criteria for randomization in the double-blind phase. To meet the expected number of 196 patients (98 per treatment group) to be randomized in the double-blind phase, a total of 392 patients are expected to be enrolled. The total number of patients enrolled will depend on the time that it takes to obtain 70 relapse events. Blinded surveillance of the total number of events in the double-blind phase will be performed during the study to assess the appropriateness of the 50% dropout assumption and the total number of patients enrolled may be increased up to a maximum of 500.

7.3. Efficacy Analyses

7.3.1. Primary and Secondary Analysis

The primary analysis for efficacy will be carried out on the ITT population. The primary efficacy end point for this study is the time between patient randomization into the double-blind phase and the first documentation of a relapse event. Patients who meet at least 1 of the criteria for relapse while on double-blind treatment at the time of study completion for the primary analysis are considered to have had a relapse event. All other patients without a relapse at the end of study (end of double-blind phase) will be considered censored.

The cumulative distribution function of the time to relapse will be estimated by the Kaplan-Meier method. Time to relapse will be summarized (number of events, number of censored patients, median, and 25th and 75^{th} percentile of time to events) and treatment differences will be compared using a 2-sided log-rank test. The estimate of the hazards ratio and its 95% confidence interval will be based on the Cox proportional hazards model.

Treatment comparison between PP3M and placebo for the change from baseline to endpoint of PANSS total score, PSP, and CGI-S during the double-blind phase will be performed using an analysis of covariance 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 will be presented. In addition, descriptive statistics of PANSS, CGI-S, and PSP will be summarized for the transition and maintenance phases.

7.3.2. Interim Analysis

An interim analysis will be conducted after 60% (ie, 42 events) of the projected relapse events have occurred. An IDMC will review the efficacy data and provide recommendations about stopping or continuing the study based on the results of an interim efficacy and safety analysis. An analysis for futility will not be performed. If the result of the interim analysis is significant, and based on the recommendation of the IDMC, the study will be stopped and the interim analysis of the primary efficacy endpoint will be considered the primary result for this study. Succeeding events after the decision to stop will be included in a secondary analysis of the primary efficacy endpoint. If the study is not stopped based upon the interim analysis, it will be continued until all relapse events are obtained, at which time the final analysis will be conducted. Based on the O'Brien-Fleming approach, the interim analysis will be performed at a significance level of 0.0101 and if not terminated, the final analysis performed at the 0.0464 significance level.

7.3.3. Independent Data Monitoring Committee

An IDMC will be established to monitor data on an ongoing basis and will consist of at least one medical expert in the relevant therapeutic area and at least one statistician. The committee will meet periodically to review interim safety data and will meet once to review efficacy data after the interim analysis has been completed. After the review, the IDMC will make recommendations regarding the continuation of the study. The details will be provided in a separate IDMC charter.

7.4. Pharmacokinetic Analyses

Pharmacokinetic analyses will be done by the sponsor or under the authority of the sponsor. Data will be listed for all patients with available paliperidone plasma concentrations from the maintenance and double-blind phases per PP3M dose. Patients will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK parameters (eg, incomplete administration of the study agent; concentration data not sufficient for PK parameter calculation due to missing PK draws at multiple visits; or early discontinuation from the study).

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentation. Concentrations below the lowest quantifiable

concentration will be treated as zero in the summary statistics and for the calculation of PK parameters. All patients and samples excluded from the analysis will be clearly documented in the study report.

For each dosage, descriptive statistics, including arithmetic mean, SD, coefficient of variation, geometric mean, median, minimum, and maximum will be calculated for the paliperidone plasma concentrations at each sampling time. For other demographic and injection-related covariates, as specified in the PK analysis plan, descriptive statistics will also be calculated.

Mean and/or median plasma paliperidone concentration-time profiles will be plotted. Individual plasma concentration-time profiles may also be plotted. Plasma paliperidone concentrations and summary statistics may be presented graphically as scatter plots or box plots to support subgroup or meta-analyses.

For demographic and injection-related covariates, as specified in the PK analysis plan, descriptive statistics of the PK parameters may be calculated.

Population PK analysis of plasma concentration-time data of paliperidone will be performed using nonlinear mixed-effects modeling. Data may be combined with those of a selection of phase 1 studies and studies with PP1M to support a relevant structural model. Available patient characteristics (demographics, laboratory variables, genotypes, etc.) will be tested as potential covariates affecting PK parameters. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report.

7.5. Safety Analyses

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs with onset during the respective treatment phase will be included in the analysis. For each AE, the percentage of patients who experience at least 1 occurrence of the given event will be summarized by treatment group.

Special attention will be given to those patients who discontinue treatment due to an AE or who experience a severe AE or serious AE.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at transition/maintenance phase baseline and double-blind Phase baseline to each scheduled time point in that phase of the study. A listing of patients with any laboratory results outside the reference ranges will be provided. A listing of patients with any markedly abnormal laboratory results will also be provided.

Electrocardiograms

The ECG variables that will be analyzed are heart rate, PR interval, QRS interval, QT interval, and corrected QT (QTc) interval using the following correction methods: QT corrected according to Bazett's formula (QTcB), QT corrected according to Fridericia's formula (QTcF), and QT correction derived by linear regression (QTcLD).

Descriptive statistics of QTc intervals and changes from transition/maintenance phase baseline and double-blind phase baseline will be summarized at each scheduled time point in that phase of the study. The percentage of patients with QTc interval >450 ms, >480 ms, or >500 ms will be summarized, as will the percentage of patients with QTc interval increases from baseline >30 ms or >60 ms.

All important abnormalities in ECG waveform that are changes from the baseline readings will be reported (eg, changes in T-wave morphology or the occurrence of U-waves).

Vital Signs

Change from transition/maintenance phase baseline and double-blind phase baseline in vital signs measurements will be presented descriptively. In addition, a frequency table of the occurrence of orthostatic hypotension will be presented. Orthostatic hypotension is defined as a decrease in systolic (>20 mmHg) or diastolic (>10 mmHg) blood pressure after standing for at least 2 minutes that is associated with an increase in pulse rate of >15 bpm compared with supine measurement.

Extrapyramidal Symptom Scales

The results of the EPS scales (AIMS, BARS, and SAS) will be summarized descriptively at each time point.

Weight and BMI

Change in body weight and BMI from transition/maintenance phase baseline and double-blind phase baseline will be summarized descriptively. The incidence of increases/decreases from baseline ≥7% in body weight will be summarized in a frequency table by treatment group.

Columbia Suicide Severity Rating Scale

Suicide-related thoughts and behaviors based on the C-SSRS scale will be summarized by treatment group in incidence and shift tables.

Injection Site Evaluation

The results of the subjective and objective injection site evaluations will be summarized descriptively at each assessment time point.