Janssen Scientific Affairs, LLC*

Clinical Protocol

A Prospective, Matched-Control, Randomized, Open-Label, Flexible-Dose, Study in Subjects with Recent-Onset Schizophrenia or Schizophreniform Disorder to Compare Disease Progression and Disease Modification Following Treatment with Paliperidone Palmitate Long-Acting Injection or Oral Antipsychotics

Disease Recovery Evaluation and Modification (DREaM) Study

Protocol R092670SCH3013; Phase 3b
AMENDMENT 2

R092670 (paliperidone palmitate)

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This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

Status:	Approved
Date:	2 November 2017
Prepared by:	Janssen Scientific Affairs, LLC
EDMS no:	EDMS-ERI-89097435, 3.0

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	28 January 2015
Amendment 1	7 June 2017
Amendment 2	02 November 2017

Amendments are listed beginning with the most recent amendment.

Amendment 2 (2 November 2017)

This amendment is considered 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 is to allow for additional dose titration using PP1M in subjects who are not responding adequately to the PP3M dose administered.

Applicable Section(s)	Description of Change(s)
Rationale: Allow for additional dose titration using PP1M in subjects who are not responding adequately to the PP3M dose administered.	
Synopsis, Time and Event Schedule and footnotes, Section 3.1, 3.2.2, 16.1; Figure 1 footnote.	Added text: "For optimal management of symptoms/tolerability, subjects receiving PP3M (during either Part II or Part III) may go back to treatment with PP1M (monthly injections of 78, 117, 156 or 234 mg, flexibly dosed) for further dose adjustment or for the duration of the trial with the approval of the medical monitor." (to improve achieving an appropriate paliperidone palmitate dose)
Rationale: Clarification of protocol conduct (nonsubstantial)	
Throughout the protocol	Minor grammatical, formatting, spelling changes, etc

Amendment 1 (7 June 2017)

This amendment is considered 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 is to make the possible treatments during the run-in phase consistent with labeling instructions for paliperidone palmitate and to improve the overall design and conduct of the study. When example text is shown below, new text is shown in italics and text that is removed is shown in strike out. Individual rationale for each change is added in parentheses.

Applicable Section(s)	Description of Change(s)
Rationale: Oral risperidone has been added as an optional treatment to oral paliperidone extended release (ER) during the run-in period (Part I) and adjustment of dose range for the run-in treatments.	
Synopsis, Time and Event Schedule footnotes, Section 1.1.2, 2.1, 3.1, 3.2.2.3, 3.2.3, 4.1.2, 6.1, 6.2.1, 6.2.2, 8, 9.1.2, 9.1.3, 9.2.2,	Inclusion of an optional use of oral risperidone (1-6 mg) during the run-in period (Part I) instead of oral paliperidone ER. (To be consistent with labeling instructions for treatment preceding paliperidone palmitate)

10.2, 11.2, 14.1, 15, 16.1, Figure 2	
Synopsis, Time and Event Schedule footnotes, Section 3.1, 6.1, 6.2.1.1	The lower limit of the dose range for oral paliperidone ER was changed from 3 mg/day to 1.5 mg/day (To account for subjects who are naive to oral paliperidone ER treatment)
Synopsis, Section 1.2, 3.1, 3.2.3	Subjects should be able to tolerate a minimum dose of oral paliperidone ER (3 mg) or oral risperidone (2 mg) for at least 2 weeks before entering Part II. (To be aligned with the lowest available dose of PP1M to be administered in Part II)
Section 6.1	Addition of instructions for dosing with oral risperidone (To adjust dosing with risperidone during the run-in phase)
Synopsis, Time and Event Schedule footnotes, Section 3.1, 6.2.1	Addition of the following text to Part II for the PP treatment group who will receive a minimum of 5 doses of PP1M followed by PP3M once every 12 weeks: "At the Day 120 visit (±7 days), subjects will start PP3M treatment if in the investigator's judgment, the subject is receiving an optimal maintenance dose of PP1M." "In some cases, if on Day 120 the investigator feels they have not identified the appropriate maintenance dose of PP1M, with approval of the medical monitor and sponsor, the subject may continue to receive flexible doses of PP1M injections on Day 120, 148, and 176, and on Day 204 receive an injection of PP3M (using a 3.5-fold multiple of the PP1M dose received on Day 176) either in the deltoid or gluteal muscle. If required, supplemental oral paliperidone ER (up to ~~at a dosage of 1.5~~ 6 mg/day or oral risperidone (up to 3 mg/day may be given. It should be noted that adding oral paliperidone/oral risperidone will not be considered a treatment failure unless supplemental oral paliperidone ER/oral risperidone is given for a combined total of more than 84 days or if oral paliperidone ER doses exceed 6 mg/day or oral risperidone doses exceed 3 mg/day." (to be consistent with the labeling statement of a minimum of 4 months of PP1M necessary to transition to PP3M treatment to ensure that the correct maintenance dose is identified, to provide sufficient time for dose finding, and to expand the dose ranges to be consistent with the expansion in the oral run-in phase)
Rationale: Changes to clarify study conduct	
Section 3.2.2.3, Table 1 and Table 2	Starting dose of PP1M to be administered is based on the final oral paliperidone ER or oral risperidone dose received during the run-in phase and is specified in 2 added tables (clarification)
Synopsis, Section 3.1	"Approximately half of the enrolled subjects will also undergo brain magnetic resonancy imaging (MRI) scans for assessment of ICM volume and other exploratory MRI endpoints. In addition, approximately 20 healthy control subjects (comparable in age, sex, race, and highest parental education to the subjects with schizophrenia/schizophreniform disorder undergoing MRI scans) will be identified at each MRI center and followed as controls for the MRI machine calibration for the duration of the study without treatment." (clarification)
Rationale: Improvements in the conduct of the protocol (nonsubstantial)	

Throughout the protocol	Changes for consistency between sections and for clarification of text were made that had no impact on safety Minor updates to content resulting from completion of previously ongoing study (R092670-PSY-3011) and approval of PP3M
Throughout the protocol	Minor grammatical, formatting, spelling changes, etc

SYNOPSIS

A Prospective, Matched-Control, Randomized, Open-Label, Flexible-Dose, Study in Subjects with Recent-Onset Schizophrenia or Schizophreniform Disorder to Compare Disease Progression and Disease Modification Following Treatment with Paliperidone Palmitate Long-Acting Injection or Oral Antipsychotics

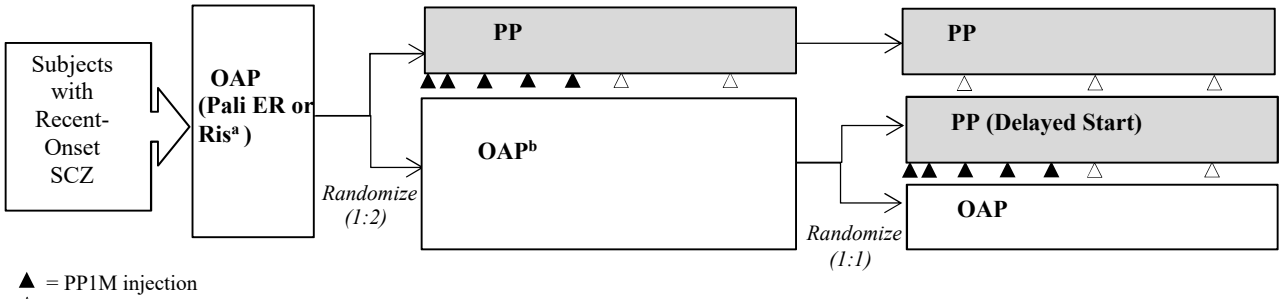
Paliperidone is a monoaminergic antagonist that exhibits the characteristic dopamine type 2 (D_2) combined with predominant serotonin (5-hydroxytryptamine type 2A [$5HT_{2A}$]) antagonism of the newer, or second-generation, antipsychotic drugs. Paliperidone palmitate is the ester prodrug of paliperidone and is formulated as an aqueous suspension for intramuscular (IM) injection. Two formulations of paliperidone palmitate have been developed: the first formulation has a 1-month injection interval (PP1M; INVEGA SUSTENNA® or XEPLION®) and the second formulation has a 3-month injection interval (PP3M; INVEGA TRINZA® or TREVICTA®). Both formulations are approved in the United States (US) and numerous other countries for the treatment of schizophrenia in adults.

The current study will compare paliperidone palmitate versus oral antipsychotic (OAP) treatment in subjects with recent-onset schizophrenia or schizophreniform disorder. Subjects randomized to paliperidone palmitate will receive PP1M for a minimum of 4 months prior to transitioning to PP3M; this treatment sequence starting with stabilization on PP1M followed by PP3M treatment will hereafter be referred to as 'PP'.

OBJECTIVES AND HYPOTHESES

The study includes 3 treatment phases: a 2-month, open-label, flexible-dose, oral run-in phase (Part I), and 2 sequential, 9-month, matched-control, randomized, open-label, active-controlled, flexible-dose treatment phases (Part II, referred to as the 'Disease Progression Phase' and Part III, referred to as the 'Extended Disease Progression and Disease Modification Phase'). Part II and Part III each have their own objectives.

An overview of the study design is provided below:



[a] All subjects will be started on oral paliperidone ER or oral risperidone. Subjects who find oral paliperidone ER/oral risperidone intolerable will be withdrawn from the study; subjects who tolerate oral paliperidone ER/oral risperidone but find it inadequately efficacious may be switched to another protocol-specified OAP at the discretion of the investigator.

[b] Subjects randomized to the OAP treatment group will continue their OAP treatment (ie, oral paliperidone ER, or other OAP) from Part I.

Note: For optimal management of symptoms/tolerability, subjects receiving PP3M (during either Part II or Part III) may go back to treatment with PP1M (monthly injections of 78, 117, 156 or 234 mg, flexibly dosed) for further dose adjustment or for the duration of the trial with the approval of the medical monitor.

OAP=oral antipsychotic; Pali ER=paliperidone extended-release; Ris=oral risperidone; PP=paliperidone palmitate; PP1M=paliperidone palmitate 1-month injection; PP3M=paliperidone palmitate 3-month injection; SCZ=schizophrenia or schizophreniform disorder.

Part II Objectives: Disease Progression

Subjects who complete the Part I oral run-in phase will enter Part II and will be randomized in a 1:2 ratio to either start PP treatment (ie, PP1M followed by PP3M) or to continue their OAP treatment from Part I. It is expected that most subjects will be receiving either oral paliperidone ER or oral risperidone at the start of Part II, but some subjects may be on an alternative OAP. The Part II treatment duration is 9 months.

Primary Objective

- To compare the effectiveness of PP versus OAP treatment (ie, oral paliperidone ER, oral risperidone. or other OAP) in delaying time to first treatment failure over 9 months' treatment in subjects with recent-onset schizophrenia or schizophreniform disorder (Refer to **EFFICACY EVALUATIONS** section below for a definition of treatment failure).

Key Secondary Objectives:

- To evaluate changes in cognition as measured by the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) composite score following 9 months' treatment with PP compared to 9 months' treatment with OAP.
- To evaluate changes in functioning as measured by the Personal and Social Performance scale (PSP) following 9 months' treatment with PP compared to 9 months' treatment with OAP.
- To evaluate changes in brain intracortical myelin (ICM) volume as measured by inversion recovery (IR) and spin echo (SE) magnetic resonance imaging (MRI) in the frontal lobe following 9 months' treatment with PP compared to 9 months' treatment with OAP.

Secondary Objectives:

- To evaluate changes in cognition as measured by the individual domains of the MCCB (ie, working memory, verbal learning, speed of processing, attention/vigilance, visual learning, reasoning and problem solving, and social cognition) following 9 months' treatment with PP compared to 9 months' treatment with OAP.
- To evaluate changes in illness severity as measured by the Clinical Global Impression-Severity scale (CGI-S) following 9 months' treatment with PP compared to 9 months' treatment with OAP.
- To evaluate changes in severity of psychotic symptoms, as measured by the 8 items of the Clinician-Rated Dimensions of Psychosis Symptom Severity scale (CRDPSS) (ie, delusions, hallucinations, disorganized speech, abnormal psychomotor behavior, negative symptoms [restricted emotional expression or avolition], impaired cognition, depression, and mania) following 9 months' treatment with PP compared to 9 months' treatment with OAP.
- To evaluate changes in medication satisfaction as measured by the Medication Satisfaction Questionnaire (MSQ) [patient-reported outcome] following 9 months' treatment with PP compared to 9 months' treatment with OAP.
- To assess overall safety of PP.

Exploratory Objectives:

- To assess changes in resting state functioning MRI (fMRI), and changes in cortical thickness, gray matter volume, white matter volume, ventricular volume, intrasulcal cerebrospinal fluid (CSF) volume, and subcortical myelin integrity, as measured by MRI following 9 months' treatment with PP compared to 9 months' treatment with OAP.

- To explore the overall healthcare resource utilization use as measured by the Resource Utilization Questionnaire (RUQ) following 9 months' treatment with PP compared to 9 months' treatment with OAP.
- To explore differences in satisfaction with goal setting following 9 months' treatment with PP compared to 9 months' treatment with OAP.
- To explore quantitative assessments of daily activities following 9 months' treatment with PP compared to 9 months' treatment with OAP.

Part III Objectives: Extended Disease Progression and Disease Modification

Subjects who complete Part II will be eligible to enter Part III. At the start of Part III, subjects treated with OAP during Part II will be re-randomized in a 1:1 ratio to either continue treatment with OAP (OAP-OAP group) or to switch to PP (OAP-PP group). Subjects treated with PP during Part II will continue the same treatment (PP-PP group). The Part III treatment duration is 9 months.

The *Extended Disease Progression* objectives will focus on comparisons between the OAP-OAP and PP-PP groups; the *Disease Modification* objectives will focus on comparisons between the PP-PP and OAP-PP groups (ie, subjects who started treatment with PP early vs. subjects who started PP treatment 9 months later).

Extended Disease Progression Objectives

Primary Objective

- To evaluate changes in cognition as measured by the MCCB composite score following 18 months' treatment with PP compared to 18 months' treatment with OAP in subjects with recent-onset schizophrenia or schizophreniform disorder.

Key Secondary Objectives:

- To evaluate changes in functioning as measured by the PSP following 18 months' treatment with PP compared to 18 months' treatment with OAP.
- To evaluate changes in brain ICM volume in the frontal lobe following 18 months' treatment with PP compared to 18 months' treatment with OAP.

Secondary Objectives:

- To evaluate changes in cognition as measured by the individual domains of the MCCB following 18 months' treatment with PP compared to 18 months' treatment with OAP.
- To evaluate changes CGI-S following 18 months' treatment with PP compared to 18 months' treatment with OAP.
- To evaluate changes in severity of psychotic symptoms, as measured by the 8 items of the CRDPSS following 18 months' treatment with PP compared to 18 months' treatment with OAP.
- To evaluate changes in medication satisfaction as measured by the MSQ (patient-reported outcome) following 18 months' treatment with PP compared to 18 months' treatment with OAP.
- To evaluate differences in time to first treatment failure and subsequent treatment failures over 18 months' treatment with PP compared to 18 months' treatment with OAP.
- To assess overall safety of PP.

Exploratory Objectives:

- To assess changes in resting state fMRI, and changes in cortical thickness, gray matter volume, white matter volume, ventricular volume, intrasulcal CSF volume, and subcortical myelin integrity, as measured by MRI following 18 months' treatment with PP compared to 18 months' treatment with OAP.
- To explore the overall healthcare resource utilization use as measured by the RUQ following 18 months' treatment with PP compared to 18 months' treatment with OAP.
- To explore differences in satisfaction with goal setting following 18 months' treatment with PP compared to 18 months' treatment with OAP.
- To explore quantitative assessments of daily activities following 18 months' treatment with PP compared to 18 months' treatment with OAP.

Disease Modification Objectives:

Primary Objective

- Using a delayed-start approach, to compare changes in cognition as measured by the MCCB composite score following 9 months' additional PP treatment in subjects originally randomized to PP (PP-PP group) compared to 9 months' delayed-start PP treatment in subjects originally randomized to OAP treatment (OAP-PP group).

Key Secondary Objectives:

- Using a delayed-start approach, to compare changes in functioning as measured by the PSP following 9 months' additional PP treatment in subjects originally randomized to PP (PP-PP group) compared to 9 months' delayed-start PP treatment in subjects originally randomized to OAP treatment (OAP-PP group).
- Using a delayed-start approach, to compare changes in brain ICM volume in the frontal lobe following 9 months' additional PP treatment in subjects originally randomized to PP (PP-PP group) compared to 9 months' delayed-start PP treatment in subjects originally randomized to OAP treatment (OAP-PP group).

Hypothesis

The overall primary hypothesis to be tested in this study is that 9 months' treatment with PP is superior to 9 months' treatment with OAP in delaying time to first treatment failure in subjects with recent-onset schizophrenia or schizophreniform disorder. The primary efficacy null hypothesis is that there is no difference in the distribution of time to first treatment failure in Part II between the PP and OAP treatment groups.

OVERVIEW OF STUDY DESIGN

This is a prospective, matched-control, randomized, open-label, active-controlled, flexible-dose, multicenter study designed to compare the effectiveness of PP versus OAP in delaying time to first treatment failure in subjects with recent-onset schizophrenia or schizophreniform disorder. The study will also evaluate whether long-acting injectable (LAI) treatment with PP can slow disease progression and possibly modify disease course compared to OAP medications, by tracking changes in cognition, functioning, and frontal lobe ICM volume. Other efficacy, safety, and exploratory endpoints will also be assessed.

Approximately 275 men and women between the age of 18 and 35 years, who have a Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) diagnosis of schizophrenia or schizophreniform disorder who experienced their first psychotic episode within 2 years of study entry

will be enrolled. The total study duration for each subject will be approximately 86 weeks, including a screening phase (up to 4 weeks), a 2-month oral run-in phase (Part I), and two 9-month treatment phases (Part II and Part III). The study periods are briefly described below:

- **Screening (up to 4 weeks; Day -28 to -1):** Subjects who provide written informed consent will undergo the screening procedures, including a review of the study entry criteria. Any prestudy OAP other than oral risperidone or oral paliperidone ER will be tapered off and must be discontinued by Week 5 of Part I. Subjects already being treated with oral risperidone or oral paliperidone ER should be continued at the dose deemed to be most appropriate by the investigator). Tapering of the previous OAP can start at the beginning of the screening period. Tapering and discontinuation should be managed by the investigator, as clinically appropriate.
- **Part I, Oral Run-In Phase (2 months):** After completing the screening period, subjects meeting the inclusion and exclusion criteria will be entered into Part I, a 2-month oral run-in phase. All subjects will initially receive flexible dosing with oral paliperidone ER (1.5-12 mg/day) OR oral risperidone (1-6 mg). Treatment with oral paliperidone ER or oral risperidone will enable investigators to establish tolerability prior to randomization to the LAI formulation in Part II. Subjects who find either oral paliperidone ER or oral risperidone intolerable will be withdrawn from the study. To be eligible for randomization in Part II, subjects must be able to tolerate a minimum dose of 3 mg of oral paliperidone or 2 mg of oral risperidone for at least 2 weeks prior to entry to Part II. Subjects who tolerate oral paliperidone ER or oral risperidone but find it inadequately efficacious after treatment for an adequate duration at an adequate dosage (per clinical judgment), may be switched to another protocol-specified OAP at the discretion of the investigator. Any of the following 7 OAPs are permitted: aripiprazole, haloperidol, olanzapine, oral paliperidone ER, perphenazine, quetiapine, and risperidone. The following demographic and baseline characteristics and clinical data will be collected during Part I to be used for matching during randomization into Part II and Part III: age, gender, race, prior antipsychotic exposure, substance use history, MCCB composite score, and PSP total score.
- **Part II, Disease Progression Phase (9 months):** Subjects who complete Part I with appropriate tolerability of oral paliperidone or oral risperidone (as described above) will be eligible to enter Part II. On Day 1 of Part II (Day 57 of Part I), subjects will be randomized in a 1:2 ratio to open-label treatment with either PP or to continued OAP treatment for 9 months. Dynamic central randomization will be performed, based on matching criteria determined in Part I. It is estimated that approximately 225 subjects will be randomized in Part II, ie, approximately 75 subjects will be randomized to the PP treatment group and 150 subjects to the OAP treatment group.
  - Subjects randomly assigned to the OAP treatment group will continue their OAP treatment from Part I. It is expected that most subjects will be receiving oral paliperidone ER or oral risperidone, but some subjects may be receiving an alternative OAP. Investigators are encouraged to continue the OAP prescribed at the Part II baseline) as monotherapy throughout the remainder of the study but, if clinically indicated, a switch to an alternative OAP or add-on of an additional OAP is permitted after the first randomization visit. Switching or add-on of another OAP due to inadequate efficacy, tolerability, or safety will be assessed as a treatment failure (see definition of treatment failure in **EFFICACY EVALUATIONS**). Subjects with treatment failure will continue participation in the study. Multiple switches (ie, treatment failures) are permitted during the study. The same 7 OAPs identified in Part I are allowed (ie, aripiprazole, haloperidol, olanzapine, oral paliperidone ER, perphenazine, quetiapine, and risperidone).
  - Subjects randomly assigned to the PP treatment group will receive a minimum of 5 doses of PP1M followed by PP3M once every 12 weeks. PP1M initiation dosing (first injection 234 mg [150 mg eq.] on Day 1 of Part II and second injection 156 mg [100 mg eq.] on Day 8, both in the deltoid muscle) followed by 3 injections of flexible doses of PP1M (78-234 mg [50-150mg eq.]) on Days 36, 64, and 92, either in the deltoid or gluteal muscle. On Day 120, subjects will

receive an injection of PP3M (using a 3.5-fold multiple of the PP1M dose received on Day 92) either in the deltoid or gluteal muscle. On Day 204, subjects will receive a flexible dose of PP3M (273-819 mg [175-525 mg eq.]) either in the deltoid or gluteal muscle. In some cases, if on Day 120 the investigator feels they have not identified the appropriate maintenance dose of PP1M, with approval of the medical monitor and sponsor the subject may continue to receive flexible doses of PP1M injections on Day 120, 148, and 176, and on Day 204 receive an injection of PP3M (using a 3.5-fold multiple of the PP1M dose received on Day 176) either in the deltoid or gluteal muscle. Investigators are encouraged to use PP1M and PP3M as antipsychotic monotherapy and to adjust the injection dose for management of symptoms/tolerability. If required, supplemental oral paliperidone ER (up to 6 mg/day) or oral risperidone (up to 3 mg/day) may be given during PP1M or PP3M treatment. It should be noted that adding oral paliperidone/oral risperidone will not be considered a treatment failure unless supplemental oral paliperidone ER/oral risperidone is given for a combined total of more than 84 days or if oral paliperidone ER doses exceed 6 mg/day or oral risperidone doses exceed 3 mg/day (see further details in the **DOSAGE AND ADMINISTRATION SECTION**). Adding any other antipsychotic will also be considered a treatment failure. Subjects with treatment failures will continue the study unless the PP injection is discontinued permanently.

- **Part III, Extended Disease Progression and Disease Modification Phase (9 months):** Subjects who complete Part II will be entered into Part III. On Day 1 of Part III (Day 260 of Part II), subjects in the OAP treatment arm will be re-randomized in 1:1 ratio to continued treatment with their OAP (OAP-OAP group) or to PP (OAP-PP or 'Delayed-start PP' arm). The Delayed-start PP arm will receive PP1M and PP3M treatment as described in Part II (ie, a minimum of 5 doses of PP1M followed by PP3M once every 12 weeks). Subjects previously assigned to treatment with PP in Part II will continue in that treatment group with paliperidone palmitate treatment (PP-PP group). Randomization will be based on matched criteria identified in Part I. Subjects will be followed for an additional 9 months.

For optimal management of symptoms/tolerability, subjects receiving PP3M (during either Part II or Part III) may go back to treatment with PP1M (monthly injections of 78, 117, 156 or 234 mg, flexibly dosed) for further dose adjustment or for the duration of the trial with the approval of the medical monitor.

Subjects will be assessed for treatment failure at all visits during Part II and Part III. Other efficacy assessments (MCCB, PSP, CGI-S, CRDPSS, and MSQ) will be performed as specified in the Time and Events Schedule. Safety will be monitored through evaluation of AEs, clinical laboratory parameters, vital signs, electrocardiograms (ECGs), body weight, ESRS, ISST-Plus, and physical examination findings. Resource use (measured using the RUQ), goal setting experience, and quantitative assessment of daily activities will be assessed as exploratory endpoints. A pharmacogenomic blood sample will be collected from subjects who consent separately to this component of the study (where local regulations permit). Subject participation in pharmacogenomic research is optional.

Approximately half of the enrolled subjects will also undergo brain MRI scans for assessment of ICM volume and other exploratory MRI endpoints. In addition, approximately 20 healthy control subjects (comparable in age, sex, race, and highest parental education to the subjects with schizophrenia/schizophreniform disorder undergoing MRI scans) will be identified at each MRI center and followed as controls for the MRI machine calibration for the duration of the study without treatment.

Note that subjects who experience a treatment failure and do not withdraw consent or meet the criteria for withdrawal from the study will continue in the study and be followed through to the end of the study.

Subjects, who miss scheduled injections or visits, are allowed to re-enter the same assigned treatment group of the study as long as their re-entry is within the same part of the study (ie, Part I, Part II or Part III) based on their original visit schedule. In all cases of re-entry, the site should contact the medical monitor to determine the best way to re-enter the subject and re-initiate treatment.

SUBJECT POPULATION

Subjects with schizophrenia or schizophreniform disorder: Approximately 275 subjects who meet all inclusion and none of the exclusion criteria will be enrolled in the study. Refer to the main text for a complete list of inclusion and exclusion criteria.

The key inclusion criteria include the following: men and women aged 18 to 35 years, inclusive, current diagnosis of schizophrenia (295.90) or schizophreniform disorder (295.40) as defined by DSM-5 and confirmed by the Structured Clinical Interview for DSM-5 Disorders (SCID) with a first psychotic episode within the 24 months prior to the Screening visit, and requiring treatment with an antipsychotic medication or a change in antipsychotic medication due to lack of efficacy, tolerability, safety issues, or investigator/subject preference.

The key exclusion criteria include: positive urine drug screen test for cocaine, amphetamines, opiates, or phencyclidine (PCP) at screening; current DSM-5 diagnosis of dissociative disorder, bipolar disorder, major depressive disorder, schizoaffective disorder, autistic disorder, or intellectual disabilities; and meets the DSM-5 definition of moderate or severe substance use disorder (except for nicotine) within 2 months prior to screening.

Healthy Control Subjects: Each MRI site will identify and enroll approximately 20 healthy control subjects who will undergo MRI assessments only. These healthy control subjects should be comparable in age, sex, race, and highest parental education to the subjects with schizophrenia/schizophrenia disorder undergoing MRI scans. Refer to the main text for a complete list of inclusion and exclusion criteria.

Key exclusion criteria are: evidence of a known psychiatric disorder, neurological disorder (eg, epilepsy) or significant head injury; first degree relative who has schizophrenia, schizophreniform, schizoaffective, or bipolar disorder; or meets the DSM-5 definition of moderate or severe substance use disorder (except for nicotine) within 2 months prior to screening. Subjects who are unable to undergo MRI scan for any reason, including because of body size (unable or difficult to fit in MRI instrument) or MRI contraindicated due to presence of metallic objects (pacemaker, etc.) will also be excluded.

DOSAGE AND ADMINISTRATION

Part I, Oral Run-In Phase

During Part I, all subjects will initially be treated with either oral paliperidone ER (1.5 to 12 mg/day) or oral risperidone (1-6 mg/day). Any prestudy OAP other than risperidone or oral paliperidone ER will be tapered off and must be discontinued by Week 5 of Part I. Subjects already being treated with oral risperidone or oral paliperidone ER should be continued at the dose deemed to be most appropriate by the investigator). Adjustment of the dosage will be done at the investigator's discretion, based on the individual subject's clinical response to and tolerability of the study drug. To be eligible for randomization in Part II, subjects must be able to tolerate a minimum dose of 3 mg of oral paliperidone or 2 mg of oral risperidone for at least 2 weeks prior to entry to Part II. Subjects who find either oral paliperidone ER or oral risperidone intolerable will be withdrawn from the study. Subjects who tolerate oral paliperidone ER/oral risperidone but find it inadequately efficacious after treatment for an adequate duration at an adequate dosage (per clinical judgment), may be switched to another protocol-specified OAP at the discretion of the investigator. The following 7 OAPs are permitted: aripiprazole, haloperidol, olanzapine, oral paliperidone ER, perphenazine, quetiapine, and risperidone.

Part II and Part III, Active-Controlled Treatment Phases

Paliperidone Palmitate (PP1M/PP3M)

All drug injections must be administered by an individual who has received appropriate medical training to administer an IM injection.

Subjects who are randomly assigned to the PP treatment group at the start of Part II will discontinue their OAP treatment from Part I and will be started on PP1M. Subjects will be subsequently switched to PP3M following a minimum of 5 injections of PP1M. A transition period of a maximum of 5 weeks will be allowed for the previous OAP.

PP1M will be administered IM once-monthly, after the first 2 injections that are given one week apart (Day 1 and Day 8). The first two doses will be administered through a deltoid injection on alternating arms. The subsequent injections can be given either in the deltoid or the gluteal muscle. The first dose of PP1M will be 234 mg given in the deltoid muscle at Day 1 of the treatment phase. The second dose of PP1M will be 156 mg given in the deltoid muscle at Day 8 of the treatment phase. Subsequent doses of PP1M will be given every 28 (±7) days in either the deltoid or gluteal muscle. The investigator may select from 78, 117, 156, or 234 mg, according to the subjects' clinical needs. Subjects will continue to return to the study site every 4 weeks for injections and for study evaluations.

At the Day 120 visit (±7 days), subjects will start PP3M treatment if in the investigator's judgment, the subject is receiving an optimal maintenance dose of PP1M. If on Day 120 the investigator feels they have not identified the appropriate maintenance dose of PP1M, with approval of the medical monitor and sponsor the subject may continue to receive flexible doses of PP1M injections on Day 120, 148, and 176, and on Day 204 start PP3M treatment. The initial PP3M dose will be calculated as 3.5-fold multiple of the final PP1M dose administered on Day 92 (or Day 176). Subjects will receive PP3M injections once every 12 weeks (±14 days). Investigators will be permitted to flexibly adjust the dose of PP3M as clinically necessary with the dose options for PP3M being 273, 410, 546, or 819 mg. Injections of PP3M may be administered in either the deltoid muscle or the upper outer portion of the gluteal muscle. The side of each injection (left or right) should be alternated and recorded. For optimal management of symptoms/tolerability, subjects receiving PP3M (during either Part II or Part III) may go back to treatment with PP1M (monthly injections of 78, 117, 156 or 234 mg, flexibly dosed) for further dose adjustment or for the duration of the trial with the approval of the medical monitor.

Supplemental OAP Use in the PP Treatment Group: Investigators are strongly encouraged to use PP1M and PP3M as antipsychotic monotherapy and to adjust the injection dose for management of symptoms/tolerability. Subjects in the PP treatment group who are tolerating the medication but experience symptom exacerbation during the study will be allowed to have supplemental antipsychotic medication, ie, oral paliperidone ER (up to 6 mg/day or oral risperidone (up to 3 mg/day, for no longer than a total of 84 days during the total PP treatment period. If the supplemental treatment with oral paliperidone ER/oral risperidone is longer than 84 days or if oral paliperidone ER doses exceed 6 mg/day or oral risperidone doses exceed 3 mg/day, the subject will be considered a treatment failure. Adding any other antipsychotic will also be considered a treatment failure.

A switch to an alternative antipsychotic is not permitted in the PP treatment group. If it is deemed clinically necessary to stop paliperidone palmitate in a subject assigned to PP treatment, the subject will be withdrawn from the study and discontinuation of PP will be recorded as a treatment failure.

Oral Antipsychotic Treatment

Subjects randomly assigned to the OAP treatment group at the start of Part II will continue their OAP treatment from Part I. It is expected that most subjects will be receiving oral paliperidone ER or oral risperidone, but some subjects may be receiving an alternative OAP at entry into Part II.

Investigators are encouraged to continue the OAP prescribed at Part II baseline as monotherapy throughout the remainder of the study, and to adjust the OAP dose for management of symptoms/tolerability at any time. After the initial randomization visit, a switch to a different OAP or the addition of another OAP is allowed in the OAP treatment arm if clinically indicated; however, switching or add-on of another OAP due to inadequate efficacy, tolerability, or safety will be assessed as a treatment failure (see definition of treatment failure in **EFFICACY EVALUATIONS**). The same 7 OAPs specified for Part I (aripiprazole, haloperidol, olanzapine, oral paliperidone ER, perphenazine,

quetiapine, and risperidone) will be permitted. Multiple switches to other protocol-specified OAPs will be allowed during the study. Any change in antipsychotic medication (switching, discontinuation, or add-on) must be evaluated against the treatment failure criteria.

Administration of PP or an alternative LAI antipsychotic is prohibited in subjects assigned to OAP treatment. If an LAI agent is deemed clinically necessary for subjects assigned to the OAP group, their data will be censored as a treatment failure and they will be discontinued from the study.

Subjects should generally be treated within the approved label for all OAPs. Any exceptions should first be discussed with the medical monitor.

EFFICACY EVALUATIONS

Subjects will be assessed at each visit during Part II and Part III for the occurrence of treatment failure. Treatment failure is defined as any of the following: 1) Psychiatric hospitalization due to worsening symptoms (including Emergency Room visits ≥23 hours, and not including hospitalization due to social reasons); 2) Any deliberate self-injury, suicidal ideation or behavior, homicidal ideation or violent behavior that is clinically significant and needs immediate intervention as determined by the study physician; 3) New arrest or incarceration (not related to probation or existing warrant); 4) Discontinuation of antipsychotic treatment due to inadequate efficacy as determined by the study physician;
5) Discontinuation of antipsychotic treatment due to safety or tolerability as determined by the study physician; 6) Treatment supplementation with another antipsychotic due to inadequate efficacy as determined by the study physician (note: use of oral paliperidone ER in the PP treatment group will not be considered a treatment failure unless supplemental treatment with oral paliperidone ER or oral risperidone is longer than 84 days or if oral paliperidone ER doses exceed 6 mg/day or oral risperidone doses exceed 3 mg/day); 7) Increase in the level of psychiatric services (such as from office visit to day hospitalization) in order to prevent imminent psychiatric hospitalization as determined by the study physician.

Any changes in antipsychotic medications (switching, discontinuation, or add-on) must be evaluated against the treatment failure criteria. If any of these changes do not meet the treatment failure criteria, these must be documented and recorded in the eDC.

Other efficacy assessments include measures of cognition (MCCB), patient functioning (PSP), disease severity (CGI-S), schizophrenia symptoms (CRDPSS), and a patient-reported outcome of medication satisfaction (MSQ).

MRI BRAIN IMAGING

Selected sites will perform MRI brain imaging. All images will be sent to a central site for analysis. The imaging raters at the central site will not be otherwise involved with the conduct of the study, and will be blind to clinical characteristics, treatment assignment, and demographic characteristics of subjects.

A separate manual will be provided to the relevant sites with detailed information regarding MRI procedures. In brief, brain ICM volume will be measured by IR and SE MRI sequences focused on the frontal lobe. The cortical thickness, gray matter and white matter volumes will be measured by 3D MPRAGE MRI. The ventricular volume and intrasulcal CSF will be measured by SE MRI sequences. The subcortical myelin will be measured by MRI sequences optimized for diffusion tensor imaging (DTI). Resting state fMRI will also be measured.

EXPLORATORY ASSESSMENTS

Exploratory evaluations include assessment of medical resource use (based on the RUQ), goal setting experiences, and quantitative assessment of daily activities.

PHARMACOGENOMIC (DNA) EVALUATIONS

A pharmacogenomic blood sample will be collected to allow for pharmacogenomic research, as necessary (where local regulations permit). Subject participation in the pharmacogenomic research is optional.

SAFETY EVALUATIONS

Safety evaluations include the monitoring of adverse events, clinical laboratory tests, ECGs, vital sign measurements (temperature, pulse, and blood pressure), body weight, and the monitoring of extrapyramidal symptoms using the Extrapyramidal Symptom Rating Scale-Abbreviated (ESRS-A). Suicidality will be assessed using the InterSePT Scale for Suicidal Thinking-Plus (ISST-Plus).

STATISTICAL METHODS

A brief description of the statistical methods is provided in the protocol. Additional details of the statistical analysis will be described in the statistical analysis plan (SAP).

Sample Size Determination

The primary efficacy null hypothesis is that there is no difference in the distribution of time to treatment failure between the PP and OAP in the treatment of recent-onset schizophrenia or schizophreniform subjects in Part II. Treatment differences will be compared using a log-rank test. It is assumed that treatment failure rate in Part II is approximately 40% for the OAP group and 20% for the PP group at Month 9 with a corresponding hazard ratio of 0.44. It is also assumed that the hazard rates of treatment failure for the two groups are proportional. Additional assumptions made to calculate the expected number of subjects that need to be randomized to obtain the required number of treatment failures are:

- In both treatment groups, 10% of the randomized subjects will be lost-to-follow-up.
- Uniform accrual rate during the 15-month accrual period.

With these assumptions, it is planned to randomize at least 225 (75 in PP and 150 in OAP group) subjects in a 1:2 ratio to receive either PP or OAP to obtain at least 62 treatment failures to show that PP is significantly different from OAP at the 2-sided significance level of 0.05, with 80% power to detect a hazard ratio of 0.44 using a log rank test.

Blinded surveillance of the total number of events in Part II will be performed during the study to assess the appropriateness of the assumptions. The number of subjects enrolled and the number of subjects who discontinue before entering the Part II will be closely monitored.

Assuming 20% attrition rate during the 2-month Run-in period (Part I), the total number of subjects to be enrolled in Part I will be approximately 275.

Efficacy Analyses

Part II: Disease Progression

At the completion of Part II, the database will be locked and data analyzed.

Primary endpoint: The primary endpoint in Part II is time to treatment failure. Treatment differences will be compared using a log-rank test. The cumulative distribution function of the time to treatment failure will be estimated by the Kaplan-Meier method. The 95% confidence intervals (CIs) for the median treatment failure rates, as well as the failure rates at 3 months, 6 months, and at 9 months will be provided. In addition, the estimate of the hazard ratio and its 95% CI will be provided by treatment group based on the Cox proportional hazards model. The reasons for treatment failure will be summarized.

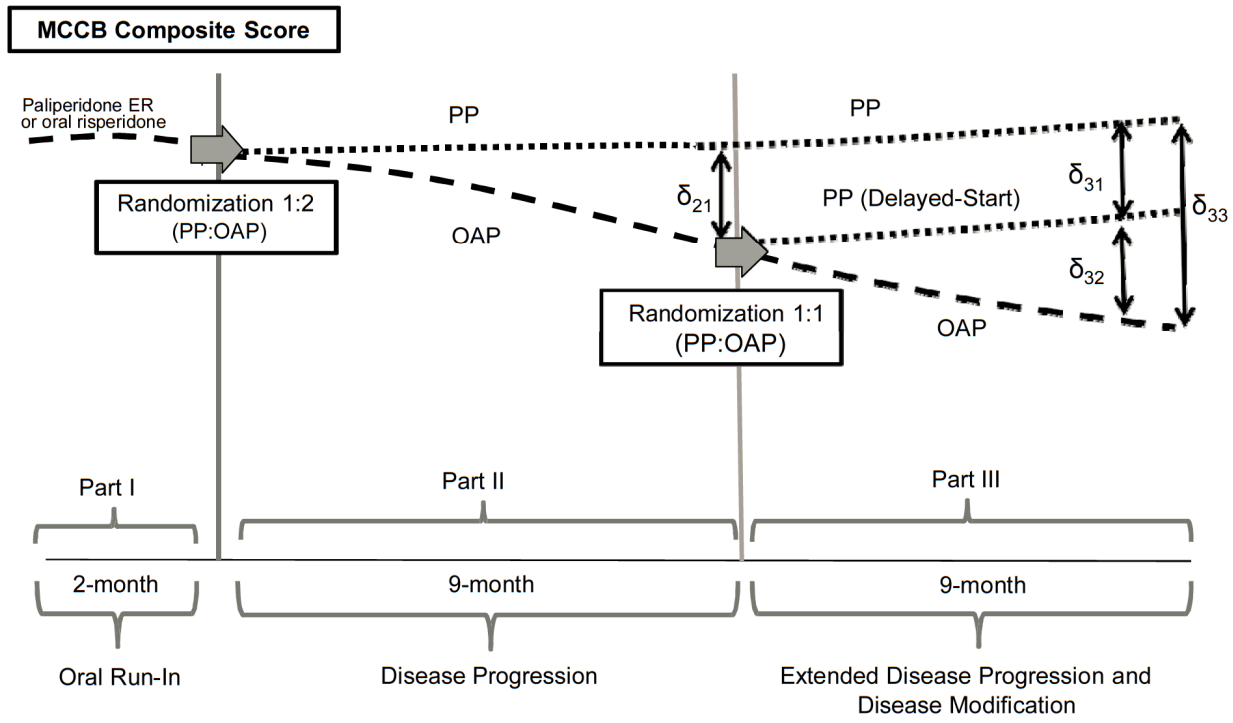
Key secondary endpoints: The change from baseline in MCCB composite score will be analyzed using a mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) model. The analysis will be based on observed data, ie, data collected at each time point without carrying forward previous values. Changes in ICM volume and PSP total score will be analyzed using the same method as the MCCB analysis. At each PSP assessment point, frequency counts, percentages, and cumulative percentages of subjects reporting each PSP level will also be summarized by treatment group for the observed cases and last observation carried forward (LOCF) data. Time to 7-point worsening in PSP will be analyzed using the similar methodology for the primary endpoint.

Part III: Extended Disease Progression and Disease Modification

At the conclusion of Part III, the database will be locked again and data analyzed to assess superiority of PP versus OAP on *Disease Progression* and *Disease Modification.*

Three effects (outcomes) will be analyzed: δ_{31}, δ_{32}, and δ_{33}. These are illustrated in the figure below, based on the hypothesized change in MCCB composite score over time. These effects will be assessed for the MCCB composite score (primary endpoint), and for PSP total score and ICM volume (key secondary endpoints).

Hypothesized Disease Progression and Disease Modification Effect at Completion of Part III (Based on Change in MCCB Composite Score Over Time [for Illustration Purposes Only])



ER= extended-release; MCCB= MATRICS Consensus Cognitive Battery; OAP=other antipsychotic; PP=paliperidone palmitate
δ_{21}:Treatment effect on disease progression; δ_{31}: Lead treatment effect; δ_{32}: Delayed-start treatment effect on disease progression;
δ_{33}: Overall effect of treatment.

The quantity δ_{31} represents the lead treatment effect after an early start with 18 months of PP treatment and shows the lead effect remaining in the early start group over the delayed-start effect after a 9-month treatment duration. The quantity δ_{32} represents the delayed-start effect on disease progression for PP compared to continuing OAP after 9 months of additional treatment. The quantity δ_{33} represents the

cumulative effect on extended disease progression at the end of Part III following early start for PP compared to continuing OAP after a total of 18 months of treatment.

Extended Disease Progression Analyses:

The objective of these analyses is to examine the quantity δ_{33}. The change from baseline in MCCB composite score at the end of Part III will be analyzed using a MMRM ANCOVA model. Changes in ICM volume and PSP total score will be analyzed using the same method as the MCCB analysis. Treatment differences for time to 7-point worsening in PSP score will be compared using a log-rank test and Cox's proportional hazards model.

Disease Modification Analyses:

The quantity δ_{31} (lead treatment effect) will be examined as a function of δ_{21} (treatment effect on disease progression) at the end of Part III using Part III baseline scores. The observed score differences in MCCB composite score will be analyzed using a MMRM ANCOVA model. Changes in ICM volume and PSP total score will be analyzed using the same method as the MCCB analysis as a function of corresponding δ_{21} value.

The quantity δ_{32} (the delayed-start effect on disease progression) will be examined using change scores from Part III baseline to Part III endpoint. The differences in scale scores will be analyzed using MMRM ANCOVA models.

Positive results (δ_{33} is significant [a differential treatment effect is still evident] **and** δ_{31} is significant [the lead effect remains significant after 9 months]) will be used to support a conclusion of disease modification using MCCB composite score. Similar observations for changes in PSP and ICM will be assessed. The quantity δ_{31} (lead treatment effect) will also be examined using Bayesian repeated measures analysis for each endpoint. Bayesian approach based on Markov Chain Monte Carlo will be employed to make an inference on significance of δ_{31} as a function of δ_{21}. This analysis will also use all observed scores including assessments from the unscheduled visits.

Safety Analyses

For each study phase and each treatment group, adverse events, clinical laboratory results, vital signs, and ECGs will be summarized using descriptive statistics and listed for each subject at each measurement time point. The results of the ESRS-A will be summarized using descriptive statistics and frequency counts on changes from Part II or Part III baseline values. Suicidality data collected using ISST-Plus will be summarized descriptively.

TIME AND EVENTS SCHEDULE: SCREENING

Treatment Phase	Screening
Visit:	**1**
Day (Part I)	-28 to -1
Screening/Administrative	
Informed consent	X
Informed consent for optional genetic research samples	X
Inclusion/exclusion criteria	X
Medical and psychiatric history	X
SCID	X
Pre-morbid IQ estimate (WTAR)[a]	X
Urine Drug Screen	X
Informed consent for the subject's designated individual	X
Efficacy Assessments	
MCCB	X
PSP	X
CRDPSS (DSM-5)	X
CGI-S	X
MSQ	X
Safety Assessments	
Physical examination	X
ECG	X
Clinical laboratory tests	X
Urine Pregnancy test	X
ESRS-A	X
ISST-Plus Short form[b]	X
Vital signs (blood pressure, pulse rate) and weight	X
Adverse Events	X
Concomitant medication	X

[a] An alternative test will be defined by the sponsor if the study is conducted in countries other than the United States.

[b] If suicidality is identified (ie, 'yes' is answered to questions 1.0, 2.2, 2.3, or 2.4 of the ISST-Plus Short Form) the full ISST-Plus must be administered in its entirety.

KEY: CGI-S=Clinical Global Impression-Severity scale; CRDPSS=Clinician-Rated Dimensions of Psychosis Symptom Severity; DSM-5=Diagnostic and Statistical Manual of Mental Disorders, 5th edition; ECG=electrocardiogram; ESRS-A=Extrapyramidal Symptom Rating Scale-Abbreviated; IQ=intelligence quotient; ISST-Plus=InterSePT Scale for Suicidal Thinking-Plus; MCCB=MATRICS Consensus Cognitive Battery; MSQ=Medication Satisfaction Questionnaire; PSP=Personal and Social Performance scale; SCID=Structured Clinical Interview for DSM-5 Disorders; UV=unscheduled visit; WTAR=Wechsler Test of Adult Reading

TIME AND EVENTS SCHEDULE: PART I, PART II, AND PART III

Treatment Phase:	Part I[a] (Oral Run-in)					Part II (Disease Progression)										Part III (Extended Disease Progression and Disease Modification)											
Visit:	2	3	4	5	6	7[p]	8	9	10	11	12	13[s]	14	15	16[s]	17[p]	18	19[o]	20	21	22	23[s]	24	25	26[s]	27/EOS[p]	UV[m]
Day (Part I)	1	8	15	29	43	57																					
Day (Part II)						1	8	36	64	92	120	148	176	204	232	260											
Day (Part III)																1	8	36	64	92	120	148	176	204	232	260	
Visit window		±4	±4	±4	±4	±7	±4	±7	±7	±7	±7	±7	±7	±7[n]	±7	±7	±4	±7[n]	±7	±7	±7[n]	±7	±7	±7[n]	±7		
Administrative																											
Inclusion/exclusion criteria	X																										
Urine Drug Screen						X										X									X	
Randomization						X[b]										X[c]											
Contact designated individual[d]				X		X		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	
Blood sample collection for DNA[r]	X																										
Study Drug Administration/Prescription[e]																											
Administer study drug (PP)[f]	O	O	O	O	O	1M	1M	1M	1M	1M	3M[u]	-	-	3M[v]	-	-	-[s]	3M[v]	-	-	3M[v]	-	-	3M[v]	-	-	
or provide prescription (O)[g]						O	O[s]	O	O	O	O	O	O	O	O	1M	1M	1M	1M	1M	3M[u]	-	-	3M[v]	-	-	
																O	O[s]	O	O	O	O	O	O	O	O	-	
Efficacy Assessments[h]																											
Assessment for treatment failure							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[h]
MCCB[i]				X		X				X			X			X				X			X			X	X[h]
PSP				X		X				X			X			X				X			X			X	X[h]
CRDPSS (DSM-5)	X			X		X				X			X			X				X			X			X	X[h]
CGI-S	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X[h]
MSQ	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X[h]
Imaging[h,t]																											
MRI						X				X						X				X						X	X[h]
Exploratory Assessments																											
Goal setting and review[j]	X			X		X		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	
Assessment of daily activities	X					X				X			X			X				X			X			X	
RUQ	X					X				X			X			X				X			X			X	
Safety Assessments																											
Physical examination																										X	
ECG						X										X										X	
Clinical laboratory tests						X										X										X	
Urine Pregnancy test						X										X										X	
ESRS-A						X				X			X			X				X			X			X	
ISST-Plus Short form[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs[l] and weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] During Part I, all subjects will initially receive flexible doses of oral paliperidone ER (1.5-12 mg/day) or 1-6 mg/day of oral risperidone. Subjects who find oral paliperidone ER or oral risperidone intolerable will be withdrawn from the study. Subjects who tolerate oral paliperidone ER or oral risperidone but find it inadequately efficacious may be switched to another protocol-specified OAP. Any of the following 7 OAPs will be permitted during Part I: aripiprazole, haloperidol, olanzapine, oral paliperidone ER, perphenazine, quetiapine, and risperidone.

[b] At the start of Part II, subjects will be randomized in a 1:2 ratio to start PP injections or to continue OAP treatment from Part I.

[c] At the start of Part III, subjects who were randomized to OAP in Part II will be re-randomized in a 1:1 ratio to continue OAP from Part II (OAP-OAP group) or switch to PP injections (OAP-PP group). Subjects randomized to PP in Part II will continue the same treatment (PP-PP group).

[d] The subject's designated individual should be contacted to check on the subject's well-being, such as subject's general health, common daily activities and progress in personal or health goals. Contact may be by telephone if the designated individual does not accompany the subject at the scheduled visit.

[e] All procedures should be performed prior to study drug administration/prescription, except for MRI, which does not need be performed on the day of a scheduled visit, but should be completed within ±7 days.

[f] Subjects who are randomly assigned to start PP treatment will receive PP1M injections on Day 1, Day 8 (±4 days), Day 36 (±7 days), Day 64 (±7 days), and Day 92 (±7 days). The first dose of PP3M will be given on Day 120 (±7 days) if in the investigator's judgment the subject is receiving an optimal maintenance dose of PP1M, and then every 12 weeks (±14 days) thereafter. If these windows are exceeded, contact the medical monitor. Refer to Section 6.2.1 for details on PP dosing as well as re-initiation of PP in cases of missed doses.

[g] Subjects who are randomly assigned to the OAP treatment group will continue their OAP treatment from Part I. Subjects will be provided a voucher to present at a local pharmacy to receive their assigned study drug. Following the initial randomization visit, a switch to a different OAP or the addition of another OAP is allowed in the OAP treatment group if clinically indicated; however, switching or add-on of another OAP due to inadequate efficacy, safety, or tolerability will be assessed as a treatment failure. Refer to Section 9.2.2.1 for definition of treatment failure. Any of the following 7 agents will be permitted during Part II and Part III: aripiprazole, haloperidol, olanzapine, oral paliperidone ER, perphenazine, quetiapine, and risperidone. Multiple switches to alternative OAPs (ie, multiple treatment failures) are allowed during the study.

[h] All efficacy assessments and MRI scans (in the subgroup of subjects undergoing MRI assessment) must be completed at the first occurrence of treatment failure, or as soon as possible, even they are not scheduled to be done for the visit or for the unscheduled visit. At subsequent treatment failures, PSP, CGI-S, CRDPSS, and MSQ assessments should be performed.

[i] For every individual subject, MCCB should be administered at the same time of day (±1 hour from the first assessment) for subsequent evaluations.

[j] Patient Happiness Assessment and Goal Setting Preparation will be performed at Day 1 Part I only; Patient Goal Setting Documentation will be completed on Day 1 of Part I, II, and III; Assessment of Patient Goal Attainment will be assessed by the subject every month.

[k] If suicidality is identified (ie, 'yes' is answered to questions 1.0, 2.2, 2.3, or 2.4 of the ISST-Plus Short Form) the full ISST-Plus must be administered in its entirety.

[l] Blood pressure and pulse rate.

[m] Unscheduled visits should be performed, as necessary for the following reasons:

- Unscheduled visits that are clinically indicated: Unscheduled visits should be performed as necessary in the judgment of the physician for appropriate clinical care, including reasons of safety or tolerability.
- Unscheduled visits for investigational purposes: Any subject who experiences a protocol-defined treatment failure event after randomization to Part II (Visit 7) should undergo an unscheduled visit. This applies to every treatment failure episode; not just the initial one. If an unscheduled visit can't be performed before the next scheduled protocol visit, applicable unscheduled visit procedures should be performed during the scheduled visit even when they are not normally part of the scheduled visit. Note that subjects who experience a treatment failure event should continue in the study, unless they meet study withdrawal criteria.

[n] At these visits (Visit 15, 19, 22, and 25), the treatment window for PP3M dosing will be ±14 days, except for the first PP3M injection, which will be ±7 days.

[o] In order to synchronize visit dates for all 3 treatment arms, Visit 19 occurs 92 days (instead of 84 days, ie, 12 weeks) after the previous PP3M injection. However, it is still within the ±14-day window.

[p] Note that completion and discontinuation will be recorded in the CRF for each treatment phase.

[r] The pharmacogenomic (DNA) sample should be collected at the specified time point, however if necessary it may be collected at a later time point without constituting a protocol deviation.

[s] These visits can be conducted by telephone.

[t] Approximately half the subjects will undergo MRI scans at selected study sites. MRI assessments are optional to subjects. MRI scans will also be performed in the healthy control group; the schedule for MRI assessments in healthy control subjects will be provided in a separate MRI manual.

[u] At the Day 120 visit (±7 days), subjects will start PP3M treatment if in the investigator's judgment the subject is receiving an optimal maintenance dose of PP1M. If on Day 120 the investigator feels they have not identified the appropriate maintenance dose of PP1M, with approval of the medical monitor and sponsor the subject may continue to receive flexible doses of PP1M injections on Day 120, 148, and 176, and on Day 204 will start PP3M treatment.

[v] For optimal management of symptoms/tolerability, subjects receiving PP3M (during either Part II or Part III) may go back to treatment with PP1M (monthly injections of 78, 117, 156 or 234 mg, flexibly dosed) for further dose adjustment or for the duration of the trial with the approval of the medical monitor.

KEY: CGI-S=Clinical Global Impression-Severity scale; CRDPSS=Clinician-Rate Dimensions of Psychosis Symptom Severity; CRF=case report form; ECG=electrocardiogram; EOS=end of study; ESRS-A=Extrapyramidal Symptom Rating Scale-Abbreviated; ISST-Plus= InterSePT Scale for Suicidal Thinking-Plus; MCCB=MATRICS Consensus Cognitive Battery; MRI=magnetic resonance imaging; MSQ=Medication Satisfaction Questionnaire; O=oral antipsychotic; 1M=paliperidone palmitate 1-month formulation; 3M=paliperidone palmitate 3-month formulation; PP=paliperidone palmitate; PSP=Personal and Social Performance scale; RUQ=Resource Use Questionnaire; UV=unscheduled visit

ABBREVIATIONS

$5HT_{2A}$	5-hydroxytryptamine type 2A
ANCOVA	analysis of covariance
ANOVA	analysis of variance
APA	American Psychiatric Association
AUC	area under the concentration-time curve
BACS	Brief Assessment of Cognition in Schizophrenia
BMI	body mass index
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness e
CDM	Clinical Data Manager
CGI-S	Clinical Global Impression-Severity scale
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
C_{max}	maximum plasma concentration
CRDPSS	Clinician-Rated Dimensions of Psychosis Symptom Severity scale (DSM-5)
CRF	case report form (paper or electronic as appropriate for this study)
CSF	cerebrospinal fluid
D_2	dopamine type 2
d_v50	volume based median diameter, ie, the median or the 50th percentile of the particle size distribution as measured by volume
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (4th edition)
DSM-5	Diagnostic and Statistical Manual of Mental Disorders (5th edition)
DTI	diffusion tensor imaging
ECG	Electrocardiogram
eDC	electronic Data Capture
eITT	explanatory intent-to-treat
EOS	end-of-study
ER	extended release
ESRS-A	Extrapyramidal Symptom Rating Scale-Abbreviated
EU	European Union
EUFEST	European First Episode Schizophrenia Trial
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEE	Generalized Estimation Equations
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Conference on Harmonisation
ICM	intracortical myelin
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IM	Intramuscular
IR	inversion recovery
IRB	Institutional Review Board
ISST-Plus	InterSePT Scale for Suicidal Thinking-Plus
ITT	intent-to-treat
IVRS	interactive voice response system
IWRS	interactive web response system
LAI	long-acting injectable
LOCF	last-observation-carried-forward
LS	least squares
MATRICS	Measurement and Treatment Research to Improve Cognition in Schizophrenia
MCCB	MATRICS Consensus Cognitive Battery
MedDRA	Medical Dictionary for Regulatory Activities
mg eq	milligrams equivalent of paliperidone
MMRM	mixed model repeated measures
MRI	magnetic resonance imaging
MSQ	Medication Satisfaction Questionnaire

NDA	New Drug Application
NIMH	National Institute of Mental Health
OAP	oral antipsychotic
PANSS	Positive and Negative Syndrome Scale
PCP	Phencyclidine
PD	proton density
PI	package insert
PK	Pharmacokinetic
PP	paliperidone palmitate treatment sequence (PP1M followed by PP3M)
PP1M	paliperidone palmitate 1-month injection
PP3M	paliperidone palmitate 3-month injection
PQC	product quality complaint
PSP	Personal and Social Performance scale
Ris	Risperidone
RUQ	Resource Use Questionnaire
SAP	statistical analysis plan
SCID	Structured Clinical Interview for DSM-5 Disorders
SE	spin echo
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
US	United States
UV	unscheduled visit
VAS	visual analog scale

DEFINITIONS OF TERMS

OAP-OAP	Subject group treated with OAP in Part II and Part III
OAP-PP	Subject group treated with OAP in Part II and PP in Part III (Delayed-Start PP)
PP-PP	Subject group treated with PP in Part II and Part III
δ_{21}	Treatment effect on disease progression at end of Part II
δ_{31}	Lead treatment effect at end of Part III
δ_{32}	Delayed-start treatment effect on disease progression at end of Part III
δ_{33}	Overall effect of treatment at end of Part III

1. INTRODUCTION

Paliperidone (9-hydroxy-risperidone) is a monoaminergic antagonist that exhibits the characteristic dopamine type 2 (D_2) and serotonin (5-hydroxytryptamine type 2A [$5HT_{2A}$]) antagonism of the newer, or second-generation, antipsychotic drugs. Three formulations of paliperidone have been developed: an oral extended-release (ER) osmotic pump technology (OROS®) tablet formulation (oral paliperidone ER tablets, INVEGA®) and 2 long-acting injectable (LAI) formulations: paliperidone palmitate 1-month injection (PP1M; INVEGA SUSTENNA® or XEPLION®) and paliperidone palmitate 3-month injection (PP3M; INVEGA TRINZA® or TREVICTA®).

Paliperidone palmitate is an aqueous suspension for intramuscular (IM) injection. Based on its extremely low water solubility, paliperidone palmitate dissolves slowly after injection before being hydrolyzed to paliperidone, which then enters the systemic circulation. By slowly releasing paliperidone from the injection site, the paliperidone palmitate formulation enables a dosing interval that achieves potentially therapeutic plasma concentrations of paliperidone for 1 month (PP1M) or 3 months (PP3M), depending on the particle size and dose.

The oral formulation of paliperidone (INVEGA) has been approved for the treatment of schizophrenia and schizoaffective disorder in the United States (US) and numerous other countries. The PP1M formulation (INVEGA SUSTENNA) is also approved in the US and numerous countries for the treatment of schizophrenia and for the treatment of schizoaffective disorder in US.

The PP3M formulation has been approved in the US and other countries for the treatment of schizophrenia in adults. This formulation has been developed building upon the extensive knowledge collected during the development of the PP1M formulation. This formulation contains the same drug substance and similar excipients as the PP1M formulation and is manufactured using the same equipment and process.[22] The main differences between PP3M and PP1M are the suspension strength, particle size (d_v50 ~7 µm vs. ~1 µm), and the fill volume for injection. These formulation changes enable a longer dosing interval and allow maintenance of therapeutic paliperidone plasma concentrations during a 3-month dosing interval. The indication for PP3M is for the treatment of adults with schizophrenia who have been adequately treated with PP1M for a minimum of 4 months.[22] Due to the slow release characteristics of PP3M, the product is not intended to be used for initiation of treatment in acutely symptomatic patients or in patients who are immediately transitioning from oral to LAI antipsychotic therapy. Rather, PP3M is intended to be used in patients who have already demonstrated therapeutic effect and tolerability with PP1M during treatment over a period of at least 4 months at the time of initiation of PP3M. With this approach, treatment with PP3M can be initiated with a dose equivalent to the dose of PP1M achieved at the end of the period of prior treatment, without the need for concurrent use of PP3M with oral paliperidone ER or PP1M. This also ensures that adequate paliperidone plasma concentrations can be maintained or attained without delay after initiation of treatment with PP3M.

The efficacy, safety, tolerability, and pharmacokinetics (PK) of PP3M are supported by the results of 2 completed studies: a single-dose, Phase 1 safety/PK study (R092670-PSY-1005) and a Phase 3, double-blind, placebo-controlled, relapse prevention study in subjects with schizophrenia (R092670-PSY-3012). A Phase 3, randomized, double-blind, noninferiority study found PP3M to be non-inferior to PP1M (R092670-PSY-3011).

The current study is a multi-phase, matched-control, randomized, open-label, active-controlled, flexible-dose study designed to compare the effectiveness of PP (ie, PP1M followed by PP3M) versus oral antipsychotic (OAP) treatment in delaying time to first treatment failure in subjects with recent-onset schizophrenia or schizophreniform disorder. Using a novel, multi-phase, study design, the study will also examine the possibility that LAI treatment with PP can slow down disease progression and possibly modify disease course in recent-onset subjects compared to OAP medications, by tracking changes in cognition, functioning, and brain imaging assessments.

For the most comprehensive nonclinical and clinical information regarding oral paliperidone ER, risperidone, PP1M, and PP3M, refer to the latest version of the Investigator's Brochures,[102] or the current local prescribing information for paliperidone ER, PP1M, PP3M or risperidone. The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

In this document, all paliperidone palmitate quantities (PP1M and PP3M) are expressed in milligrams (mg); the correspondence between mg of paliperidone palmitate and milligram equivalents (mg eq.) of paliperidone are provided in Table 3.

1.1. Background

Background regarding nonclinical and clinical experience with paliperidone palmitate, including the PP1M and PP3M formulations, is provided below.

1.1.1. Nonclinical Studies

Paliperidone is a monoaminergic antagonist with high affinity for $5HT_{2A}$ and D_2 receptors. Paliperidone also binds to α_1-adrenergic receptors and, with lower affinity, to H_1-histaminergic and α_2-adrenergic receptors. It has no affinity for cholinergic receptors. It has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of D_2 and $5HT_2$ receptor antagonism. Antagonism at receptors other than D_2 and $5HT_{2A}$ may explain some of its other effects.[102]

The nonclinical profile of paliperidone has been extensively evaluated during the development of the approved oral and PP1M formulations. Paliperidone is neither mutagenic nor teratogenic and is associated with toxicologic effects typical of D_2 receptor antagonists.[102] The PP1M and PP3M formulations showed comparable local tolerability in 2 minipig studies[90,91] when tested up to the maximum dose level used in humans (234 mg for PP1M and 819 mg for PP3M).

Paliperidone undergoes little or no metabolism following incubation with human liver microsomes, and does not affect cytochrome P450 activity at clinically relevant in vitro concentrations. Paliperidone is mainly metabolized by alicyclic hydroxylation, oxidative

N dealkylation, and benzisoxazole scission; alcohol dehydrogenation is an additional pathway in humans and dogs. The major route of excretion in humans (79.63%) and dogs (59.8%) was via the urine.[102]

1.1.2. Clinical Studies

1.1.2.1. Human Pharmacokinetics

Due to the very low solubility of the drug substance, paliperidone palmitate particles dissolve very slowly in the muscle and allow the release of the active substance over an extended period after injection. During development of PP1M, particle size and injected dose (injection volume and suspension strength) were shown to be key determinants of the release rate of paliperidone from the palmitate formulation. The PP3M formulation differs from the PP1M formulation in its suspension strength (200 mg eq./mL vs. 100 mg eq./mL), particle size (~7 µm vs. ~1 µm), and higher fill volume in order to ensure a physically and chemically stable 3-month formulation that is easily resuspendable and minimizes injection force.[22,102]

Paliperidone Palmitate 1-Month Injection (PP1M)

The PP1M formulation produces a slowly increasing plasma concentration of paliperidone that peaks at about 2 to 3 weeks after dosing. Potentially therapeutic plasma concentrations can be reached as early as Day 8 after administration of the recommended initiation regimen (ie, an initial IM injection of PP1M 234 mg on Day 1 and a second injection of 156 mg on Day 8, both in the deltoid muscle). Plasma concentrations decline with an average $t_{½}$ of 20 to 50 days. The total exposure (AUC) of paliperidone increased dose proportionally over the dose range studied (39 to 234 mg) in both deltoid and gluteal muscles. The C_{max} for the dose range of 39 to 234 mg increased less than dose proportionally. The C_{max} is approximately 45% higher following deltoid injections compared with gluteal injections; AUC_{∞} is similar for these injection sites.[102]

Administration of PP1M at once-monthly intervals leads to steady-state paliperidone concentrations after the fourth to fifth injection and a peak-to-trough variation of 1.7 to 2.1. The time-to-peak after repeated injections was shorter (t_{max} 3 to 5.5 days) than after single injections. For the different doses, the accumulation ratio (based on AUC) was 1.7 to 3.6.[102]

Paliperidone Palmitate 3-Month Injection (PP3M)

Following a single IM dose of 117 to 819 mg PP3M in the gluteal or deltoid muscle, paliperidone was slowly absorbed, reflected by a median t_{max} of approximately 23 to 34 days and an apparent half-life ($t_{½}$) of approximately 2 to 4 months (Study PSY-1005). These results were in general agreement with those from the population-PK model in which t_{max} was achieved within 30 to 33 days after a single injection of PP3M (273 to 819 mg), and the apparent half-life was in the range of 84 to 95 days following a deltoid injection and 118 to 139 days following a gluteal injection. The apparent half-life estimates for paliperidone after administration of PP3M from Study PSY-1005 and from the population-PK model support a once every 3 months injection cycle for PP3M.

The multiple-dose PK profile of PP3M was characterized in Study PSY-3012. Overall, steady-state conditions were maintained after switching from the PP1M formulation to the PP3M formulation. Median paliperidone predose plasma concentrations after administration of 117, 156, and 234 mg PP1M in the Transition Phase were comparable to paliperidone predose plasma concentrations after administration of the corresponding 3.5-fold higher PP3M doses (410, 546, and 819 mg, respectively) in the maintenance and double-blind phases, providing further support for the once every 3 months injection cycle for PP3M. When steady state was achieved with PP3M, the median peak-to-trough ratio (based on the population PK model) was 1.6 to 1.7 following gluteal and deltoid administrations, which is similar to the median peak-to-trough concentration ratios following deltoid PP1M injections.

Based on the population PK models developed for paliperidone when administered as PP3M, PP1M, and oral paliperidone ER, between subject variability after multiple injections of PP3M over a 3-month period was similar to the variability seen with once daily oral paliperidone ER.

Dose-proportionality of paliperidone PK was evaluated in subjects with schizophrenia and schizoaffective disorder after single-dose injection of 117 to 819 mg PP3M into both the deltoid and gluteal muscle (Study PSY-1005). Total paliperidone exposure (area under concentration time curve (AUC) and maximum plasma concentration (C_{max}) increased proportionally with dose after a single-dose injection of PP3M in either injection site. Results of the population PK analysis that included data from Study PSY-1005 and PSY-3012 also found that the PK of PP3M was dose proportional for paliperidone overall exposure and approximately dose-proportional for C_{max} over a dose range of 273 to 819 mg.

Pharmacokinetics During Conversion from PP1M to PP3M

Paliperidone plasma concentration-time profiles after at least 4 months of treatment with PP1M, followed by a transition to PP3M, were simulated for the various PP3M dose levels (273, 410, 546, and 819 mg) and compared with simulated paliperidone plasma concentration-time profiles during continuous treatment with PP1M or with the oral paliperidone ER formulation.[22]

Based on the simulations, was concluded that:[22]

- PP3M (273 to 819 mg injected once every 3 months), when administered at doses that are 3.5-fold higher than those of PP1M, appears to result in paliperidone exposure similar to the exposures obtained with doses of PP1M (78 to 234 mg once every 4 weeks) and oral paliperidone ER (4 to 12 mg once daily. The exposure range for PP3M was encompassed within the exposure range for the approved dose strengths of oral paliperidone ER.
- Based on the visual inspection of the simulation results, the between-subject variability after multiple injections of PP3M was higher over a 3-month timeperiod than the variability observed for PP1M over a 1-month time period and similar to the variability for once daily oral paliperidone ER.
- Paliperidone plasma concentrations are stable after injection of the fourth PP3M dose.

1.1.2.2. Efficacy/Safety Studies

Paliperidone Palmitate 1-Month Injection (PP1M)

Efficacy: Paliperidone palmitate 1-month injection (INVEGA SUSTENNA [or XEPLION in the European Union]) is approved in the US and numerous other countries for the treatment of schizophrenia. INVEGA SUSTENNA is also approved for the treatment of schizoaffective disorder in the US. Pivotal clinical studies supporting the safety and efficacy of PP1M in the treatment of schizophrenia include 4 short-term double-blind, randomized, placebo-controlled, fixed-dose Phase 2/3 studies in acutely relapsed subjects (R092670-SCH-201,[36] -PSY-3003, [28] -PSY-3004,[29] –PSY-3007[32]) and one long-term double-blind, placebo-controlled Phase 3 relapse prevention study (R092670-PSY-3001[25]). Additional supportive studies include a long-term Phase 1 safety study (R092670-PSY-1008[24]), three Phase 3 noninferiority studies comparing PP1M and risperidone LAI (R092670-PSY-3006,[31] -PSY-3008,[33] and -PSY-3002[26,27]), and an injection site [deltoid-gluteal] cross-over trial (R092670-PSY-3005[30]). These studies demonstrated the efficacy of PP1M (39 to 234 mg) in the treatment of the acute symptoms of schizophrenia as well as for the prevention of relapse during maintenance treatment. Long-term safety and efficacy of PP1M in schizoaffective disorder was demonstrated in one 15-month double-blind, placebo-controlled Phase 3B relapse prevention study (R092670-SCA-3004).[35]

The efficacy of PP1M compared with OAP treatment in subjects with schizophrenia has been assessed in 2 Phase 3B studies: Study R092670SCH3006 and R092670SCH3005. These studies are discussed in more detail below:

- Study R092670SCH3006[38] (also known as the PRIDE study): This was a Phase 3B, 15-month, randomized, prospective, open-label, active-controlled, parallel-group, multicenter study comparing treatment with PP1M versus OAP in prevention of treatment failure in subjects with schizophrenia. For eligibility, subjects had to have been placed into custody (ie, documented involuntary detainment by an officer of the law) at least twice, with at least one of them leading to incarceration within the 24 months before study start, and were released from the most recent custody within 90 days before the start of the screening period. The study consisted of a screening period (up to 14 days) and a 15-month open-label treatment period.

  Results from the primary efficacy analysis demonstrated that treatment with PP1M (50-150 mg eq.) was superior to treatment with an OAP in delaying time to first treatment failure ($p = 0.011$), with a hazard ratio of 1.43 (95% CI: 1.09, 1.88). A total of 90 (39.8%) subjects in the PP1M group and 117 (53.7%) subjects in the OAP group had a treatment failure event. The estimated median time (95% CI) to first treatment failure was 416 days (285, not estimable [could not be reliably estimated due to study duration]) for subjects treated with PP1M, compared with 226 days (147, 304) for subjects treated with OAP. The overall findings from this study demonstrated the efficacy and safety of PP1M in adults with schizophrenia who had been incarcerated and supported previous findings regarding the long-term efficacy and safety of PP1M in schizophrenia.

- Study R092670SCH3005 (PROSIPAL)[37]: This was a Phase 3B, randomized, open-label, rater-blinded study to compare treatment with PP1M versus treatment as usual with frequently prescribed OAPs in subjects with recently diagnosed schizophrenia who were

experiencing an acute schizophrenic episode. For eligibility, subjects needed to have been diagnosed with schizophrenia within the 1 to 5-year period before screening, with a history of treatment with antipsychotics, 2 or more relapses requiring psychiatric hospitalization in the preceding 24 months, and predicted (by the treating physician) to benefit from a switch of antipsychotic medication to either PP1M or one of the pre-specified OAPs. The study consisted of an initial acute oral treatment phase (2 weeks) and a core treatment phase (until relapse or maximally 24 months).

The primary endpoint was the time to relapse during the 24-month core treatment phase, with relapse defined according to the criteria of Csernansky et al.[40]

Based on the pre-specified relapse criteria, treatment with PP1M significantly delayed the time to relapse compared with treatment as usual with OAP during the 24-month core treatment period in subjects with recently diagnosed schizophrenia in this study (p=0.0191). A total of 52 (14.8%) subjects in the PP1M group and 76 (20.9%) subjects in the OAP group had a relapse event during the 24-month core treatment phase (p=0.0323), reflecting a 29.4% relative risk reduction for PP1M treatment versus OAPs. There was also a significantly greater improvement in psychotic symptoms at Day 8 and a trend for better symptom control at endpoint in favor of PP1M.

Overall, findings from this study provide support that long-acting treatment with PP1M is efficacious and well tolerated and may provide favorable relapse prevention compared to treatment as usual with OAP in subjects with recently diagnosed schizophrenia.

Safety: The safety profile of PP1M is well established based on the clinical trial data and the postmarketing evidence. Up to the most recent clinical cutoff date of 31 December 2013, a total of 6,160 adult subjects with schizophrenia or schizoaffective disorder have been exposed to at least one dose of PP1M in completed clinical studies (5,008 in Phase 2/3 studies and 1,152 in Phase 1 studies). Based on the 4,535,916 syringes of PP1M distributed worldwide, the estimated exposure of PP1M from launch to 31 December 2013 is 467,637 person-years.[102]

The most common treatment-emergent adverse events reported during the development program of PP1M (incidence ≥ 5% and occurring at least twice as often as placebo) were injection site reactions, somnolence/sedation, dizziness, akathisia, and extrapyramidal disorder.[68] With respect to findings possibly associated with antipsychotic use in schizophrenia or predicted by paliperidone pharmacology, unwanted cardiovascular and central nervous system effects were not common.[102] As with other drugs that antagonize D_2 receptors, paliperidone administration is associated with increases in prolactin levels, but prolactin-related adverse events were rarely reported. Metabolic issues (glucose dysregulation, obesity, and hyperlipidemia) were seldom reported, but body weight and body mass index (BMI) increased after administration of PP1M, generally in a dose-related manner, and decreased after placebo administration. Injections of PP1M were generally characterized by good local injection site tolerability; there is no evidence for a clinically notable safety risk with regard to potential systemic post-injection side effects.[102]

Refer to the Investigator's Brochure for paliperidone[102] or the current local health authority approved prescribing information for PP1M for more complete information.

Paliperidone Palmitate 3-Month Injection (PP3M)

Paliperidone palmitate 3-month injection is approved in the US and numerous other countries. The efficacy and safety of PP3M in the treatment of schizophrenia is supported by the results of a Phase 3 relapse prevention study (R092670-PSY-3012).[34] Additional safety data are available from a completed, single-dose, Phase 1 safety/PK study (R092670-PSY-1005),[23] and from a completed Phase 3 noninferiority study comparing PP3M with the PP1M formulation (R092670-PSY-3011).[22,100]

Overall, the number of adult subjects with schizophrenia who have received at least 1 dose of PP3M across the 3 completed clinical studies is 1,191. This includes 379 who received exposure to PP3M in Study PSY-3012 (at least 1 dose in Maintenance Phase), 308 who received a single dose of PP3M in Study PSY-1005, and 504 who received treatment with PP3M during the double-blind phase of Study PSY-3011.[22]

Administration of all formulations of paliperidone (oral paliperidone ER, PP1M, and PP3M) results in exposure to the same pharmacologically-active moiety, paliperidone (9-hydroxy-risperidone). Therefore, the safety of PP3M is further supported by the extensive clinical and postmarketing experience with the oral and PP1M formulations. Refer to the Investigator's Brochure[102] for the most complete information regarding paliperidone. Results of the pivotal Phase 3 study (R092670-PSY-3012) are discussed further below.

Phase 3 Study with PP3M (R092670-PSY-3012)

Study R092670-PSY-3012 was a Phase 3, randomized, multicenter, double-blind, relapse prevention study designed to evaluate the efficacy of PP3M compared with placebo in delaying the time to first occurrence of relapse in subjects with schizophrenia. This study consisted of 4 phases: a Screening Phase (up to 3 weeks); a 17-week open-label Transition Phase; a 12-week open-label Maintenance Phase; and a randomized, double-blind, fixed-dose, placebo-controlled relapse prevention phase (referred to as the Double-blind Phase) of variable duration. Men or women between 18 and 70 years of age (inclusive) who met the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV-TR) criteria of schizophrenia for at least 1 year before screening and had a Positive and Negative Syndrome Scale (PANSS) total score of <120 at screening and baseline (Day 1) were eligible for enrollment. A total of 506 subjects entered the study and received at least 1 dose of study drug during the Transition Phase; 379 subjects received at least 1 dose during the Maintenance Phase, and 305 received at least 1 dose during the Double-blind Phase.

During the Transition Phase, subjects were treated with PP1M (78-234 mg) for 17 weeks. Subjects completing the Transition Phase, and with a PANSS total score <70 at Week 17, were entered into the open-label Maintenance Phase where they received a single dose of PP3M. The dose of PP3M administered in the Maintenance Phase was 273, 410, 546, or 819 mg, calculated using a 3.5 multiple of the final PP1M dose administered during the Transition Phase (see Table 3). Subjects who met pre-defined stability criteria during the 12-week Maintenance Phase were eligible to enter the Double-blind Phase. At entry into the Double-blind Phase, subjects were randomized in a 1:1 ratio to receive PP3M (n=160) or Placebo (n=145) and monitored for

relapse. The dose of PP3M remained fixed throughout the Double-blind Phase, using the same dose level administered in the Maintenance Phase (ie, 273, 410, 546, or 819 mg), administered in the deltoid or gluteus.

Efficacy: The primary efficacy variable was time to relapse during the Double-blind phase. These relapse criteria were identical to those used in the PP1M relapse prevention study (R092670-PSY-3001).[25]

A group sequential design was utilized with one interim analysis for efficacy. Based on the preplanned interim analysis conducted by the Independent Data Monitoring Committee (IDMC) after 42 relapse events had occurred, 31 (23.0%) of 135 subjects randomly switched from open-label PP3M to double-blind placebo experienced a relapse event compared with 11 (7.4%) of 148 subjects randomized to remain on PP3M. Subjects who continued treatment on PP3M during the double-blind phase experienced relapse significantly later than those who were switched to placebo ($p<0.001$, based on log rank test). The median time to first relapse, based on Kaplan-Meier estimation, was 274 days in the placebo group and was not estimable in the PP3M group. Based on these positive findings, Study PSY-3012 was terminated as per the recommendations of the IDMC.

The final analysis of the relapse data confirmed the findings of the interim analysis. There was a statistically significant difference between the 2 treatment groups in the time to relapse with a longer time to relapse in subjects assigned to PP3M ($p<0.001$). Three times as many subjects in the Placebo group (29.0%) as in the PP3M group (8.8%) experienced a relapse event. The median estimated time to relapse was 395 days for subjects in Placebo group and not estimable for PP3M group. The 25% quantile of time to relapse was 141 days in the Placebo group and not estimable in the PP3M group, based on the Kaplan-Meier estimates. The instantaneous risk (Hazard Ratio) for relapse of schizophrenia symptoms was 3.81 (95% CI: 2.08, 6.99) ie, a subject switching to placebo was 3.81 times more likely to experience a relapse than a subject continuing to receive PP3M in the final analysis. The most common reasons for relapse were increase in PANSS total score and psychiatric hospitalization.

Safety: The PP3M formulation was generally safe and well tolerated in the R092670-PSY-3012[34] study, with a safety profile broadly consistent with that of PP1M. Across the 379 subjects who received at least 1 dose of PP3M in Study PSY-3012, the combined exposure to PP3M was 160.18 patient-years, and 28 subjects received at least 48 weeks of exposure to PP3M.[22]

During the Open-label Phase (ie, Transition Phase and Maintenance Phase combined; N=506), TEAEs were reported in 65.2% of subjects. The most common TEAEs (>5% of the subjects) in the Open-label Phase were weight increased (10.1%), insomnia (9.9%), anxiety and injection site pain (each 8.7%), and headache (6.5%). When TEAEs were assessed for the Maintenance Phase only (N=379), 42.7% subjects experienced at least 1 TEAE and the most common TEAEs were anxiety (5.8%), insomnia (4.7%), weight increased (4.5%), and headache (2.9%).

During the Double-blind Phase, 61.9% of subjects in the PP3M group and 57.9% of subjects in the Placebo group experienced at least 1 TEAE that was new in onset or worsened in severity

after the first dose of double-blind treatment. The TEAEs that were reported more frequently in the Placebo group than in the PP3M group (≥3% difference between groups) were insomnia (11.7% vs. 6.9%), schizophrenia (10.3% vs. 1.3%), and weight decreased (7.6% vs. 1.3%). The TEAEs that occurred more frequently in the PP3M group than in the Placebo group were weight increased (8.8% vs. 3.4%), headache (8.8% vs. 4.1%), nasopharyngitis (5.6% vs. 1.4%), and akathisia (4.4% vs. 0.7%).

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

PP3M injections in both deltoid and gluteal muscles were safe and well tolerated. Six PP3M and no placebo subjects reported injection site-related TEAEs during the Double-blind Phase. Investigator evaluations of swelling, redness and induration were similar across treatment groups, as were subject evaluations of injection pain as measured by a visual analog scale (VAS). No apparent dose-related effects were observed. While all injection site adverse events with objective findings and a severity assessment of “moderate” or “severe” were to be photographed, no such photographs or biopsies were taken by the investigators, indicating the well tolerated nature of observed events and supporting the overall benign tolerability profile of PP3M injectable formulation.

Overall, safety findings from study PSY-3012 were generally similar to those observed in previous studies with PP1M. Specifically, the types and incidences of AEs and ADRs, including AEs of special interest for class of atypical antipsychotics and injection site reactions, were generally consistent with those previously observed for subjects with schizophrenia treated with a once-monthly injection of PP1M. No new safety signals were detected.[22,34]

1.2. Comparator Drugs

All subjects will initially be treated with oral paliperidone ER or oral risperidone during the Part I oral run-in phase. Subjects who find either oral paliperidone ER or oral risperidone intolerable will be withdrawn from the study. Subjects who tolerate oral paliperidone ER or oral risperidone but find it inadequately efficacious after treatment for an adequate duration at an adequate dosage, per clinical judgment, may be switched to another protocol-specified OAP during Part I at the discretion of the investigator. To be eligible for randomization in Part II, subjects must be able to tolerate a minimum dose of 3 mg of oral paliperidone or 2 mg of oral risperidone for at least 2 weeks prior to entry to Part II. Subjects who enter Part II and are randomly assigned to the OAP treatment group will continue their OAP treatment from Part I. Subjects are encouraged to continue their original OAP throughout the remainder of the study, but a switch to another protocol-specified OAP is permitted if clinically indicated.

The following commercially available OAPs will be permitted: aripiprazole, haloperidol, olanzapine, oral paliperidone ER, perphenazine, quetiapine, and risperidone.

All OAPs have indications for schizophrenia. For the most up-to-date safety and efficacy information regarding these comparator drugs, please refer to the relevant local health authority approved prescribing information.

1.3. Overall Rationale for the Study

Schizophrenia is a chronic disease characterized by an early deterioration in functioning, recurrent psychotic exacerbations, and persistent deficits in cognition.[5,78] Antipsychotic medications are the cornerstone of treatment for schizophrenia, and effective management of schizophrenia requires long-term treatment to maintain symptom control and prevent relapse.[5] Discontinuation and/or intermittent use of currently available OAP drugs, however, is widespread, particularly during the early stages of the disorder.[13,115] In one study analyzing data from 2,588 patients recovering from a first psychotic episode, only 58% collected their prescription during the first 30 days of hospital discharge, and only 46% continued their initial treatment for 30 days or longer.[109] Other studies show more than 30% to 40% of patients with first-episode schizophrenia are nonadherent and discontinue medication during the first 9 months of treatment,[85,86] at which point the chances of relapse increase dramatically.[55,103,108] A recent review of clinical trials investigating relapse of symptoms following effective treatment of first-episode psychosis estimated the risk of relapse within the first year following medication discontinuation to be approximately 77% compared to a 1-year risk of relapse of 3% with continued antipsychotic therapy.[118] With each relapse, recovery is slower and less complete, the level of functioning declines, and disabling treatment-resistant symptoms may develop.[47,50,116]

Antipsychotic treatment lowers the risk of relapse and reduces the psychotic symptoms of schizophrenia[5]; however, currently available OAP medications have not received recognition to have significant benefit in terms of improving other aspects of the disorder, such as cognitive impairment. Establishing treatments for cognitive impairment is particularly important as it is highly correlated with functional ability and long-term outcome[60,66]; the search for pro-cognitive treatments that also improve functional outcomes has therefore become an important, but as yet unrealized, goal in the treatment of schizophrenia.

Recurrent relapses and persisting cognitive deficits are thought to contribute to clinical and functional deterioration in patients with recent-onset schizophrenia.[50,80] Although the course of deterioration varies, most of it occurs within the first 5 years following the onset of symptoms, and this period is considered to represent a critical period in the pathophysiology of the disease.[15,80] Imaging data also suggest that there are structural brain changes that occur early in the course of the disorder that may be exacerbated by relapses.[2,3] Furthermore, longitudinal studies show that brain tissue loss continues to progress over time, and is related to declines in cognition,, functioning, illness course and treatment outcome.[3,65,95] In addition, recent MRI studies show that deficits in some brain areas (eg, frontal lobe intracortical myelin [ICM]) can be slowed or even improved with use of antipsychotic medications.[9,10,11] These findings provide evidence that the pathophysiology of schizophrenia is progressive after the onset of illness,[45] highlighting the importance of early intervention in schizophrenia to improve adherence, reduce relapse, and prevent further disease progression.

Long-acting injectable antipsychotic formulations may offer particular advantages over OAP agents in the treatment of recent-onset schizophrenia. Clinical studies examining effectiveness of LAI antipsychotic drugs in the early stages of schizophrenia are limited, but reports in the literature suggest that atypical LAI antipsychotics are associated with good adherence and clinical outcomes in subjects with first-episode or recent-onset schizophrenia,[6,51,109,113,114] and may reduce discontinuation, relapse, and rehospitalization rates in these subjects compared with OAP agents.[52,77,107,109] Recent work by Nuechterlein, Bartzokis and Subotnik also suggest that LAI agents may be associated with greater improvements in cognition and functioning compared with OAPs in subjects with first-episode schizophrenia, and may be more effective at preserving ICM volume in the brain.[9,10,94] These results suggest that the use of an LAI antipsychotic early in the course of schizophrenia may slow disease progression and possibly modify the trajectory of the disorder, potentially leading to improved long-term outcomes.

The current study has been designed to build upon previous work by Nuechterlein, Bartzokis and Subotnik.[9,10,94] This study will compare the effectiveness of PP versus OAP treatment on delaying time to treatment failure in subjects with recent-onset schizophrenia or schizophreniform disorder. Using a novel, multi-phase study design, the study will also evaluate whether LAI treatment with PP can slow down disease progression and possibly modify disease course compared to OAP medications by tracking changes in cognition, functioning, and brain ICM volume.

2. OBJECTIVES AND HYPOTHESES

The study includes 3 treatment phases: a 2-month, open-label, flexible-dose, oral run-in phase (Part I), and 2 sequential 9-month, matched-control, randomized, open-label, active-controlled, flexible-dose treatment phases (Part II, referred to as the 'Disease Progression Phase' and Part III, referred to as the 'Extended Disease Progression and Disease Modification Phase') [see Figure 1]. Part II and Part III each have their own objectives.

2.1. Part II Objectives: Disease Progression

Subjects who complete the Part I oral run-in phase will enter Part II and will be randomized in a 1:2 ratio to either start PP treatment (ie, PP1M followed by PP3M) or to continue OAP treatment from Part I. It is expected that most subjects will be receiving oral paliperidone ER or oral risperidone at the start of Part II, but some subjects may be on an alternative OAP. The Part II treatment duration is 9 months.

Primary Objective

- To compare the effectiveness of PP versus OAP treatment (ie, oral paliperidone ER, oral risperidone, or another OAP) in delaying time to first treatment failure over 9 months' treatment in subjects with recent-onset of schizophrenia or schizophreniform disorder (see definition of treatment failure in Section 9.2.2.1, Treatment Failure).

Key Secondary Objectives:

- To evaluate changes in cognition as measured by the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB)

composite score following 9 months' treatment with PP compared to 9 months' treatment with OAP.

- To evaluate changes in functioning as measured by the Personal and Social Performance scale (PSP) following 9 months' treatment with PP compared to 9 months' treatment with OAP.
- To evaluate changes in brain ICM volume as measured by inversion recovery (IR) and spin echo (SE) magnetic resonance imaging (MRI) in the frontal lobe following 9 months' treatment with PP compared to 9 months' treatment with OAP.

Secondary Objectives:

- To evaluate changes in cognition as measured by the individual domains of the MCCB (ie, working memory, verbal learning, speed of processing, attention/vigilance, visual learning, reasoning and problem solving, and social cognition) following 9 months' treatment with PP compared to 9 months' treatment with OAP.
- To evaluate changes in illness severity as measured by the Clinical Global Impression-Severity scale (CGI-S) following 9 months' treatment with PP compared to 9 months' treatment with OAP.
- To evaluate changes in severity of psychotic symptoms, as measured by the 8 items of the Clinician-Rated Dimensions of Psychosis Symptom Severity scale (CRDPSS) (ie, delusions, hallucinations, disorganized speech, abnormal psychomotor behavior, negative symptoms [restricted emotional expression or avolition], impaired cognition, depression, and mania).
- To evaluate changes in medication satisfaction as measured by the Medication Satisfaction Questionnaire (MSQ) [patient-reported outcome] following 9 months' treatment with PP compared to 9 months' treatment with OAP.
- To assess overall safety of PP.

Exploratory Objectives:

- To assess changes in resting state functioning MRI (fMRI), and changes in cortical thickness, gray matter volume, white matter volume, ventricular volume, intrasulcal CSF volume, and subcortical myelin integrity, as measured by MRI, following 9 months' treatment with PP compared to 9 months' treatment with OAP.
- To explore the overall healthcare resource utilization use as measured by the Resource Utilization Questionnaire (RUQ) following 9 months' treatment with PP compared to 9 months' treatment with OAP.
- To explore differences in satisfaction with goal setting following 9 months' treatment with PP compared to 9 months' treatment with OAP.
- To explore quantitative assessments of daily activities following 9 months' treatment with PP compared to 9 months' treatment with OAP.

2.2. Part III Objectives: Extended Disease Progression and Disease Modification

Subjects who complete Part II will be eligible to enter Part III. At the start of Part III, subjects treated with OAP during Part II will be re-randomized in a 1:1 ratio to either continue treatment

with OAP (OAP-OAP group) or to switch to PP (OAP-PP group). Subjects treated with PP during Part II will continue the same treatment (PP-PP group). The Part III treatment duration is 9 months.

The *Extended Disease Progression* objectives will focus on comparisons between the OAP-OAP and PP-PP groups; the *Disease Modification* objectives will focus on comparisons between the PP-PP and OAP-PP groups (ie, subjects who started treatment with PP early vs. subjects who started PP treatment 9 months later).

Extended Disease Progression Objectives

Primary Objective:

- To evaluate changes in cognition as measured by the MCCB composite score following 18 months' treatment with PP compared to 18 months' treatment with OAP in subjects with recent-onset schizophrenia or schizophreniform disorder.

Key Secondary Objectives:

- To evaluate changes in functioning as measured by the PSP following 18 months' treatment with PP compared to 18 months' treatment with OAP.
- To evaluate changes in brain ICM volume in the frontal lobe following 18 months' treatment with PP compared to 18 months' treatment with OAP.

Secondary Objectives:

- To evaluate changes in cognition as measured by the individual domains of the MCCB following 18 months' treatment with PP compared to 18 months' treatment with OAP.
- To evaluate changes CGI-S following 18 months' treatment with PP compared to 18 months' treatment with OAP.
- To evaluate changes in severity of psychotic symptoms, as measured by the 8 items of the CRDPSS following 18 months' treatment with PP compared to 18 months' treatment with OAP.
- To evaluate changes in medication satisfaction as measured by the MSQ (patient-reported outcome) following 18 months' treatment with PP compared to 18 months' treatment with OAP.
- To evaluate differences in time to first treatment failure and subsequent treatment failures over 18 months' treatment with PP compared to 18 months' treatment with OAP.
- To assess overall safety of PP.

Exploratory Objectives:

- To assess changes in resting state fMRI, and changes in cortical thickness, gray matter volume, white matter volume, ventricular volume, intrasulcal CSF volume, and subcortical myelin integrity, as measured by MRI following 18 months' treatment with PP compared to 18 months' treatment with OAP.
- To explore the overall healthcare resource utilization use as measured by the RUQ following 18 months' treatment with PP compared to 18 months' treatment with OAP.

- To explore differences in satisfaction with goal setting following 18 months' treatment with PP compared to 18 months' treatment with OAP.
- To explore quantitative assessments of daily activities following 18 months' treatment with PP compared to 18 months' treatment with OAP.

Disease Modification Objectives:

Primary Objective

- Using a delayed-start approach, to compare changes in cognition as measured by the MCCB composite score following 9 months' additional PP treatment in subjects originally randomized to PP (PP-PP group) compared to 9 months' delayed-start PP treatment in subjects originally randomized to OAP treatment (OAP-PP group).

Key Secondary Objectives:

- Using a delayed-start approach, to compare changes in functioning as measured by the PSP following 9 months' additional PP treatment in subjects originally randomized to PP (PP-PP group) compared to 9 months' delayed-start PP treatment in subjects originally randomized to OAP treatment (OAP-PP group).
- Using a delayed-start approach, to compare changes in brain ICM volume in the frontal lobe following 9 months' additional PP treatment in subjects originally randomized to PP (PP-PP group) compared to 9 months' delayed-start PP treatment in subjects originally randomized to OAP treatment (OAP-PP group).

2.3. Hypothesis

The overall primary hypothesis to be tested in this study is that 9 months' treatment with PP is superior to 9 months' treatment with OAP in delaying time to first treatment failure in subjects with recent-onset schizophrenia or schizophreniform disorder. The primary efficacy null hypothesis is that there is no difference in the distribution of time to first treatment failure in Part II between the PP and OAP treatment groups.

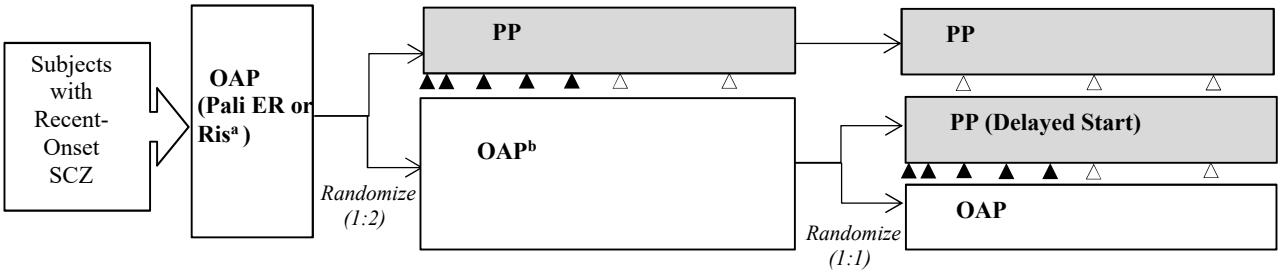
See Section 11.1, Hypotheses, for details regarding additional hypotheses to be evaluated in this study.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a prospective, matched-control, randomized, open-label, active-controlled, flexible-dose, multicenter study to assess time to treatment failure and to measure changes in cognition, functioning, and ICM volume in subjects with recent-onset schizophrenia or schizophreniform disorder treated with PP versus OAPs. Other efficacy, safety, and exploratory endpoints will also be assessed. An overview of the study design is provided in Figure 1.

Figure 1: Overview of the Study Design



▲ = PP1M injection
△= PP3M injection

[a] All subjects will be started on oral paliperidone ER or oral risperidone. Subjects who find oral paliperidone ER/oral risperidone intolerable will be withdrawn from the study; subjects who tolerate oral paliperidone ER/oral risperidone but find it inadequately efficacious may be switched to another protocol-specified OAP at the discretion of the investigator.

[b] Subjects randomized to the OAP treatment group will continue their OAP treatment (ie, oral paliperidone ER, or other OAP) from Part I.

Note: For optimal management of symptoms/tolerability, subjects receiving PP3M (during either Part II or Part III) may go back to treatment with PP1M (monthly injections of 78, 117, 156 or 234 mg, flexibly dosed) for further dose adjustment or for the duration of the trial with the approval of the medical monitor.

OAP=oral antipsychotic; Pali ER=paliperidone extended-release; Ris= oral risperidone; PP=paliperidone palmitate; PP1M=paliperidone palmitate 1-month injection; PP3M=paliperidone palmitate 3-month injection; SCZ=schizophrenia or schizophreniform disorder.

Approximately 275 men and women between the age of 18 and 35 years with a Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) diagnosis of schizophrenia or schizophreniform disorder who experienced their first psychotic episode within 2 years of study entry will be enrolled in this study. Refer to Section 4.1 for further details regarding inclusion/exclusion criteria. The total study duration for each subject will be approximately 86 weeks, including a screening phase (up to 4 weeks), a 2-month oral run-in phase (Part I), and two 9-month treatment periods (Part II and Part III). The study periods are briefly described below:

- **Screening phase (up to 4 weeks; Day -28 to -1):** Subjects who provide written informed consent will undergo the screening procedures, including a review of the study entry criteria. Any prestudy OAP other than oral risperidone or oral paliperidone ER will be tapered off and must be discontinued by Week 5 of Part I. Subjects already treated with oral risperidone or oral paliperidone ER should be continued at the dose deemed to be most appropriate by the investigator). Tapering of the previous OAP can start at the beginning of the screening period. Tapering and discontinuation should be managed by the investigator, as clinically appropriate.
- **Part I: Oral Run-In Phase (2 months):** After completing the screening period, subjects meeting the inclusion and exclusion criteria will be entered into Part I, a 2-month oral run-in phase. All subjects will initially receive flexible dosing with oral paliperidone ER (1.5-12 mg/day) or with oral risperidone (1-6 mg/day). Treatment with oral paliperidone ER or oral risperidone will enable investigators to establish tolerability of paliperidone prior to randomization to the LAI formulation in Part II. Subjects who find either oral paliperidone ER OR oral risperidone intolerable will be withdrawn from the study. Subjects who tolerate oral paliperidone ER/oral risperidone but find it inadequately efficacious after treatment for an adequate duration at an adequate dosage (per clinical judgment) may be switched to another protocol-specified OAP. Any of the following 7 OAPs are permitted: aripiprazole, haloperidol, olanzapine, paliperidone ER, perphenazine, quetiapine, and risperidone. The

following demographic, baseline characteristic, and clinical data will be determined during Part I to be used for matching during randomization into Part II and Part III: age, gender, race, prior antipsychotic exposure, substance use history, MCCB composite score, and PSP total score (see Section 5, Treatment Allocation and Blinding). To be eligible for randomization in Part II, subjects must be receiving a minimum dose of 3 mg of oral paliperidone ER or of 2 mg of oral risperidone for at least 2 weeks prior to entry to Part II.

- **Part II: Disease Progression Phase (9 months):** Subjects who complete Part I with acceptable run-in dosages will be eligible to enter Part II. On Day 1 of Part II (Day 57 of Part I), subjects will be randomized in a 1:2 ratio to open-label treatment with either PP or continued OAP treatment for 9 months. Dynamic central randomization will be performed based on matching criteria determined in Part I. It is estimated that approximately 225 subjects will be randomized in Part II; therefore approximately 75 subjects will be randomized to the PP treatment group and 150 subjects to the OAP group.
  - Subjects randomly assigned to the OAP treatment group will continue their OAP treatment from Part I. It is expected that most subjects will be receiving oral paliperidone ER or oral risperidone, but some subjects may be receiving an alternative OAP. Investigators are encouraged to continue the original OAP (ie, the OAP prescribed at Part II baseline) as monotherapy throughout the remainder of the study but, if clinically indicated, a switch to an alternative OAP or add-on of an additional OAP is permitted after the first randomization visit. Switching or add-on of another OAP due to inadequate efficacy, tolerability, or safety will be assessed as a treatment failure (see definition of treatment failure, Section 9.2.2.1, Treatment Failures). Subjects with treatment failure will continue participation in the study. The same 7 OAPs indicated for Part I are allowed (ie, aripiprazole, haloperidol, olanzapine, paliperidone ER, perphenazine, quetiapine, and risperidone).
  - Subjects randomly assigned to the PP treatment group will receive a minimum of 5 doses of PP1M followed by PP3M once every 12 weeks. PP1M initiation dosing (first injection 234 mg on Day 1 of Part II and second injection 156 mg on Day 8, both in the deltoid muscle) followed by 3 injections of flexible doses (78, 117, 156, or 234 mg) of PP1M on Days 36, 64, and 92, either in the deltoid or gluteal muscle. On Day 120, subjects will receive an injection of PP3M (using a 3.5-fold multiple of the PP1M dose received on Day 92) either in the deltoid or gluteal muscle, if in the investigator's judgment, the subject is receiving an optimal maintenance dose of PP1M. On Day 204, subjects will receive injections of flexible doses (273, 410, 546, or 819 mg) of PP3M either in the deltoid or gluteal muscle. In some cases, if on Day 120 the investigator feels they have not identified the appropriate maintenance dose of PP1M, with approval of the medical monitor and sponsor the subject may continue to receive flexible doses of PP1M injections on Day 120, 148, and 176, and on Day 204 receive an injection of PP3M (using a 3.5-fold multiple of the PP1M dose received on Day 176) either in the deltoid or gluteal muscle. Investigators are encouraged to use PP1M and PP3M as antipsychotic monotherapy and to adjust the injection dose for management of symptoms/tolerability. If required, supplemental oral paliperidone ER (up to 6 mg/day) or oral risperidone (up to 3 mg/day) may be given between injections. It should be noted that adding oral paliperidone or oral risperidone will not be considered a treatment failure unless supplemental oral paliperidone ER or oral risperidone is given for a combined total of more than 84 days or if oral paliperidone ER doses exceed 6 mg/day or oral risperidone doses exceed 3 mg/day (see Section 0 for further details on allowed

OAP usage in the PP treatment group). Adding any other antipsychotic will also be considered a treatment failure. Subjects with treatment failures will continue the study unless the PP injection is discontinued permanently.

- **Part III: Extended Disease Progression and Disease Modification (9 months):** Subjects who complete Part II will be entered into Part III. On Day 1 of Part III (Day 260 of Part II), subjects in the OAP treatment group will be re-randomized in 1:1 ratio to continued treatment with their OAP (OAP-OAP group) or to PP (OAP-PP or 'Delayed-start PP' group). The Delayed-start PP group will receive PP1M and PP3M treatment as described in Part II (ie, a minimum of 5 doses of PP1M followed by PP3M once every 12 weeks). Subjects previously assigned to treatment with PP in Part II will continue in that treatment group with PP3M injections every 12 weeks for a total of 3 injections (PP-PP group). Randomization will be based on matched criteria identified in Part I. Subjects will be followed for an additional 9 months.
- Subjects will be assessed for treatment failure at all visits during Part II and Part III. Efficacy assessments (MCCB, PSP, CGI-S, CRDPSS, and MSQ) will be performed as specified in the Time and Events Schedule. Safety will be monitored through evaluation of AEs, clinical laboratory parameters, vital signs, ECGs, body weight, ESRS, ISST-Plus, and physical examination findings. Resource use (measured using the RUQ), goal setting experience, and quantitative assessment of daily activities will be assessed as exploratory endpoints. A pharmacogenomic blood sample will be collected from subjects who consent separately to this component of the study (where local regulations permit). Subject participation in pharmacogenomic research is optional.
- For optimal management of symptoms/tolerability, subjects receiving PP3M (during either Part II or Part III) may go back to treatment with PP1M (monthly injections of 78, 117, 156 or 234 mg, flexibly dosed) for further dose adjustment or for the duration of the trial with the approval of the medical monitor.

Approximately half of the enrolled subjects will also undergo brain MRI scans for assessment of ICM volume and other exploratory MRI endpoint at selected study sites. In addition, approximately 20 healthy control subjects (comparable in age, sex, race, and highest parental education to the subjects with schizophrenia/schizophreniform disorder undergoing MRI scans) will be identified at each MRI center and followed as controls for the MRI machine calibration for the duration of the study without treatment.

Note that subjects who experience a treatment failure and do not withdraw consent or meet the criteria for withdrawal (see Section 10.2, Withdrawal from the Study) will continue in the study and be followed through to the end of the study.

Subjects who miss scheduled injections or visits are allowed to re-enter the same assigned treatment group of the study (see Section 9.1.7, Re-Entry Following Missed Injections).

3.2. Study Design Rationale

3.2.1. Overall Design Concept

The primary objective of Part II is to compare effectiveness of PP versus OAP on delaying time to treatment failure in subjects with recent-onset schizophrenia. Treatment failure was selected as

the primary outcome because stopping or changing medication is a frequent occurrence in patients with recent-onset schizophrenia, and discontinuation or inconsistent use of antipsychotic medication can have a significant impact on symptom control and disease course.[50] This measure integrates assessments of efficacy, safety, and tolerability and also captures potential outcomes of treatment failure (eg, hospitalization, arrest) to provide a global effectiveness measure that reflects 'real-world' treatment scenarios.

The study will also measure changes in cognition (MCCB), functioning (PSP), brain imaging assessments (ICM volume), and overall treatment response in order to examine whether LAI treatment with PP can slow disease progression and possibly modify disease course compared to OAP medications in subjects with recent-onset schizophrenia or schizophreniform disorder. The underlying premise is that changes in these measures represent a way to track disease progression (ie, disease worsening) in patients with schizophrenia/schizophreniform disorder. Changes in frontal lobe ICM will be measured to extend earlier work by Nuechterlein, Bartzokis, and Subotnik[9,10,94] suggesting that these neuroanatomical changes track with changes in cognition and functioning. Other efficacy, safety, and exploratory assessments will also be measured; see Section 9 for full details.

Disease modification is defined as a modification of the underlying pathophysiology of the disease that results in a beneficial outcome on the overall course of the disorder. In order to evaluate disease modification, the sponsor has developed a unique clinical trial design which builds upon the randomized delayed-start design proposed by Dr. Paul Leber in 1996.[79] In the traditional delayed-start design,[79] subjects are initially randomized to an active intervention arm or to placebo. After an interval of time sufficient to demonstrate a difference in an efficacy measure between the two groups, the placebo group switches to the active drug. If subjects who begin active drug late 'catch up' with those who begin the active drug earlier, the treatment response is assumed to be symptomatic; if on the other hand, the delayed treatment arm fails to improve to the degree demonstrated by the active treatment arm, then disease 'modification' is supported. In this design, the underlying interpretive principle is that early treatment with a disease modifying drug should continue to provide a benefit compared to later initiation of treatment; that is, early (longer) treatment provides a persistent benefit that cannot be achieved if treatment is delayed, presumably due to an effect on the underlying pathology that cannot be "re-captured".

There are several challenges associated with the traditional delayed-start design.[41,42] In this setting, it is uncertain how long subjects might require treatment before a therapeutic response could be demonstrated. In addition, the 2 arms of the trial are starting at different levels of disease severity, and it is not clear how this might affect the calculation of therapeutic response. Interpretation of results is also hampered by the need for long follow-up periods and the effect of dropouts, particularly if this is different in the two periods. Although here has been regulatory support for this study design,[49,53,81] there have been few applications and, to date, this approach has not been successfully used in a clinical trial to establish a disease modifying effect.

In order to address some of the limitations of traditional delayed-start designs, the sponsor has built in some modifications into the current study; these modifications include a hybrid of

randomized and epidemiologic design approaches that introduces a run-in period (Part I) and implements a second randomization at the start of the delayed-start treatment phase (Part III). The run-in period will be used to collect demographic and baseline characteristic data (including age, gender, race, prior antipsychotic exposure, MCCB composite score, PSP score, and substance use history) which will be used as the basis for a matched-control analysis for evaluating disease modification in Part III. This treatment phase will also help to identify subjects who have a propensity to discontinue the study, and so will help reduce dropouts during the Part II/Part III treatment phases.

Strong efforts will be made to retain subjects in the study by allowing flexibility in treatment and 'real-world' visit structure. Nevertheless, it is inevitable that some subjects will drop out early which could result in a discontinuation bias. Management of this potential bias will be addressed by re-randomizing subjects at the onset of Part III of this trial using a matched pairing approach and analyzing results according to the intent-to-treat (ITT) principle.

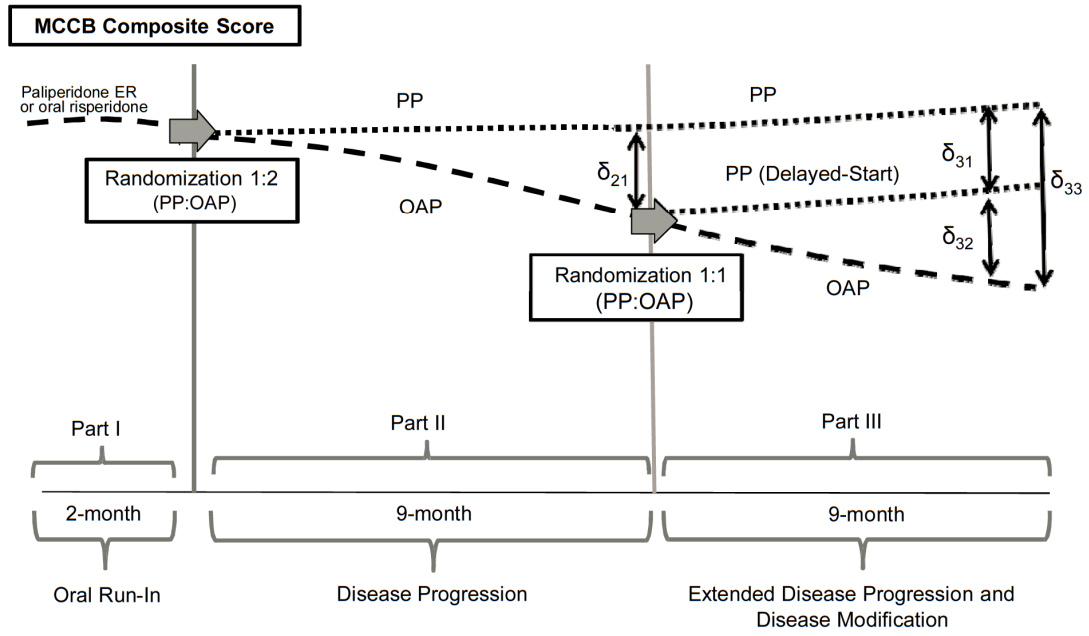
The hypothesized effect of PP versus OAP on Disease Progression and Disease Modification is summarized in Figure 2, based on the predicted change from baseline in the MCCB composite score over time.

At the end of Part II, the database will be locked and data analyzed to determine if there is an early treatment effect (δ_{21}= treatment effect on disease progression) demonstrating superiority of PP relative to oral control. Differences between the 2 treatment groups will be assessed for cognition (MCCB), functioning (PSP), and ICM volume.

At the onset of Part III subjects in the OAP arm will be re-randomized to continued treatment with their prior OAP or to PP. Subjects will be followed for an additional 9 months. Three effects (outcomes) will be assessed for a given endpoint: δ_{31}, δ_{32}, and δ_{33}. The quantity δ_{31} represents the lead treatment effect after an early start with 18 months of PP treatment and shows the lead effect remaining in the early start group over the delayed-start effect after a 9-month treatment duration. The quantity δ_{32} represents the delayed-start effect on disease progression for PP compared to continuing OAP after 9 months of additional treatment. The quantity δ_{33} represents the cumulative effect on extended disease progression at the end of Part III following early start for PP compared to continuing OAP after a total of 18 months of treatment.

At the end of Part III, the database will again be locked and data analyzed to assess response in variables δ_{31}, δ_{32}, and δ_{33}. Positive results (δ_{33} is significant [a differential treatment effect is still evident] **and** δ_{31} is significant [the lead effect remains significant after 9 months]) will be used to support a conclusion of disease modification using MCCB composite score. Similar observations for changes in PSP and ICM will be assessed.

Figure 2: Hypothesized Disease Progression and Disease Modification Effect (Based on Change in MCCB Composite Score Over Time [for Illustration Purposes Only])



ER= extended-release; MCCB= MATRICS Consensus Cognitive Battery; OAP=other antipsychotic; PP=paliperidone palmitate
δ_{21}:Treatment effect on disease progression; δ_{31}:Lead treatment effect; δ_{32}:Delayed-start treatment effect on disease progression; δ_{33}:Overall effect of treatment.

3.2.2. General Design Elements

3.2.2.1. Subject Selection Criteria

Subjects with Schizophrenia or Schizophreniform Disorder

The study will enroll men and women between the age of 18 and 35 years with a DSM-5 diagnosis of schizophrenia or schizophreniform disorder who experienced their first psychotic episode within 24 months prior to the screening visit.

Evidence suggests that schizophrenia is particularly progressive during the first years after initial manifestation of symptoms, and that this period represents a critical period in the pathophysiology of the disease.[15,80] Recurrent relapses (often due to nonadherence to antipsychotic medications) and persisting cognitive deficits are thought to play a role in the clinical and functional deterioration in patients with recent-onset schizophrenia.[50,80] Although the extent of deterioration can vary across individual patients, the deterioration process predominantly occurs in the early phases of the illness—in the prepsychotic prodromal period and during the first 5 to10 years after the initial episode.[80] Brain imaging studies also show there are volumetric changes in the brain that are rapidly progressing during the early stages of the disease,[3,65,95] which may be exacerbated by relapse.[2,110] These results highlight the importance of early intervention in patients with recent-onset schizophrenia to prevent further relapses, reduce clinical deterioration and to improve long-term outcomes.

It is hypothesized that the improved adherence and consistent antipsychotic coverage that can be achieved with an LAI formulation may offer particular advantages over OAP agents in the treatment of recent-onset schizophrenia or schizophreniform disorder. Studies comparing LAI agents versus OAP agents in the treatment of recent-onset schizophrenia are limited, but available data suggest LAI agents may improve adherence, reduce relapse,[77,107] improve cognitive and functional outcomes,[94] and preserve ICM volume in the brain[9,10] more effectively than oral agents. This study seeks to extend these findings using the LAI formulation of paliperidone.

Subjects within a limited age range (18 to 35 years) will be enrolled; this age range is inclusive of the age of onset for the large majority of patients who are able to give informed consent to participate in such a study. Expanding the age group beyond 35 may result in inclusion of persons who have had an undiagnosed but active disease which is already considerably progressed and may be less impacted by this treatment approach.

Inclusion of a Healthy Control Group

A separate cohort of healthy subjects who are comparable in age, sex, and race to the subjects with schizophrenia/schizophreniform disorder undergoing MRI scans will be identified at each MRI center and followed as controls for the MRI machine calibration for the duration of the study without treatment. These individuals will receive MRI scans but will not undergo any other study assessments. The purpose of inclusion of a healthy control group that undergoes MRI scans over a similar time period is to standardize the change in ICM for the patient group relative to normal controls, and to detect and correct magnetic drift of the MRI machine during the study.

3.2.2.2. Selection of Efficacy and Safety Evaluations

Efficacy Evaluations

Treatment Failure

Discontinuation and frequent switching of antipsychotic medication are common in the treatment of patients with recent-onset schizophrenia. The main reasons for discontinuing or changing antipsychotic medications can include lack of efficacy, tolerability issues, poor adherence, patient lack of insight, or patient preference.[64] Ideally the clinician is involved in patient decisions regarding medication changes, but this is not always the case. In these situations, the first indication that a subject has discontinued treatment may be when symptom recurrence leads to hospitalization, arrest, or even suicide. Multiple relapses are associated with clinical and functional deterioration, and relapse may also have a negative impact on the neuroanatomy of the brain in patients with schizophrenia.[2,5,50] Therefore, maintaining patients on consistent antipsychotic therapy is an important aim, particularly during the early stages of the disorder.

The primary endpoint of Part II is time to treatment failure. Treatment failure is a robust and well-characterized endpoint including a composite of various measures (see definition in Section 9.2.2.1, Treatment Failure). This endpoint integrates measures of efficacy, safety, and tolerability to provide a global measure of effectiveness which reflects real-world treatment

scenarios. Its clear definition allows investigators to apply it consistently under most circumstances, making it well suited to pragmatic study designs.

Cognition (MCCB)

Neurocognitive impairment is a core and enduring component of schizophrenia. Measures of certain crucial functions, such as attention, memory, executive functions, and motor speed, in patients have been reported to reach 2 standard deviations below the mean for healthy comparison subjects.[63,73] Neurocognitive impairment is usually already present at the first episode of psychosis, and patients with a first episode of psychosis may be as severely impaired in many cognitive domains as patients with chronic schizophrenia.[14,67,83,92,105]

Neurocognitive impairment is associated with key features of schizophrenia, such as outcome and adaptive dysfunction, including the inability to acquire skills, poor social problem solving, and poor community functioning.[58,60,62,66] Indeed, there is increasing evidence that cognitive impairment may be a stronger correlate of poor outcome than other symptom domains.[60,66] The severity of cognitive impairment also predicts poorer treatment adherence and increased relapse risk in first-episode patients.[19,20,101] Due to the clinical relevance of neurocognitive impairment in schizophrenia and in particular its relationship to poor functional outcomes, development of new approaches to enhance cognition in schizophrenia remains one of the most pressing challenges in psychopharmacology.

Overall, first-generation (typical) antipsychotics have had little benefit in treating the cognitive disturbances of patients with schizophrenia. Oral atypical antipsychotics (clozapine, risperidone, olanzapine, and quetiapine) have been reported to result in some improvement in cognitive performance.[74,75,117] However, data from the National Institute of Mental Health (NIMH)-sponsored Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) and the European First Episode Schizophrenia Trial (EUFEST) trials have failed to confirm the superiority of atypical agents vs. typical agents on cognitive function,[43,71] and patients treated with atypical antipsychotics continue to show marked deficits in cognition. Furthermore, some studies suggest that the improvements in neurocognition observed with atypical antipsychotics may be no greater than placebo or practice effects.[56]

In response to the lack of effective cognitive treatments, the NIMH sponsored the MATRICS initiative in order to bring together academic, industrial, and governmental bodies to address this unmet therapeutic need.[59,73] This initiative facilitated the development of guidelines for the design of clinical trials of drugs for neurocognitive impairment in schizophrenia,[16,17] and created the MCCB[72,76,93] for measuring cognitive treatment outcomes in schizophrenia. The MCCB has been endorsed by the FDA as the gold standard for use in trials of pharmacological agents targeting cognition in schizophrenia,[17] and will be the primary cognitive endpoint in this study.

Functioning (Personal and Social Performance Scale)

Improving patient functioning and preventing further deterioration of functioning is an important goal in the treatment of schizophrenia.[16] Several instruments have been proposed over the years

to measure functioning in schizophrenia. Of these, the PSP captures information about several functional domains as well as providing an overall score, and has been shown to be useful across cultures. It has been proposed as being well suited for measurement of functioning in schizophrenia,[18,88,97] and will be used in this study. The validity and reliability of the PSP in patients with schizophrenia have been previously reported.[69,88,89,98]

Other Efficacy Assessments

Schizophrenia symptoms will be assessed throughout the study using the CGI-S[61] and the DSM-5 CRDPSS.[4] The CGI-S provides a global assessment of disease severity and is a well-accepted tool that has been widely used in clinical trials and is easy to administer in general practice. The CRDPSS is one of the 'emerging measures' developed by the American Psychiatric Association (APA) to monitor treatment progress in patients with schizophrenia.[4] This measure assesses the severity of mental health symptoms that are important across psychotic disorders, including delusions, hallucinations, disorganized speech, abnormal psychomotor behavior, negative symptoms (restricted emotional expression or avolition), impaired cognition, depression, and mania. The severity of these symptoms can predict important aspects of the illness, such as the degree of cognitive and/or neurobiological deficits.

The MSQ, a patient-reported outcome, will be used to assess subjects' general medication satisfaction. Previous research in patients with schizophrenia has demonstrated that positive symptom improvement is associated with increased medication satisfaction measured by MSQ.[54,112]

Brain Imaging Assessments

Structural and functional brain abnormalities have been extensively and consistently described in patients with schizophrenia. High-resolution MRI studies evaluating brain volume measurements in patients with schizophrenia at the time of illness onset have indicated that patients have smaller mean volumes in many regions, particularly the frontal lobes, when compared with healthy volunteers. Furthermore, longitudinal studies have shown that the mean differences in brain volumes continue to progress over time, and are related to illness course and treatment outcome.[3,65,95] These findings suggest that although schizophrenia may arise from a neurodevelopmental diathesis, its pathophysiology may be progressive after the onset of illness.[45]

Results of a recent longitudinal MRI study in patients with first-episode schizophrenia suggest that progressive brain changes are most pronounced during the early years after onset of schizophrenia,[3] and that the magnitude of these changes may be related to relapse duration.[2] Results of this study showed significant decreases in both white matter and gray matter regions and an increase in CSF over time in patients with schizophrenia compared with healthy controls.[3] One possible explanation for a decline in white matter after the clinical onset of schizophrenia is that normal processes are diminished, eg, normal white matter expansion[8] is reduced, because of an impairment in myelination and factors that affect it.[12]

The importance of myelin pathology in schizophrenia is widely recognized.[7,12,44,48] Imaging and post-mortem studies provide converging evidence that patients with schizophrenia have a dysregulated frontal lobe myelination.[12] A dysregulation in this myelination process is hypothesized to result in an insufficient capacity to maintain temporal synchrony of the brain's widely distributed functional neural networks and thus manifest in the heterogeneity of symptoms and cognitive impairments that characterize disorders such as schizophrenia.[7,12,48]

A method has recently been developed using IR MRI images that measures myelinated white matter and ICM volumes.[11] Initial studies using this method indicate that atypical antipsychotics may increase ICM volume in patients with schizophrenia, and that this effect is most pronounced with LAI antipsychotic formulations.[9,10,11] In a recent randomized study, patients with first-episode schizophrenia treated with the LAI formulation of risperidone for 6 months showed a significant increase in ICM volume when compared with healthy control subjects, whereas patients receiving oral risperidone for 6 months showed no change in ICM volume versus healthy subjects. Increased myelin volume was also found to be significantly associated with improved cognitive function, with faster reaction times observed on 2 higher-order executive tasks involving working memory and mental flexibility.[9] Results of this prospective study suggest that, early in the course of illness, antipsychotic medications may act, at least in part, by increasing ICM in patients with schizophrenia. In addition, the data suggest that medication delivery mode (LAI vs. oral) may have a significant differential effect on ICM volume.[9,10] Therefore, ICM volume is selected as a pathophysiology biomarker for evaluating disease progression and disease modification in this study.

Exploratory Assessments

The RUQ will be administered to capture information related to socio-demographics (eg, education level, employment status), daily living (eg, accommodation status, financial management), hospitalizations, emergency room visits, partial hospitalizations, outpatient and additional services.

Subjects will set up to 3 personal goals and up to 3 health goals at the start of each treatment phase. The patient goals are not binding but progress towards attaining these goals will be followed throughout the study. Learning to set and work towards personal goals is an important aspect of recovery in those with serious mental illness. Self-determination and self-direction are the foundations for recovery as individuals define their own life goals and design their unique path(s) towards those goals. Individuals optimize their autonomy and independence to the greatest extent possible by leading, controlling, and exercising choice over the services and supports that assist their recovery and resilience. In doing so, they are empowered and provided the resources to make informed decisions, initiate recovery, build on their strengths, and gain or regain control over their lives.[104]

The Quantitative Assessment of Daily Activities is a patient-reported outcome which will be used to document the time a subject spends in a broad array of common daily activities. Categories include sleep and rest, self-care, work, recreation and social activities.

DNA Collection

It is recognized that genetic variation can be an important contributory factor to interindividual differences in drug distribution and response and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain interindividual variability in clinical outcomes and may help to identify population subgroups that respond differently to a drug. The goal of the pharmacogenomic component is to collect DNA to allow the identification of genetic factors that may influence the pharmacodynamics, efficacy, safety, or tolerability of paliperidone palmitate compared with oral antipsychotics, and to identify genetic factors associated with schizophrenia or schizophreniform disorder.

Safety Evaluations

Safety evaluations for this study will include the monitoring of adverse events, clinical laboratory tests, ECGs, vital sign measurements (temperature, pulse, and blood pressure), weight, and the monitoring of extrapyramidal symptoms using the Extrapyramidal Symptom Rating Scale-Abbreviated (ESRS-A). The risk of suicide is elevated in patients with schizophrenia compared with the general population,[96] particularly in recent-onset patients.[99] Suicidality will be assessed by the InterSePT Scale for Suicidal Thinking (ISST-Plus).

3.2.2.3. Treatment and Dose Selection Rationale

Oral Antipsychotic Treatment Group

This study is designed to compare the effectiveness of PP to OAP treatment in subjects with recent-onset schizophrenia. Oral antipsychotics were selected as the active comparator because this is the standard therapy for the large majority of recent-onset patients (nearly 100%) yet it is associated with very high long-term non-adherence.[39,70,84] According to the literature, at least 30% to 40% of patients will discontinue treatment within the first 9 months, [85,86] with these proportions increasing to 50% within 1 year and 75% within 2 years of beginning treatment.[57,115]

In this study, all subjects will initially receive treatment with oral paliperidone ER or oral risperidone during the Part I oral run-in phase. Subjects who find oral paliperidone ER or oral risperidone inadequately efficacious after treatment for an adequate duration at an adequate dosage per clinical judgment, may be switched to another protocol-specified OAP during Part I at the discretion of the investigator. Subjects who find either oral paliperidone ER or oral risperidone intolerable will be withdrawn from the study prior to randomization. It is expected that most subjects will be on oral paliperidone ER or oral risperidone treatment at the end of Part I. To be eligible for randomization in Part II, subjects must be able to tolerate a minimum dose of 3 mg of oral paliperidone or 2 mg of oral risperidone for a minimum of 2 weeks prior to entry to Part II.

At Day 1 of Part II, subjects will be randomized in a 1:2 ratio to either start PP or to continue their OAP treatment from Part I. Before randomization, subjects must be evaluated by the investigator to assess their suitability to enter Part II. If for any reason the investigator considers it clinically inappropriate for a given subject to be randomized to PP, the subject should be

withdrawn from the study prior to randomization. After the initial randomization visit, subjects in the OAP group will have the flexibility to switch to another OAP or add another OAP if clinically indicated. This flexibility has been incorporated to address the unique risk:benefit profile of each individual patient, to improve subject retention, and to mimic real-world practice as much as possible. While such medication changes are permitted in the OAP group, investigators are encouraged to continue the original OAP (ie, the OAP prescribed at Part II baseline) as monotherapy throughout the study, and to only make switches or use add-on OAP treatment if clinically required. Any switch to an alternative OAP or add-on of another OAP due to inadequate efficacy, tolerability, or safety will be considered a treatment failure (see Section 9.2.2.1, Treatment Failure).

Subjects who complete Part II will be eligible to enter Part III. The second randomization will be performed on Day 1 of Part III for the subjects who are randomized to OAP treatment during Part II. These subjects will be randomized in a 1:1 ratio to either start PP or to continue their OAP treatment from Part II. Before randomization, subjects must be evaluated by the investigator to assess their suitability to enter Part III. If for any reason the investigator considers it clinically inappropriate for a given subject to be randomized to PP, the subject should be withdrawn from the study prior to randomization. Similarly, as in Part II, subjects in the OAP group will have the flexibility to switch to another OAP or add another OAP if clinically indicated during Part III. Any switch to an alternative OAP or add-on of another OAP due to inadequate efficacy, tolerability, or safety will be considered a treatment failure.

Seven OAP agents will be permitted in the OAP treatment group: aripiprazole, haloperidol, olanzapine, paliperidone ER, perphenazine, quetiapine, and risperidone. These agents were selected as they have all demonstrated efficacy in the treatment of schizophrenia, and represent the most commonly used antipsychotics in US. All OAPs should be administered in accordance with the label.

Paliperidone Palmitate (PP1M/PP3M)

Subjects randomized to the PP treatment group will be initiated on PP1M and then transitioned to PP3M. Subjects previously stabilized on a range of doses of oral paliperidone ER or oral risperidone can attain similar paliperidone steady-state exposure during maintenance treatment with PP1M monthly dosing (following standard initiation dosing; see Section 6.2.1). Table 1 and Table 2 provide suggestions for maintenance doses of PP1M based on the selected treatment dose of oral paliperidone ER or oral risperidone, respectively.

Table 1: Doses of Oral Paliperidone ER and PP1M Needed to Attain Similar Steady-State Paliperidone Exposure During Maintenance Treatment

Formulation	Oral Paliperidone ER	PP1M
Dosing Frequency	Once Daily	Once Every 4 Weeks (deltoid or gluteal)
Dose	3 mg	78 mg
	6 mg	117 mg
	9 mg	156 mg
	12 mg	234 mg

Table 2: Doses of Oral Risperidone and PP1M Needed to Attain Similar Steady-State Paliperidone Exposure During Maintenance Treatment

Formulation	Oral Risperidone [a]	PP1M Monthly Maintenance Injection
Dosing Frequency	Daily	Once Every 4 Weeks (deltoid or gluteal)
Dose		
	2 mg	78 mg
	3 mg	117 mg
	4 mg	156 mg
	6 mg	234 mg

[a] Conversion factor: 1 mg oral RIS = 39 mg PP1M. Note: The conversion does not take into account the potential effects of CYP2D6 inhibitors (i.e. paroxetine, sertraline or fluoxetine) or inducers (i.e. carbamazepine) on active moiety concentrations.

The indication for PP3M is for the treatment of schizophrenia in adults who have been adequately treated with PP1M for at least 4 months. As PP3M has a very long elimination half-life and requires extended time to reach steady state plasma concentrations, subjects need to be stabilized on PP1M before transitioning to the longer-acting injectable PP3M. A 4-month treatment period with PP1M allows for four complete 4-week intervals between administrations of PP1M after the initial 1-week PP1M initiation regimen. Four months is considered sufficiently long for subjects with schizophrenia to successfully switch to a new treatment. A flexible-dose regimen with PP1M will allow clinicians to establish an efficacious and tolerable dose for each subject, and to allow transition to PP3M to occur within a limited period of time. PP1M will be administered in line with the label, with the exception that 39 mg will not be included in this study.[68]

The selection of the PP3M dose is based on a fixed ratio (1:3.5) relative to the dose of PP1M that affords an acceptable benefit:risk during initiation of treatment. The PP3M doses evaluated in this study will be 273, 410, 546, or 819 mg, which correspond to a 3.5-fold multiple of marketed PP1M doses of 78, 117, 156, or 234 mg, respectively (see Table 3). This is consistent with the PP3M/PP1M dose range that was evaluated in the pivotal Phase 3 PP3M relapse prevention study (R092670-PSY-3012). PP1M is also available commercially at a lower, 39 mg dose level. This dose level represents less than 1% of the PP1M syringes distributed in the US and worldwide as of 31 December 2013, and for this reason, the sponsor has no plans to develop a PP3M dose corresponding to the 39-mg dose of PP1M. Therefore, the lower 39 mg dose of PP1M will not be evaluated in this study.

For optimal management of symptoms/tolerability, subjects receiving PP3M (during either Part II or Part III) may go back to treatment with PP1M (monthly injections of 78, 117, 156 or 234 mg, flexibly dosed) for further dose adjustment or for the duration of the trial with the approval of the medical monitor.

Supplementation with OAP medications is not required with PP1M or PP3M. However, due to the long-acting nature of these formulations, it can take time for dosage adjustments to take effect. Therefore, oral supplementation with paliperidone ER or oral risperidone will be allowed in the PP treatment group if required (eg, during periods of acute symptom exacerbation, or to provide additional antipsychotic coverage in subjects requiring a dose increase), and such use will not be considered a treatment failure unless the use of oral paliperidone ER or oral risperidone exceeds the dose levels or treatment durations specified in Section 0. Supplemental use of any other OAP in the PP treatment group will be considered a treatment failure.

Unlike the OAP treatment group, subjects receiving PP will not have the option to change medications. If it is deemed clinically necessary to stop PP1M/PP3M in a subject assigned to PP treatment, the subject will be withdrawn from the study and discontinuation of PP will be recorded as a treatment failure.

3.2.3. Phase-Specific Design Considerations

Screening

A screening phase of up to 4 weeks was chosen to allow adequate time for completion of all screening procedures with results available to the investigator before enrolling a subject into the study.

Part I, Oral Run-In Phase

All subjects will initially be treated with oral paliperidone ER or oral risperidone during the Part I oral run-in phase. Use of oral paliperidone ER or oral risperidone will allow the investigator to evaluate the efficacy and tolerability of paliperidone or oral risperidone prior to randomization to the LAI formulation of paliperidone.

Those subjects who find oral paliperidone ER or oral risperidone inadequately efficacious after treatment for an adequate duration at an adequate dosage per clinical judgment will have the option to switch to another protocol-specified OAP at the discretion of the investigator. However, subjects who find either oral paliperidone ER or oral risperidone intolerable will be withdrawn from the study.

The objective of this phase is to transition subjects to treatment with oral paliperidone ER or oral risperidone and to collect demographic and baseline characteristic data (including age, gender, race, prior antipsychotic exposure, substance use history, PSP, and MCCB composite score) for matching during randomization of subjects into Parts II and III of this study. This phase will also help identify those subjects who have a higher propensity to discontinue the study and therefore potentially help to reduce dropouts during Part II/Part III.

All subjects who complete Part I and have tolerated a minimum of 3 mg oral paliperidone ER or 2 mg oral risperidone for a minimum of 2 weeks will be eligible to enter Part II.

Part II and Part III, Randomized, Active-Controlled Treatment Phases

Treatment during Part II and Part III will be open-label and the treating clinician will have the flexibility to adjust PP1M/PP3M and OAP doses according to patient's individual needs. Rater blinding will be used to minimize bias in the evaluation of brain imaging endpoints, but other assessments will be performed in an open-label fashion, consistent with real-world clinical practice.

The Part II treatment duration is 9 months. There are limited data available in the literature comparing oral and LAI antipsychotic agents in recent-onset schizophrenia, but based on prior work by Nuechterlein, Bartzokis and Subotnik,[9,10,94,107] 9 months is estimated to be a sufficient period to detect a difference between an oral versus LAI formulation on time to treatment failure, ICM, and cognitive and functional endpoints.[94]

Efforts consistent with ethical good clinical practice will be made to retain subjects in this study. Subjects in the oral arm will be allowed multiple switches to alternative oral medications. However, in order to answer the primary questions associated with this study, if it is deemed clinically necessary to stop PP1M/PP3M in a subject assigned to PP treatment, the subject will be withdrawn from the study.

4. SUBJECT POPULATION

Approximately 275 subjects with a recent-onset DSM-5 diagnosis of schizophrenia or schizophreniform disorder will be enrolled in this study. The inclusion and exclusion criteria for enrolling these subjects are described in Section 4.1. Screening for eligible subjects will be performed within 28 days before administration of the study drug.

In addition, approximately 20 healthy volunteers will be enrolled at each MRI center; the inclusion and exclusion criteria for enrolling the healthy control subjects are described in Section 4.2. Screening for healthy controls will occur when each MRI center has enrolled the first patient.

If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the medical monitor before enrolling a subject in the study.

For a discussion of the statistical considerations of subject selection, refer to Section 11.2, Sample Size Determination.

4.1. Selection Criteria for Subjects with Schizophrenia or Schizophreniform Disorder

4.1.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study.

1. Subject must be a man or woman 18 to 35 years of age, inclusive.

2. Subject must have a current diagnosis of schizophrenia (295.90) or schizophreniform disorder (295.40) as defined by DSM-5 and confirmed by the Structured Clinical Interview for DSM-5 Disorders (SCID) with a first psychotic episode within the last 24 months prior to the screening visit.

3. Subject requires treatment with an antipsychotic medication or a change in antipsychotic medication due to lack of efficacy, tolerability, safety issues, or investigator/subject preference.

4. Each subject must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and are willing to participate in the study.

5. Subject must have available a designated individual (eg, family member, significant other, friend) who has knowledge of the subject and is generally aware of the subject's daily activities, and who agrees to let the study site personnel know of changes in the subject's circumstances when the subject is not able to provide this information. The designated individual must sign an ICF.

6. Subject is anticipated to have a stable place of residence for the duration of the trial.

7. Subject must be physically healthy and medically stable on the basis of physical examination, medical history, vital signs, clinical laboratory tests, and ECG performed at screening.

8. A woman who is heterosexually active must:

   - Be surgically sterile (eg, tubal occlusion, hysterectomy, bilateral salpingectomy); or otherwise be incapable of pregnancy, or
   - Agree to abstinence or practice a highly effective method of birth control, including hormonal prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method (eg, condoms, diaphragm, or cervical cap, with spermicidal foam, cream, or gel), or male partner sterilization, consistent with local regulations regarding use of birth control methods for subjects participating in clinical studies.
   - Agree to continue using these methods of contraception throughout the study and for at least 6 months after receiving the last dose of PP1M/PP3M.
   - Have a negative urine pregnancy test at screening.

   Note: If the childbearing potential changes after start of the study (eg, woman who is not heterosexually active becomes active) a woman must begin a highly effective method of birth control, as described above.

9. A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control eg, either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm

or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository, and all men must also not donate sperm during the study and for 6 months after receiving the last dose of PP1M/PP3M.

10. Each subject must sign a separate ICF if he or she agrees to provide an optional DNA sample for research (where local regulations permit). Refusal to give consent for the optional DNA research sample does not exclude a subject from participation in the study.

4.1.2. Exclusion Criteria

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

1. Subject has a positive urine drug screen test for cocaine, amphetamines, opiates, or phencyclidine (PCP) at screening, unless they have a valid prescription. (Note: subjects excluded on this basis may return and enroll if they can achieve a clean urine screen within 7 days).

2. Subject has a current DSM-5 diagnosis of dissociative disorder, bipolar disorder, major depressive disorder, schizoaffective disorder, autistic disorder, or intellectual disabilities.

3. Subject meets the DSM-5 definition of moderate or severe substance use disorder (except for nicotine) within 2 months prior to screening.

4. Subject has evidence of clinically significant, unstable cardiovascular, renal, hepatic, gastrointestinal, neurological, immunological, endocrine, metabolic or pulmonary disease that may indicate increased risk associated with taking study medication or would interfere with study participation or make safety/efficacy results difficult to interpret.

5. Subject has a history of neuroleptic malignant syndrome.

6. Subject has known allergies, hypersensitivity, or intolerance to paliperidone or risperidone or to the excipients of the oral paliperidone ER/oral risperidone or PP1M/PP3M formulations (refer to the Investigator's Brochure).

7. Subject has a prior history of lack of response to oral or LAI risperidone or paliperidone. Lack of response is defined by failure to respond to 2 adequate trials of a minimum of 4 weeks at the subject's maximum tolerated dose.

8. Subject is at imminent risk of suicide according to the investigator's clinical judgment.

9. Subject has mental retardation, defined as pre-morbid IQ as measured by Wechsler Test of Adult Reading at screening <70. [An alternative test will be defined by the sponsor if the study is conducted in countries other than the US].

10. Subject has received LAI medication within 2 injection cycles prior to the screening visit.

11. Subject has received an investigational drug or used an investigational medical device within 1 month of the screening visit, or is currently enrolled in an investigational study.

12. Subject is a woman who is pregnant or breast-feeding, or planning to become pregnant while enrolled in this study or within 6 months after the last dose of PP1M/PP3M.

13. Subject has evidence of a known neurological disorder (eg, epilepsy) or significant head injury.

14. Subject has any condition for which, in the opinion of the investigator, participation will not be in the best interest of the subject (eg, compromise the well-being) or that can prevent, limit, or confound the protocol-specified assessments.

15. Subject previously enrolled in this study.

16. Subject is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the sponsor, the investigator or the clinical staff and the investigating site.

4.2. Selection Criteria for Healthy Controls

Approximately 20 healthy subjects at each MRI center will be included as controls for the MRI machine calibration. These subjects will undergo MRI assessments, but will not otherwise be involved with the study and will not receive study medication. These subjects will be comparable in age, gender, race, and highest parental education to the schizophrenia/schizophreniform disorder subjects undergoing MRI assessments.

Inclusion Criteria

Each potential healthy control subject must satisfy all of the following criteria to be enrolled in the study.

1. Subject must be a man or woman 18 to 35 years of age, inclusive.

2. Subject must sign 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.

Exclusion Criteria

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

1. Subject has evidence of a known psychiatric disorder, neurological disorder (eg, epilepsy) or significant head injury.
2. Subject has a first-degree relative who has schizophrenia, schizophreniform, schizoaffective, or bipolar disorder.
3. Subject meets the DSM-5 definition of moderate or severe substance use disorder (except for nicotine) within 2 months prior to screening.
4. Subject is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.
5. Subject is unable to undergo MRI scan for any reason, including because of body size (unable or difficult to fit in MRI instrument) or MRI contraindicated due to presence of metallic objects (pacemaker, etc.). Note: if the initial MRI is clinically abnormal and shows presence of a severe brain abnormality that would preclude analyses (eg, large hemangioma) the subject will be withdrawn from the study (see Section 10.2, Withdrawal From the Study).
6. Subject is a woman who is pregnant or plans to become pregnant during the course of the study.

4.3. Prohibitions and Restrictions

Note that the following prohibitions and restrictions only apply to subjects with schizophrenia or schizophreniform disorder, not to healthy controls.

4.3.1. Prohibited Medications

- Only those OAPs listed in Section 6.2.2, Oral Antipsychotic Treatment, are permitted in the OAP treatment group.
- Administration of PP1M/PP3M or an alternative LAI antipsychotic is prohibited in subjects assigned to OAP treatment. If an LAI agent is deemed clinically necessary for subjects assigned to the OAP group, their data will be censored as a treatment failure and they will be discontinued from the study.

4.3.2. Restrictions Related to Study Eligibility

Subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

- Female subjects of childbearing potential who are heterosexually active must remain on a highly effective method of birth control (see Inclusion criterion 8).
- Male subjects who are sexually active with a female partner of childbearing potential must use a double-barrier method of birth control (see Inclusion criterion 9). Male subjects must agree to not donate sperm during the study and for an additional 6 months after receiving the last dose of study drug.

5. TREATMENT ALLOCATION AND BLINDING

Procedures for Randomization and Stratification

There will be 2 randomizations in this study, once at the start of Part II and once at the start of Part III. Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

Matching will be performed using dynamic central randomization. In Part II, subjects will be assigned to receive either PP or OAP in a 1:2 ratio based on an algorithm implemented in the interactive voice response system (IVRS) or interactive web response system (IWRS) before the study. It is estimated that approximately 225 subjects will be randomized in Part II; therefore approximately 75 subjects will be randomized to the PP treatment group and 150 subjects to the OAP treatment group. Dynamic central randomization minimizes the imbalance in the distribution of the number of subjects across treatment groups within the levels of each individual stratification factor: age, race, gender, duration of previous antipsychotic usage prior to screening, baseline MCCB composite score, baseline PSP score, substance use history, MRI participation, and site. Based on the algorithm, the IVRS/IWRS will assign a unique treatment code, which will dictate the treatment assignment. The requestor must use his or her own user identification and personal identification number when contacting the IVRS/IWRS, and will then give the relevant subject details to uniquely identify the subject. To eliminate the predictability of randomization for the next subject, treatment assignment probabilities will also be utilized.

Subjects who complete Part II will be entered into Part III. On Day 1 of Part III (Day 260 of Part II), subjects in the OAP treatment arm will be re-randomized in a 1:1 ratio to continued treatment with their oral treatment or to PP (Delayed-start PP arm). The Delayed-start PP arm will receive PP1M and PP3M treatment as described in Part II. Subjects previously assigned to treatment with PP in Part II will continue with PP treatment in Part III). Randomization will be based on matched criteria identified in Part I. Similar to the Part II randomization, dynamic central randomization will be implemented for Part III. Stratification factors will include age, race, gender, duration of previous antipsychotic usage prior to screening, baseline PSP score at Part I, baseline MCCB score at Part I, substance abuse history, and site.

Subjects who re-enter the study after missing scheduled injections or visits must stay in the same assigned treatment group.

Blinding

No blinding of investigators or subjects will be used in this study.

Centralized blinded evaluations will be utilized for the assessment of imaging endpoints (eg, ICM volume) to reduce potential bias during data collection and evaluation. For the imaging endpoints, the assessment of the MRI images will be performed by a rater who is blinded to drug-treatment information and to clinical and demographic characteristics of the subjects.

MCCB assessments will be performed by raters at each study site and there is no blinding for the local MCCB raters. All MCCB data collected at each study site will be sent to central raters for review. Assessments will each be scored by central raters who are blinded to treatment information. Central raters will also review the neurocognitive data quality and correct any errors. The central raters will enter the final scores into the MCCB Scoring program to derive T-scores and composites scores and enter the raw and derived MCCB scores to the eDC.

6. DOSAGE AND ADMINISTRATION

6.1. Part I: Oral Run-In

During the Part I oral run-in phase (Day 1-56), all subjects will initially be treated with oral paliperidone ER or oral risperidone. Any prestudy OAP will be tapered off and must be discontinued by Week 5 of Part I.

The recommended dose of oral paliperidone ER is 6 mg administered once daily, although some subjects may benefit from higher or lower doses within a dose range of 1.5 to 12 mg/day. Initial dose titration is not required. Although it has not been systematically established that doses above 6 mg have additional benefit, there was a general trend for greater effects with higher doses. This must be weighed against the dose-related increase in adverse reactions. Thus, some subjects may benefit from higher doses, up to 12 mg/day, and for some subjects, a lower dose of 3 mg/day may be sufficient.

Adjustment of the dosage will be done at the investigator's discretion, based on the individual subject's clinical response to and tolerability of the study drug. Dose increases above 6 mg/day should be made only after clinical reassessment and generally should occur at intervals of more than 5 days. When dose increases are indicated, increments of 3 mg/day are recommended. The maximum dose allowed in this study is 12 mg/day. Oral paliperidone ER can be taken with or without food.

Subjects should be instructed to swallow oral paliperidone ER whole with the aid of liquids (each tablet swallowed individually). They must also be instructed not to chew, divide, or crush oral paliperidone ER tablets. The active substance is contained within a non-absorbable shell designed to release the active substance at a controlled rate. The tablet shell, along with insoluble core components, is eliminated from the body. Subjects should not be concerned if they occasionally notice in their stool something that looks like a tablet.

The recommended maintenance dose of oral risperidone is 4 mg, although some although some subjects may benefit from higher or lower doses within a dose range of 1 to 6 mg/day. Initial dose titration is suggested, with a starting dose of 2 mg (or 1 mg based on clinical judgment) and titration increments of 1-2 mg. Although it has not been systematically established that doses above 6 mg have additional benefit, there was a general trend for greater effects with higher doses. This must be weighed against the dose-related increase in adverse reactions. Thus, some subjects may benefit from higher doses, up to 6 mg/day, and for some subjects, a lower dose of 2 mg/day may be sufficient.

Subjects who find either oral paliperidone ER or oral risperidone intolerable will be withdrawn from the study (see Section 10.2, Withdrawal from the Study). Subjects who find oral paliperidone ER or oral risperidone inadequately efficacious after treatment for an adequate duration with an adequate dosage per clinical judgment may be switched to another protocol-specified OAP during Part I at the discretion of the investigator. Any of the following 7 OAPs will be permitted: aripiprazole, haloperidol, olanzapine, paliperidone ER, perphenazine, quetiapine, and risperidone.

Oral antipsychotics used during Part I will not be directly provided by the sponsor. The investigator will determine the appropriate dose for each subject and provide the subject with a voucher and prescription for the OAP that the subject can take to a local pharmacy to collect his or her medication. For countries where voucher is not applicable, the OAP will be dispensed by the study site or by a local pharmacy directly to the subject.

Subjects should generally be treated within the approved label for all antipsychotics. Any exceptions should first be discussed with the medical monitor.

Subjects should use antipsychotic monotherapy during Part I.

6.2. Part II: Disease Progression

Subjects completing Part I with specified dosing requirements will be eligible to enter Part II. At entry into Part II, subjects will be randomized in a 1:2 ratio to either PP or OAP.

6.2.1. Paliperidone Palmitate Treatment Group

Subjects who are randomly assigned to the PP treatment group will discontinue OAP treatment and will be started on PP1M. A transition period of a maximum of 5 weeks will be allowed for the previous OAP. Subjects will be subsequently switched to PP3M following a minimum of 5 injections of PP1M.

PP1M and PP3M are intended for IM use only and should be injected slowly, deep into the deltoid or gluteal muscle (please refer to the Instructions for Use). Care should be taken to avoid inadvertent injection into a blood vessel. Each injection should be administered by a health care professional. Administration should be in a single injection. Do not administer the dose in divided injections. Do not administer intravascularly or subcutaneously.

Injection site guidelines are provided in Attachment 1. Prior to administration, it is critical to shake the PP1M and PP3M containing syringes **vigorously** for at least 10 and 15 seconds, respectively. Gluteal injections should be made into the upper outer quadrant of the gluteal area and alternated between the left and right gluteal muscles. Deltoid injections should also be alternated between the left and right deltoid muscles. Refer to Attachment 1 for details on selection of needle sizes for PP1M/PP3M.

PP1M will be administered IM once-monthly, after the first 2 injections that are given one week apart (Day 1 and Day 8). The first 2 doses will be administered through a deltoid injection on alternating arms. The subsequent injections can be given either in the deltoid or the gluteal

muscle. The first dose of PP1M will be 234 mg given in the deltoid muscle at Day 1 of the treatment phase. The second dose of PP1M will be 156 mg given in the deltoid muscle at Day 8 (±4 days). Subsequent doses of PP1M will be given every 28 (±7) days on Days 36, 64, and 92 in either the deltoid or gluteal muscle. The investigator may select from 78, 117, 156, or 234 mg, according to the subjects' clinical needs. Subjects will continue to return to the study site every 4 weeks for injections and for study evaluations.

The location site and side of each injection should be noted in the case repor form (CRF) for reference at the subsequent visit.

At the Day 120 visit (±7 days), subjects will start PP3M treatment if in the investigator's judgment, the subject is receiving an optimal maintenance dose of PP1M. If on Day 120 the investigator feels they have not identified the appropriate maintenance dose of PP1M, with approval of the medical monitor and sponsor the subject may continue to receive flexible doses of PP1M injections on Day 120, 148, and 176, and start PP3M treatment on Day 204. The initial PP3M dose will be calculated as 3.5-fold multiple of the final PP1M dose administered on Day 92 (or Day 176) (see Table 3 for conversion between PP1M and PP3M doses). Subjects will receive PP3M injections once every 12 weeks with a ±14 day window as described in Time and Events Schedule. Investigators will be permitted to flexibly adjust the dose of PP3M as clinically necessary with the dose options for PP3M being 273, 410, 546, or 819 mg. Injections of PP3M may be administered in either the deltoid muscle or the upper outer portion of the gluteal muscle. The side of each injection (left or right) should be alternated and recorded in the CRF.

Table 3: Conversion Between PP1M Dose and PP3M Doses Using a 1:3.5 Fixed Ratio

PP1M Dose		Corresponding_PP3M Dose	
(mg paliperidone palmitate)	(mg eq. paliperidone)	(mg paliperidone palmitate)	(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.

mg eq.=milligram equivalents of paliperidone.
PP1M = paliperidone palmitate 1-month injection; PP3M = paliperidone palmitate 3-month injection.

An overview of the PP dosing schedule is summarized in Table 4. If subject misses a dose or receives a dose outside of these dosing windows, please contact the sponsor's medical monitor. Further details regarding handling of missed doses are provided in Section 6.2.1.2.

A switch to an alternative antipsychotic is not permitted in the PP treatment group. If it is deemed clinically necessary to stop PP1M/PP3M in a given subject, the subject's data will be censored as a treatment failure and the subject will be withdrawn from the study.

Table 4: Paliperidone Palmitate Dosing Administration Schedule

	Day 1	Day 8 (±4 days)	Day 36 (±7 days)	Day 64 (±7 days)	Day 92 (±7 days)	Day 120 (±7 days)	Every 12 wks (±14 days) (starting Day 204)
Agent	PP1M	PP1M	PP1M	PP1M	PP1M	PP3M	PP3M
Dose (mg)	234	156	78-234	78-234	78-234	273-819	273-819
Muscle	D	D	D or G	D or G	D or G	D or G	D or G

Flexible or Fixed	Fixed	Fixed	Flexible	Flexible	Flexible	Fixed[a]	Flexible

D=deltoid muscle; G=gluteal muscle; PP1M=paliperidone palmitate 1 month formulation; PP3M=paliperidone palmitate 3-month formulation.
[a] The dose of PP3M given will be a 3.5-fold multiple of the PP1M dose given on Day 92 (see Table 3).

For optimal management of symptoms/tolerability, subjects receiving PP3M (during either Part II or Part III) may go back to treatment with PP1M (monthly injections of 78, 117, 156 or 234 mg, flexibly dosed) for further dose adjustment or for the duration of the trial with the approval of the medical monitor.

6.2.1.1. Supplemental Oral Antipsychotic Medication During Paliperidone Palmitate Treatment

Investigators are strongly encouraged to use PP1M/PP3M as antipsychotic monotherapy and to adjust the injection dose for management of symptoms/tolerability. Subjects in the PP treatment group who are tolerating the medication but experience symptom exacerbation during the study will be allowed to have supplemental antipsychotic medication, ie, oral paliperidone ER (up to 6 mg/day or oral risperidone (up to 3 mg/day) may be given between injections for no longer than a total of 84 days during the total PP treatment period. If the supplemental treatment with oral paliperidone ER or oral risperidone is longer than 84 days or if oral paliperidone ER doses exceed 6 mg/day or oral risperidone doses exceed 3 mg/day, the subject will be considered a treatment failure. Adding any other OAP will also be considered a treatment failure (see Section 9.2.2.1, Treatment Failure).

6.2.1.2. Missed Doses of Paliperidone Palmitate

Please contact the sponsor immediately when subject misses an injection within the visit windows described in the Time and Events schedule. Below is the general guideline regarding management of missed doses.

Management of a Missed Second Initiation Dose of PP1M (Day 8 of Part II)

If the target date for the second PP1M injection (Day 8 ± 4 days in Part II) is missed, the recommended re-initiation depends on the length of time that has elapsed since the subject's first injection. In case of a missed second initiation dose, follow the dosing instructions provided in Table 5.

Table 5: Management of a Missed Second Initiation Dose of PP1M

Timing of Missed Second Initiation Dose	Dosing
Less than 4 weeks since first injection	**Administer the second initiation dose of 156 mg in the deltoid muscle as soon as possible.** 1. It is recommended to administer a third injection of 117 mg 5 weeks after the first injection (regardless of the timing of the second injection). 2. Thereafter, resume regular monthly dosing in either the deltoid or gluteal muscle.
4 to 7 weeks since first injection	**Resume dosing with two injections of 156 mg in the following manner:** 1. Administer a deltoid injection as soon as possible.

	2. Administer a second deltoid injection 1 week later. 3. Thereafter, resume regular monthly dosing in either the deltoid or gluteal muscle.
More than 7 weeks since first injection	**Restart dosing with recommended initiation:** 1. Administer a 234 mg deltoid injection. 2. Administer a 156 mg deltoid injection 1 week later. 3. Thereafter, resume regular monthly dosing in either the deltoid or gluteal muscle.

Management of a Missed PP1M Maintenance Dose (Days 36, 64, or 92 of Part II)

In case of a missed maintenance dose of PP1M, follow the dosing instructions provided in Table 6.

Table 6: Management of a Missed Maintenance Dose of PP1M

Timing of Missed Maintenance Dose	Dosing
4 to 6 weeks since last injection	**Resume regular monthly dosing as soon as possible and followed by injections at monthly intervals.**
More than 6 weeks to 6 months since last injection	**Resume the same dose the subject was previously stabilized on (unless the subject was stabilized on a dose of 234 mg, then the first 2 injections should each be 156 mg) in the following manner:** 1. Administer a deltoid injection as soon as possible. 2. Administer a second deltoid injection 1 week later at the same dose. 3. Thereafter, resume administering the previously stabilized dose in the deltoid or gluteal muscle 1 month after the second injection.
More than 6 months since last injection	**Restart dosing with recommended initiation:** 1. Administer a 234 mg deltoid injection. 2. Administer a 156 mg deltoid injection 1 week later. 3. Thereafter, resume administering the previously stabilized dose in the deltoid or gluteal muscle 1 month after the second injection.

Management of a Missed PP3M Dose

Missed Dose > 3½ Months up to 4 Months

If more than 3½ months (up to 4 months) have elapsed since the last injection of PP3M, the previously administered PP3M dose should be administered as soon as possible, then continue with the 3-month injections following this dose.

Missed Dose > 4 Months up to 9 Months

If more than 4 months (up to 9 months) have elapsed since the last injection of PP3M, do NOT administer the next dose of PP3M. Instead, use the re-initiation regimen shown in Table 7.

Table 7: Re-Initiation Regimen after Missing >4 Months up to 9 Months of PP3M

Last PP3M Dose	**Administer PP1M, two doses one week apart (into deltoid muscle)**		**Then administer PP3M Dose (into deltoid[a] or gluteal muscle)**
	Day 1 →	Day 8 →	1 month after Day 8

273 mg	78 mg →	78 mg →	273 mg
410 mg	117 mg →	117 mg →	410 mg
546 mg	156 mg →	156 mg →	546 mg
819 mg	156 mg →	156 mg →	819 mg

[a] See Attachment 1 for deltoid injection needle selection based on body weight.

6.2.2. Oral Antipsychotic Treatment Group

Subjects randomly assigned to the OAP treatment group will continue their OAP treatment from Part I. It is expected that most subjects will be on oral paliperidone ER or oral risperidone at entry into Part II, but some subjects may have been switched to an alternative OAP during the oral run-in phase (Part I).

Investigators are encouraged to continue the same OAP (ie, the OAP prescribed Part II baseline) as monotherapy for the remainder of the study, and to adjust the OAP dose for management of symptoms/tolerability at any time. However, after the initial randomization visit, subjects may be switched to an alternative protocol-specified OAP if clinically indicated. The same 7 agents specified for Part I are permitted: aripiprazole, haloperidol, olanzapine, paliperidone ER, perphenazine, quetiapine, and risperidone. Multiple switches to alternative OAPs are permitted. Add-on of other OAPs is also allowed. However, switching to another OAP or add-on of another OAP due to inadequate efficacy, safety, or tolerability will be assessed as treatment failures (see Section 9.2.2.1, Treatment Failure). Any change in antipsychotic medication (switching, discontinuation, or add-on) must be evaluated against the treatment failure criteria.

Oral antipsychotics will not be directly provided by the sponsor. The investigator will select the OAP treatment and the dose appropriate for the subject and provide a prescription and voucher for the assigned medication which the subject can present at a local pharmacy. For countries where voucher is not applicable, the OAP will be dispensed by the study site or by a local pharmacy directly to the subject.

Subjects should generally be treated within the approved label for all antipsychotics. Any exceptions should first be discussed with the medical monitor.

A switch to PP1M/PP3M or an alternative long-acting injectable (LAI) antipsychotic is not permitted. If a LAI agent is deemed clinically necessary for subjects assigned to the OAP group, their data will be censored as a treatment failure and they will be discontinued from the study.

Supplemental OAPs should not be used as a sleeping aid or for sedation.

Study-site personnel will instruct subjects on how to store study drug for at-home use as indicated in the local health authority approved package insert.

6.3. Part III: Extended Disease Progression and Disease Modification

All subjects completing Part II will be eligible to enter Part III. At entry into Part III, subjects in the OAP treatment group will be re-randomized in a 1:1 ratio to either continue OAP treatment or switch to PP. Subjects assigned to PP in Part II will continue the same treatment.

There will therefore be 3 treatment groups in Part III, which will be referred to as follows:

- **OAP-OAP**: This group will receive OAP in Part II and will be randomized to continue OAP treatment in Part III. OAP dosing in Part III will be the same as that specified for Part II (see Section 6.2.2, Oral Antipsychotic Treatment).
- **PP-PP**: This group will receive PP treatment in Part II and will continue PP treatment in Part III. The first dose of PP during Part III will be administered at Visit 19 (Day 36 of Part III; or Day 296 of Part II) in order to synchronize visit date for all 3 treatment arms. This visit occurs 92 days [instead of 84 days, ie, 12 weeks] after the previous PP injection). However, it is still within the ±14-day window.
- **OAP-PP (or 'Delayed-Start PP')**: This group will receive OAP in Part II and will be randomized to PP in Part III. At entry into Part III, subjects will receive PP according to the same schedule as that described for Part II (see Section 6.2.1, Paliperidone Palmitate Treatment, and Table 4). The first dose of PP1M will be given on Day 1 of Part III. A transition period of a maximum of 5 weeks will be allowed for the previous OAP.

7. TREATMENT COMPLIANCE

Paliperidone Palmitate

During Part II and Part III of the study, injections of PP1M and PP3M will be administered by qualified staff at the study site and the details of each administration will be recorded in the CRF. The investigator or designated study personnel will maintain a log of all PP1M/PP3M received and injected.

Oral Antipsychotics

Oral antipsychotics will not be directly provided by the sponsor. The investigator will determine the appropriate dose for each subject and provide the subject with a voucher and prescription for the OAP that the subject can take to a local pharmacy to collect his or her medication. For countries where voucher is not applicable, the OAP will be dispensed by the study site or by a local pharmacy directly to the subject.

This study seeks to replicate treatment reflective of regular clinical practice and there will be no pill counting to monitor treatment compliance in subjects in the OAP group.

8. PRESTUDY AND CONCOMITANT THERAPY

All co-existent diseases or conditions will be treated in accordance with prevailing medical practice.

Prestudy therapies taken by or administered to the subject up to 1 month (6 months for psychotropic medications other than antipsychotics, and life time for antipsychotics) before the first dose of study drug must be recorded at screening.

Any prestudy OAP (except oral paliperidone ER or oral risperidone) will be tapered off and must be discontinued by Week 5 of Part I. Tapering of the previous OAP can start at the beginning of the screening period. Tapering and discontinuation of the previous OAP should be managed by

the investigator as clinically appropriate. All other medications (prescription or over-the-counter) that have been established as the treatment regimen for a particular subject may be continued during the course of the study. Subjects receiving psychotherapy prior to the study may continue existing therapy for the duration of the study at the same frequency as established prestudy.

Medications for treatment of minor concurrent illnesses that arise during the treatment phases may be allowed at the discretion of the investigator. Treatment with non-antipsychotic psychotropic medications, including mood stabilizers, antidepressants, anxiolytics, hypnotics, etc, is allowed if clinically indicated. Topical anesthetic preparations (ie, lidocaine 2% cream) are allowable for the treatment of injection site pain.

Supplemental OAPs should not be used as a sleeping aid or for sedation.

If breakthrough psychotic symptoms occur during Part II or Part III, supplemental OAP treatment may be administered if considered clinically necessary based on the judgment of the investigator. However, antipsychotic monotherapy is encouraged throughout the study. If supplemental or added OAP treatment is initiated, the investigator must assess the subject for treatment failure (see Section 9.2.2.1, Treatment Failure). See Section 6, Dosage and Administration, for additional information on allowed antipsychotic use.

Concomitant therapies must be recorded throughout the study beginning with start of the first dose of study drug to the last study-related visit. Concomitant therapies should also be recorded beyond the last study-related visit only in conjunction with serious adverse events that meet the criteria outlined in Section 12.3.2. Serious Adverse Events.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies (see Section 4.3.1) are administered.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule summarizes the frequency and timing of the efficacy, imaging, pharmacogenomics, safety, and other exploratory measurements applicable to this study.

Additional urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

Healthcare resource utilization data will be collected using RUQ. Refer to Section 9.4 for details.

The total blood volume to be collected from each subject will be approximately 50 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1.2. Screening

The screening visit (Visit 1) will occur within 28 days prior to the first dose of study medication in Part I. During the screening visit, written informed consent will be obtained and subject eligibility will be assessed based on the inclusion and exclusion criteria. The screening procedures, safety, efficacy, and other assessments detailed in the Time and Events Schedule will be completed. The informed consent must be completed before initiating any study procedures. The subject's designated individual must also sign an ICF.

A urine drug screen will be performed as part of the screening procedures. If a patient tests positive on the initial test, the subject may return and be enrolled in the study if they can achieve a clean urine screen within 7 days.

Subjects may be inpatients or outpatients at the time of screening. Hospitalization during screening is allowed if the clinical condition of the prospective subject, in the opinion of the investigator, warrants hospitalization. If a subject is hospitalized, the investigator must discuss the need for continued hospitalization after 7 days and thereafter on a weekly basis with the medical monitor.

A Screening Phase of up to 28 days is allowed for completion of all assessments. Tapering of the previous OAP other than oral risperidone or oral paliperidone ER can start at the beginning of the screening period. Tapering and discontinuation of the previous OAP should be managed by the investigator as clinically appropriate. Subjects may enter directly into Part I once all screening procedures are complete and the inclusion/exclusion criteria have been met.

9.1.3. Part I: Oral Run-In

At the beginning of Part I (Visit 2, Day 1), safety, efficacy, and other study assessments will be performed as outlined in the Time and Events Schedule.

The treating clinician will determine the appropriate dose of oral paliperidone ER or oral risperidone within the ranges specified and will provide the subject with a prescription (or send an electronic prescription to a local pharmacy) and a voucher that the subject can present at a local pharmacy to collect his/her medication. For countries where the voucher system is not applicable, the OAP will be dispensed by the study site or by a local pharmacy directly to the subject.

All prestudy OAP other than oral risperidone or oral paliperidone ER must be tapered off and must be discontinued by Week 5 of Part I. Tapering and discontinuation of the previous OAP should be managed by the investigator as clinically appropriate.

Subjects who find oral paliperidone ER or oral risperidone inadequately efficacious after treatment with an adequate duration and an adequate dosage per clinical judgment, may be switched to another protocol-specified OAP at the discretion of the investigator. Subjects who find either oral paliperidone ER or oral risperidone intolerable will be withdrawn from the study. Note that medication changes made during the oral run-in phase will not be recorded as a treatment failure.

Subjects will return to the site on Days 8, 15, 29, 43, and 57. The visit on Day 57 (Visit 7) will represent the final visit of Part I, and the first visit of Part II; details of this visit are described in Section 9.1.4 below.

9.1.4. Part II: Disease Progression

At Visit 7 (Part I Day 57 or Part II Day 1), safety, efficacy and other assessments will be performed as described in the Time and Events Schedule. Results of the urine drug screen will be recorded; however, any subject that tests positive will remain eligible to continue in the study.

Subjects will be randomized in a 1:2 ratio to either start PP treatment or to continue their OAP treatment from Part I. Before randomization of a subject, the investigator must decide whether it is suitable to initiate PP treatment in that subject, in the event that he/she is randomized to the PP treatment group. If the investigator believes that starting PP1M treatment is not clinically appropriate in a given subject, the subject will be discontinued from the study prior to randomization.

Subjects randomly assigned to the PP treatment group will then receive their first dose of paliperidone palmitate (PP1M), as described in Section 6.2.1. Subjects randomized to the OAP treatment group will receive a new prescription and voucher for their OAP.

Subjects will return to the study site at the time points indicated in the Time and Events Schedule. Subjects may also be brought in for unscheduled visits as necessary (Section 9.1.6, Unscheduled Visits). Contact should also be made with the subject's designated individual at the time points indicated in the Time and Events Schedule to check on the subject's well-being, such as subject's general health, common daily activities and progress in personal or health goals. Contact with the designated individual can be made by telephone or in person.

The first post-randomization visit will occur 1 week after randomization (Visit 8; Day 8± 4 days). Visits thereafter will occur at 4-weekly intervals. A visit window of ± 7 days will be allowed. However, after Visit 15 (Part II Day 204), a visit window of ±14 days will be allowed for subjects who are on PP or OAP treatment.

At each visit, efficacy, safety, and other assessments will be performed as detailed in the Time and Events schedule. Note that all study procedures (except MRI imaging) should be completed before OAPs are prescribed or PP1M/PP3M is injected. Use of concomitant medications (eg, mood stabilizers, antidepressants, anxiolytics, and hypnotic medication regimens) will be individualized as needed.

Subjects will be assessed for the occurrence of treatment failure at all post-randomization visits (see Section 9.2.2.1, Treatment Failures, for definitions and exceptions). In addition, if a treatment failure event occurs or is suspected in between protocol-specified visits, an unscheduled visit must be performed. When a treatment failure occurs, the investigator will record the date of the treatment failure and the reason for the treatment failure in the CRF. Efficacy assessments (MCCB, PSP, CGI-S, CRDPSS, and MSQ) and MRI imaging (in the subgroup of subjects undergoing MRI assessment) must also be performed at the time of the

initial treatment failure event, or as soon as possible thereafter, even if these assessments are not scheduled to occur at the visit/unscheduled visit. At the time of any **subsequent** treatment failures (or as soon as possible thereafter), PSP, CGI-S, CRDPSS, and MSQ assessments should be performed. Subjects who experience a treatment failure should continue in the study, unless they meet criteria for withdrawal (see Section 10.2, Withdrawal From the Study).

Subjects still participating in the study at Visit 17 (Day 260) will be entered into Part III. Visit 17 will represent the final visit of Part II, and the first visit of Part III. Details of this visit are described in Section 9.1.5 below.

Completion or discontinuation of Part II will be recorded in CRF.

9.1.5. Part III: Extended Disease Progression and Disease Modification

At Visit 17 (Part II Day 260 or Part III Day 1), safety, efficacy and other assessments will be performed as described in the Time and Events Schedule. Results of the urine drug screen will be recorded; however, subjects who test positive on the drug screen will remain eligible to continue in the study. Subjects in the OAP treatment group will be re-randomized in a 1:1 ratio to either continue OAP treatment or to switch to PP treatment. Before randomization, the investigator must decide whether it is suitable to initiate PP treatment in that subject, in the event that he/she is randomized to the PP treatment group. If the investigator believes that starting PP treatment is not clinically appropriate in a given subject in the OAP treatment group, the subject will be discontinued from the study prior to randomization.

The visit windows and the schedule and order of assessments will be the same as that described for Part II above. Refer to the Time and Events schedule for Part III for additional details.

The end-of study visit will be Visit 27 (Part III Day 260) [see Section 9.1.8].

9.1.6. Unscheduled Visits

Unscheduled visits, and contact by phone as needed, will be permitted throughout the study in order to assess continued response to study medication and to monitor subjects for safety and tolerability, as determined by the clinical judgment of the investigator.

An unscheduled visit must also take place if a treatment failure occurs or is suspected in between protocol-specified visits. At the time of **first** treatment failure, or as soon as possible thereafter, all efficacy assessments (MCCB, PSP, CGI-S, CRDPSS, and MSQ) and MRI imaging (in the subgroup of subjects undergoing MRI assessment) must be performed. At the time of any **subsequent** treatment failures, or as soon as possible thereafter, PSP, CGI-S, CRDPSS, and MSQ assessments should be performed. Refer to the Time and Events schedule for the unscheduled visits.

Other procedures may also be performed at an unscheduled visit as deemed necessary according to the investigator.

Unscheduled visits will be documented on the appropriate page of the CRF.

9.1.7. Re-Entry Following Missed Injections or Visits

Subjects are allowed to continue the study if they have missed scheduled injections or visits as long as they come back within the same part of the study (ie, Part I, Part II or Part III) based on their original visit schedule, and they stay in the same assigned treatment group. In all cases of re-entry, the site should contact the medical monitor to determine the best way to re-enter the subject and re-initiate treatment. When a subject misses a visit, every possible effort should be made by the study site personnel (including contacting the subject or the subject's designated individual) to determine if a treatment failure endpoint had occurred and, if applicable, the reason for absence from the study. Refer to Section 6.2.1.2 on how to manage missed doses of PP1M/PP3M.

9.1.8. End-of-Study or Early Termination Visit

Subjects who complete the study or withdraw from the study during any period other than the screening period will have end-of-study (EOS) procedures performed at the time of completion or withdrawal from the study. The EOS procedures are detailed in the Time and Events Schedule (Visit 27/EOS).

9.2. Efficacy

The efficacy assessments for this study include evaluation of treatment failure, cognition (MCCB), functioning (PSP), disease severity (CGI-S), schizophrenia symptoms (CRDPSS), and a patient-reported outcome of medication satisfaction (MSQ).

9.2.1. Efficacy Raters

Only qualified raters who are trained professionals may administer the SCID, MCCB, CGI-S, CRDPSS, and PSP. The rater administering each scale will be identified in the source documentation.

All raters should have clinical and/or research experience with the patient population in this study and participate in study-specific training. Certification is required for MCCB. A qualified rater must meet one of the following disciplines:

- Psychiatry (eg, MD or DO)
- Senior Psychiatry Resident (eg, MD or DO) who fulfills the other requirements
- Psychology (eg, PhD)
- Clinical specialty (eg, B.A./B.S., MS or PhD) where patient care is a central component (eg, social work, counseling, psychology, and nurse practitioner), physician assistant, or registered nurse.

Exceptions to the above definition of a qualified rater will be made by the sponsor on a case-by-case basis based on a rater's previous experience.

Whenever possible, all efforts should be made to use the same raters at each site to assess the same subjects throughout the study. If this is not possible, review of the appropriate prior examinations and communication with prior raters should be conducted as needed.

9.2.2. Efficacy Evaluations

9.2.2.1. Treatment Failure

Subjects will be evaluated at the time points indicated in the Time and Events Schedule for the occurrence of any of the events below that are identified as treatment failures. Only treatment failure events occurring after randomization in Part II (up to the end of Part III) will be assessed. The investigator will determine whether the event meets one of the protocol definitions, and will provide documentation of dates and times associated with the event. Treatment failure will be defined as any of the following:

- Psychiatric hospitalization due to worsening symptoms (including Emergency Room visits ≥23 hours, and not including hospitalization due to social reasons);
- Any deliberate self-injury, suicidal ideation or behavior, homicidal ideation or violent behavior that is clinically significant and needs immediate intervention as determined by the study physician;
- New arrest or incarceration (not related to probation or existing warrant);
- Discontinuation of antipsychotic treatment due to inadequate efficacy as determined by the study physician;
- Discontinuation of antipsychotic treatment due to safety or tolerability as determined by the study physician;
- Treatment supplementation with another antipsychotic due to inadequate efficacy as determined by the study physician (note: use of oral paliperidone ER or oral risperidone in the PP treatment group will not be considered a treatment failure unless supplemental use of oral paliperidone ER or oral risperidone exceeds the dose levels or treatment durations specified in Section 0);
- Increase in the level of psychiatric services (such as from office visit to day hospitalization) in order to prevent imminent psychiatric hospitalization as determined by the study physician.

Any changes in antipsychotic medications (switching, discontinuation, or add-on) must be evaluated against the treatment failure criteria. If any of these changes do not meet the treatment failure criteria, these must be documented and recorded in the eDC.

At the time of **first** treatment failure, or as soon as possible thereafter, all efficacy assessments (MCCB, PSP, CGI-S, CRDPSS, and MSQ) and MRI imaging (in the subgroup of subjects undergoing MRI assessment) must be performed. At the time of any **subsequent** treatment failures (or as soon as possible thereafter), PSP, CGI-S, CRDPSS, and MSQ assessments should be performed.

Note that subjects who experience a treatment failure and do not withdraw consent or meet the criteria for withdrawal from the study (see Section 10.2, Withdrawal from the Study) will continue in the study and be followed through to the end of the study.

9.2.2.2. MATRICS Consensus Cognitive Battery

The MATRICS Consensus Cognitive Battery (MCCB) was developed to provide a relatively brief evaluation of key cognitive domains relevant to schizophrenia and related disorders, and is recommended as the standard outcome measure for clinical trials of cognition-enhancing drugs for schizophrenia.[16] The MCCB includes 10 tests that measure 7 cognitive domains (see Table 8).

Table 8: MCCB Tests

Cognitive Domain	Test	Description
Speed of processing	Brief Assessment of Cognition in Schizophrenia (BACS): Symbol-Coding	Timed paper-and-pencil test in which respondent uses a key to write digits that correspond to nonsense symbols
	Category Fluency: Animal Naming	Oral test in which respondent names as many animals as she/he can in 1 minute
	Trail Making Test: Part A	Timed paper-and-pencil test in which respondent draws a line to connect consecutively numbered circles placed irregularly on a sheet of paper
Attention/Vigilance	Continuous Performance Test-Identical Pairs (CPT-IP)	Computer-administered measure of sustained attention in which respondent presses a response button to consecutive matching numbers
Working memory (nonverbal)	Wechsler Memory Scale®-3rd Ed. (WMS®-III): Spatial Span	Using a board on which 10 cubes are irregularly spaced, respondent taps cubes in same (or reverse) sequence as test administrator
(verbal)	Letter-Number Span	Orally administered test in which respondent mentally reorders strings of number and letters and repeats them to administrator
Verbal learning	Hopkins Verbal Learning Test-Revised™ (HVLT-R™)	Orally administered test in which a list of 12 words from three taxonomic categories is presented and the respondent is asked to recall as many as possible after each of three learning trials
Visual learning	Brief Visuospatial Memory Test-Revised (BVMT-R™)	A test that involves reproducing six geometric figures from memory
Reasoning and problem solving	Neuropsychological Assessment Battery® (NAB®): Mazes	Seven timed paper-and-pencil mazes of increasing difficulty that measure foresight and planning
Social cognition	Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT™): Managing Emotions	Paper-and-pencil multiple-choice test that assesses how people manage their emotions

Source: MATRICS Assessment Inc. 82

The MCCB will be administered by a qualified rater at the time points indicated in the Time and Events Schedule. The MCCB assessment must also be performed at the time of first occurrence of treatment failure.

For each subject, best efforts should be made to begin all subsequent MCCB assessments within +/- 1 hour of the start time of administration of the MCCB assessments that occurred at Visit 1 (Screening). If possible, the same person should administer the tests at each occasion.

All MCCB data will be sent to central raters for review. Assessments will each be scored by central raters who are blinded to treatment information. Central raters will also review the neurocognitive data quality and correct any errors. The central raters will enter the final scores into the MCCB Scoring program to derive T-scores and composites scores. The central raters will enter the raw and derived MCCB scores to the eDC.

9.2.2.3. Personal and Social Performance Scale

The PSP scale[88,89] is a clinician-rated instrument that assesses the degree of dysfunction a subject exhibits in the past month 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 the assessment are converted to a numerical score following the PSP scoring guideline. A score between 71 and 100 indicates a mild degree of dysfunction; a score between 31 and 70 indicates varying degrees of difficulty, and a subject with a score of ≤30 has functioning so poor that he or she requires intensive supervision.

The PSP scale is to be administered by a qualified rater at the time points indicated in the Time and Events Schedule. The PSP assessment must also be conducted at the time of first occurrence of treatment failure, and should also be performed at the time of subsequent occurrences of treatment failure. If possible, the same person should administer this scale at each occasion.

9.2.2.4. Clinical Global Impression of Severity Scale

The CGI-S rating scale[61] is used to rate the severity of a subject's overall clinical condition on a 7-point scale ranging from 1 (not ill) to 7 (among the most extremely ill). This scale permits a global evaluation of the subject's condition at a given time.

This scale will be administered by a qualified rater at the time points indicated in the Time and Events Schedule. The CGI-S assessment must also be conducted at the time of first occurrence of treatment failure, and should also be performed at the time of subsequent occurrences of treatment failure. If possible, the same person should administer this scale at each occasion.

9.2.2.5. Clinician-Rated Dimensions of Psychosis Symptom Severity

The CRDPSS[4] is an 8-item measure that assesses the severity of mental health symptoms that are important across psychotic disorders, including delusions, hallucinations, disorganized speech, abnormal psychomotor behavior, negative symptoms (ie, restricted emotional expression or avolition), impaired cognition, depression, and mania. The severity of these symptoms can predict important aspects of the illness, such as the degree of cognitive and/or neurobiological deficits. This measure, developed by the APA, is intended to capture meaningful variation in the severity of symptoms, which may help with treatment planning, prognostic decision-making, and research on pathophysiological mechanisms. Each item asks the clinician to rate the severity of each symptom as experienced by the individual during the past 7 days.

Each item on the measure is rated on a 5-point scale (0=none; 1=equivocal; 2=present, but mild; 3=present and moderate; and 4=present and severe) with a symptom-specific definition of each rating level. The clinician may review all of the individual's available information and, based on

clinical judgment, select the level that most accurately describes the severity of the individual's condition. The clinician then indicates the score for each item in the "Score" column provided. The response on each item should be interpreted independently when assessing the severity of the psychotic disorder.

The CRDPSS will be completed by a qualified rater at the time points indicated in the Time and Events Schedule. The CRDPSS assessment must also be conducted at the time of first occurrence of treatment failure, and should also be performed at the time of subsequent occurrences of treatment failure.

9.2.2.6. Medication Satisfaction Questionnaire

Medication satisfaction will be assessed using the MSQ. The MSQ is a self-administered single-item questionnaire with responses on a 7-point Likert scale as follows: 1=extremely dissatisfied, 2=very dissatisfied, 3=somewhat dissatisfied, 4=neither satisfied nor dissatisfied, 5=somewhat satisfied, 6=very satisfied, 7=extremely satisfied. The MSQ has demonstrated acceptable reliability and validity,[112] making this single-item questionnaire appropriate and easy to use in clinical research. A 1-point change on the MSQ may be considered clinically meaningful.

The MSQ will be completed by the subject at the time points indicated in the Time and Events Schedule. The MSQ must also be conducted at the time of first occurrence of treatment failure, and should also be performed at the time of subsequent occurrences of treatment failure.

9.3. MRI Brain Imaging Assessments

Selected sites will be performing MRI brain imaging. Approximately half of the enrolled subjects will undergo MRI scans. MRI scans are optional to subjects. All images will be sent to a central site for analysis. The imaging raters at the central site will be blind to clinical characteristics, treatment assignment, and demographic characteristics of subjects.

Brain imaging assessments will be performed in subjects with schizophrenia/schizophreniform disorder and in healthy control subjects. Subjects with schizophrenia or schizophreniform disorder who are not able to undergo scans (eg, unable to fit or difficulty fitting in MRI instrument, or MRI contraindicated due to presence of metallic objects [pacemaker, etc.]) will be excluded from participating in MRI scans, but will still be eligible to participate in all other aspects of this study. Healthy control subjects who are not able to undergo MRI scans will not be eligible to participate in this study (see Section 4.2, Selection Criteria for Healthy Controls).

If the initial MRI is clinically abnormal and shows presence of a severe brain abnormality that would preclude analyses (eg, large hemangioma), the individual will be excluded from undergoing further MRI scans. If this occurs in a healthy control subject, the subject will be withdrawn from the study (see Section 10.2, Withdrawal from the Study). If the initial scan is abnormal in a subject with schizophrenia/schizophreniform disorder, the subject will be excluded from further MRI assessments but will continue in all other aspects of the study.

A separate MRI manual will be provided to the relevant sites with detailed information regarding the MRI procedures. In brief, brain ICM volume will be measured by IR and SE MRI sequences focused on the frontal lobe. Cortical thickness, gray matter and white matter volumes will be measured by 3D MPRAGE MRI. Ventricular volume and intrasulcal CSF will be measured by SE MRI sequences. The subcortical myelin will be measured by MRI sequences optimized for DTI. The resting state fMRI will also be measured.

Brain imaging in subjects with schizophrenia or schizophreniform disorder will be performed at the time points indicated in the Time and Events Schedule. Brain imaging must also be conducted at the time of first occurrence of treatment failure or as soon as possible thereafter.

MRI assessments in healthy control subjects will be described in the MRI manual.

9.4. Exploratory Assessments

Exploratory evaluations include assessment of medical resource use (based on the RUQ), and goal setting and daily activity evaluations.

9.4.1. Resource Utilization Questionnaire

The RUQ will be used in the study as an exploratory tool to assess utilization of resources, such as number of hospitalization days (refers to ≥1 overnight stay), emergency room visits without hospitalization, day or night clinic stays, and outpatient treatment, as well as daily living conditions and productivity of the subject. Healthcare resource utilization will be assessed through regular questioning of subject's resource utilization during visits (via the RUQ) and will be objectively verified through medical records and emergency/crisis center documents obtained by investigative site staff. Work and living status will be assessed at baseline and at regular intervals throughout the study.

9.4.2. Goal Setting and Daily Activity Evaluations

Subjects will set up to 3 personal goals and 3 health goals at the beginning of each treatment phase, which will be reviewed with the subject and by the treating clinician.

The patient goals are not binding, but progress towards attaining these goals will be followed throughout the study at the time points indicated in the Time and Events Schedule.

Patient Happiness Assessment and Goal Setting Preparation

The Patient Happiness Assessment and Goal Setting Preparation documents will be reviewed and completed by each subject at the Part I Baseline visit (Visit 2).

Patient Goal Setting Documentation

The treating clinician will review the Goal Setting Preparation document with the subject and agree with up to 3 personal goals and up to 3 health goals for the subject at the start of each treatment phase. These goals will be documented on paper and shared with the subject and the subject's designated individual. The original document will be filed at the investigative (study) site as part of the subject's study source record. The patient goals are not binding.

Patient Goals Attainment

Progress towards attaining the patient goals will be assessed by the subject at the time points indicated in the Time and Events Schedule. Satisfaction regarding the subject's progress towards meeting the goals will be rated on a Likert scale ranging from 'Extremely Dissatisfied' to 'Extremely Satisfied'.

Quantitative Assessment of Daily Activities

The Quantitative Assessment of Daily Activities is a patient-reported outcome that documents the time a subject spends in a broad array of common daily activities. Categories include sleep and rest, self-care, work, recreation and social activities. The period covered is the prior week. Refer to the Time and Event Schedule for frequency of assessment.

9.5. Pharmacogenomic (DNA) Evaluations

DNA samples will be analyzed if it is hypothesized that this may help resolve issues with the clinical data.

DNA samples will be used for research related to paliperidone palmitate or oral antipsychotics, or schizophrenia and schizophreniform disorder. They may also be used to develop tests/assays related to paliperidone palmitate or oral antipsychotics and schizophrenia and schizophreniform disorder. Pharmacogenomic research may consist of the analysis of one or more candidate genes or of the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate) in relation to paliperidone palmitate or oral antipsychotic treatment, or schizophrenia and schizophreniform disorder clinical endpoints.

9.6. Safety Evaluations

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the CRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Time and Events Schedule:

Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by the subject's designated individual/caregiver) for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology, and urine samples for urinalysis will be collected. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the CRF. The laboratory reports must be filed with the source documents.

The following tests will be performed by the central laboratory:

- Hematology Panel

  -hemoglobin
  -red blood cell (RBC) count
  -white blood cell (WBC) count with differential
  -platelet count
  -hemoglobin A1c

- Serum Chemistry Panel

  -sodium
  -potassium
  -chloride
  -bicarbonate
  -blood urea nitrogen (BUN)
  -creatinine
  -aspartate aminotransferase (AST)
  -alanine aminotransferase (ALT)
  -gamma-glutamyltransferase (GGT)
  -alkaline phosphatase
  -total bilirubin
  -prolactin
  -calcium
  -albumin
  -total protein
  -C-Reactive Protein

- Metabolic Chemistry (all fasting)

  -glucose
  -total cholesterol
  -triglycerides
  -high density lipoprotein (HDL)
  -low density lipoprotein (LDL)

- Urinalysis

  Dipstick
  -pH
  -color
  -glucose
  -protein
  -blood
  -ketones
  -bilirubin
  -urobilinogen
  -nitrite
  -leukocyte esterase

  Sediment (if dipstick result is abnormal)
  -RBCs
  -WBCs
  -epithelial cells
  -crystals
  -casts
  -bacteria

  If dipstick result is abnormal, flow cytometry will be used to measure sediment. In case of discordance between the dipstick results and the flow cytometric results, the sediment will be examined microscopically.

- Urine Pregnancy Testing, for women of childbearing potential only
- Urine Drug Screen

Electrocardiogram (ECG)

Twelve-lead ECGs will be obtained locally at screening and reviewed for data integrity and reasonableness by a licensed physician qualified to interpret ECG tracings.

A hard copy of the ECG recording must be filed with source documentation. Any findings deemed clinically significant and relevant by the investigator should be included on the Medical History case report form (CRF) and discussed with the medical monitor. ECGs should be performed prior to any scheduled blood draw.

Vital Signs

Blood pressure and pulse rate measurements will be assessed in a seated position with a completely automated device. Manual techniques will be used only if an automated device is not available.

Body Weight and Body Mass Index

Weight will be assessed at the times indicated in the Time and Events Schedule. Height will be recorded at screening only. BMI will be calculated from measurements of height and weight.

Physical Examination

A complete physical examination will be completed at the time points indicated in the Time and Events Schedule.

Extrapyramidal Symptoms Rating Scale – Abbreviated

The ESRS-A is an abbreviated manualized version of the ESRS,[21] a semistructured interview that rates parkinsonian symptoms, dystonia, dyskinesias, and akathisia over the previous 7 days. The ratings include a motor examination for rigidity, tremor, reduced facial expression or speech, impaired gait/posture, postural instability, and bradykinesia/hypokinesia. Twenty-four individual items are rated on a 6-point scale: 0=Absent, 1=Minimal, 2=Mild, 3=Moderate, 4=Severe, or 5=Extreme. Frequency is included as an index of severity. Symptoms are divided into the 4 corresponding subscales and each subscale is summarized in a Clinical Global Impression of Movement Severity (CGI-MS) score.

A qualified clinician is required to administer the ESRS-A. A trained clinician rater for these scales must meet one the following criteria: a physician (MD or DO), advanced practice nurse (NP), physician assistant, or other allied health professional who is trained and holds a valid license to perform physical examinations.

The ESRS-A will be administered at the time points indicated in the Time and Events Schedule. If possible, the same person should administer these scales at all visits.

InterSePT Scale for Suicidal Thinking – Plus

The ISST-Plus is a clinician-rated 4-part instrument for collecting data on suicidal thinking and behavior. The ISST-Plus Short Form is an abbreviated form of the ISST-Plus used to screen

subjects between ISST-Plus assessments. The ISST-Plus meets the requirements recently announced by FDA for assessment of suicidality.

The ISST-Plus includes 4 parts:

- **Part I** is designed to collect information on the severity of suicidal ideation during the ***7 days*** (or other pre-defined time frame) prior to the subject's visit. It is comprised of 13 items, with three levels of severity: 0 (none), 1 (weak), or 2 (moderate or strong).
- **Part II** is designed to collect information on suicidal behaviors that have occurred ***since the last visit or the last assessment of suicidal behavior***.
- **Part III** is a global rating of suicide ideation and behavior or status ***at the time of the subject interview*** as judged by a clinically experienced rater. It includes and integrates both Part I and Part II of the scale. It should only be completed after Parts I and II have been completed and should take all available information into consideration.
- **Part IV** is collected at the end of the study to record whether or not the subject died by suicide during the study.

Rating the ISST-Plus requires completion of a semistructured interview. Subjects who exhibit a high suicide risk as evidenced by a total score of ≥7 on the ISST-Plus Part I or a score of 2 on items 7, 10, or 11, or an ISST-Plus Part III score of ≥2 must be evaluated by either a clinical psychologist or psychiatrist, and this must be documented in the source documents. If a subject answers in the affirmative (ie, "YES") to any part of the suicidal behaviors section (Part II) of the ISST-Plus, completion of a detailed potential suicide attempt narrative is required.

The ISST-Plus Short Form will be administered at the study visits indicated in the Time and Events Schedule. If suicidality is identified (ie, 'yes' is answered to questions 1.0, 2.2, 2.3, or 2.4 of the ISST-Plus Short Form) the full ISST-Plus must be administered in its entirety.

Any clinically significant abnormalities persisting at the end of the study will be followed by the investigator until resolution or until reaching a clinically stable endpoint.

10. SUBJECT COMPLETION/WITHDRAWAL

10.1. Completion

A subject will be considered to have completed the study if he or she has completed assessments at Visit 27 (Day 260 of Part III), the end of the treatment phase. Completion and discontinuation will be examined and recorded in the CRF for each treatment phase.

10.2. Withdrawal From the Study

Subjects with Schizophrenia or Schizophreniform Disorder

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent

- Death
- Discontinuation of study treatment. A subject's study treatment will be discontinued if:
  - The investigator or sponsor believes (eg, that for safety or tolerability reasons such as an adverse event) it is in the best interest of the subject to discontinue treatment.
  - The subject becomes pregnant.
  - The subject does not tolerate oral paliperidone ER or oral risperidone treatment during Part I (oral run-in).
  - The subject is randomly assigned to receive OAP, but the investigator considers it clinically necessary to switch the subject to an LAI agent.
  - The subject is randomly assigned to receive PP, but the investigator considers it is clinically necessary to stop PP for any reason.

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

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced. If a subject withdraws from the study before the end of Part III, end-of-treatment assessments should be obtained.

A subject who withdraws from the study will have the following options regarding the optional pharmacogenomics DNA research sample:

- The collected DNA sample will be retained and used in accordance with the subject's original separate informed consent for optional research samples.
- The subject may withdraw consent for optional DNA research sample, in which case the sample will be destroyed and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor study site contact of withdrawal of consent for the optional research samples and to request sample destruction. The sponsor study site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the sample has been destroyed.

Withdrawal From the Optional DNA Research Samples While Remaining in the Main Study

The subject may withdraw consent for optional DNA research samples while remaining in the study. In such a case, the optional research sample will be destroyed. The sample destruction process will proceed as described above.

Withdrawal From the Use of DNA Samples in Future Research

The subject may withdraw consent for use of DNA samples for research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the separate ICF for optional DNA research samples.

Healthy Control Subjects

A healthy control subject can be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Death
- If the initial MRI is clinically abnormal and shows presence of a severe brain abnormality that would preclude analyses (eg, large hemangioma)
- If the subject met any of the exclusion criteria during the course of the study

11. STATISTICAL METHODS

The following presents a summary of the planned statistical analyses. A statistical analysis plan (SAP) describing in detail the analyses to be conducted will be written and finalized before the Part II database lock. Unless otherwise specified, all statistical tests will be two-sided, and the Type I error will be fixed at 0.05 (two-sided), and all confidence intervals (CIs) will be two-sided with 95% coverage.

The overall primary hypothesis to be tested in this study (see Section 2.3) is that 9 months' treatment with PP is superior to 9 months' OAP treatment in delaying time to treatment failure in subjects with recent-onset schizophrenia or schizophreniform disorder. This will be assessed at the end of Part II.

Other hypotheses to be evaluated in this study (see Section 11.1) will assess whether LAI treatment with PP can slow down disease progression and possibly modify disease course in recent-onset subjects compared to OAP medications. This will be assessed by tracking changes in cognition (MCCB composite score), functioning (PSP), and brain imaging assessments (ICM volume).

The hypothesized effect of PP versus OAP on disease progression and disease modification is summarized in Figure 2, based on the predicted change from baseline in the MCCB composite score over time. Disease progression and disease modification will be assessed for MCCB composite score, PSP total score, and for ICM volume.

Part II (Disease Progression) will enroll all subjects who complete Part I. Subjects will be randomized in a 1:2 ratio to either start treatment with PP or to continue with their OAP treatment from Part I. The early treatment effect identified after early start at the conclusion of Part II (δ_{21}) represents the treatment effect after 9 months resulting from continuous treatment

with LAI compared with oral treatment. It seeks to identify differential treatment effects between the two alternative approaches on disease progression at the end of Part II. In particular, in addition to differences in time to first treatment failure, differences in cognition, functioning, and ICM volume will be assessed. At the conclusion of Part II, the database will be locked and data analyzed to determine if there is an early treatment effect (δ_{21}= treatment effect on disease progression) demonstrating superiority of PP relative to oral treatment.

At the onset of Part III, subjects in the OAP arm will be re-randomized to continued treatment with their prior oral treatment or to PP. Subjects will be followed for an additional 9 months. Three effects will be assessed for a given endpoint: δ_{31}, δ_{32}, and δ_{33}. The quantity δ_{31} represents the lead treatment effect after an early start with 18 months of PP treatment and shows the lead effect remaining in the early start group over the delayed-start effect after a 9-month treatment duration. The quantity δ_{32} represents the delayed-start effect on disease progression for PP compared to continuing OAP after 9 months of additional treatment. The quantity δ_{33} represents the cumulative effect on extended disease progression at the end of Part III following early start for PP compared to continuing OAP after a total of 18 months of treatment. At the conclusion of Part III, the database will again be locked and data analyzed to assess response in variables δ_{31}, δ_{32}, and δ_{33}. Positive results (δ_{33} is significant [a differential treatment effect is still evident] **and** δ_{31} is significant [the lead effect remains significant after 9 months]) will be used to support a conclusion of disease modification using MCCB composite score. Similar observations for changes in PSP and ICM will be assessed.

In Part II, the overall Type I error rate for testing PP1M/PP3M versus OAP for both the primary efficacy endpoint and key secondary efficacy endpoints will be controlled at the 2-sided 0.05 significance level using a combination of fixed sequence gatekeeper approach and Holm's step-down procedure. Time to first treatment failure will be tested first, followed by change in key secondary endpoints (MCCB, PSP, and ICM). Time to first treatment failure will be examined first using the log-rank test statistics, then using a Cox's proportional hazards model to describe results based on hazard ratio. If the null hypothesis corresponding to time to first treatment failure is rejected, then the key secondary endpoints will be tested at the 5% level using Holm's step-down procedure, thus maintaining an overall Type I error rate of 5%. If the primary null hypothesis is not rejected, testing of change in key secondary endpoints will still be performed, but no unqualified statements about the statistical significance regarding change will be made. In Holm's procedure, p-values from analyses of MCCB, PSP, and ICM will be ordered from lowest to highest. Let $p(1)<p(2)<p(3)$ to be order p-values corresponding null hypotheses H(1), H(2), and H(3). In Step 1, if $p(1) < 0.05/3$ then corresponding null hypothesis will be rejected and testing will be examined in second step; otherwise, none of the hypotheses will be rejected and we will stop testing. In Step 2, if $p(2) < 0.05/2$ then corresponding null hypothesis will be rejected and move onto third step; otherwise, H(2) and H(3) will not be rejected and we will stop testing. In Step 3, p(3) will be tested at 0.05 level. All other exploratory hypotheses will be tested at the 2-sided 0.05 significance level without adjustments for multiplicity.

In Part III, for the examination of extended disease progression and disease modification, there will be no adjustments for multiplicity. During this phase, we seek to show that subjects with

recent-onset schizophrenia or schizophreniform disorder who have a delayed start in their treatment with PP fail to catch up with subjects who start 9 months earlier in the course of their disease. We hypothesize that changes on measures of a pathophysiology biomarker (ICM), clinical symptoms (CGI), cognition (MCCB) and functioning (PSP) should be relatively better in subjects who initiate treatment earlier.

11.1. Hypotheses

11.1.1. Part II: Disease Progression

As described in Section 2.3, the overall primary hypothesis in this study is that 9 months' treatment of subjects with recent-onset schizophrenia or schizophreniform disorder with PP is superior to 9 months' treatment with OAP in delaying time to first treatment failure. The primary efficacy null hypothesis is that there is no difference in the distribution of time to first treatment failure in Part II between the PP and OAP treatment groups.

The key secondary hypotheses to be tested in Part II of this study are to demonstrate that 9 months' treatment of subjects with recent-onset schizophrenia or schizophreniform disorder with PP is superior to 9 months' treatment with OAP in:

- improving or maintaining cognition (as measured by the change in MCCB composite score from baseline)
  - *The key secondary efficacy null hypothesis is that there is no difference in mean change from Part II baseline to the Part II end point in the MCCB composite score between PP and OAP*
- maintaining functioning (as measured by time to 7-point worsening in the PSP total score from baseline)
  - *The key secondary efficacy null hypothesis is that there is no difference in time to 7-point worsening in PSP total score in Part II between PP and OAP*
- increasing or preserving brain ICM volume of the frontal lobe as compared to baseline
  - *The key secondary efficacy null hypothesis is that there is no difference in mean change in ICM volume of the frontal lobe from Part II baseline to the Part II end point between PP and OAP*

11.1.2. Part III: Extended Disease Progression and Disease Modification

11.1.2.1. Extended Disease Progression

Let it be assumed that the quantity δ_{33} in Figure 2 represents the cumulative effect on disease progression at the end of Part III following early start for PP compared to continuing OAP after a total of 18 months of treatment. The Extended Disease Progression hypotheses to be tested in Part III of this study are to demonstrate that 18 months' treatment of subjects with recent-onset schizophrenia or schizophreniform disorder with PP is superior to 18 months' treatment with OAP in:

- improving or maintaining cognition (as measured by the change in MCCB composite score from baseline)

  - *The primary efficacy null hypothesis is that there is no difference in mean change from Part II baseline to the Part III end point in the MCCB composite score between PP and OAP. In other words, H_0: $\delta_{33} = 0$ for MCCB composite score.*

- maintaining functioning (as measured by time to 7-point worsening from in the PSP total score from baseline)
  - *The key secondary efficacy null hypothesis is that there is no difference in time to 7-point worsening in PSP total score from Part II baseline to the Part III end point*
- increasing or preserving brain ICM volume of the frontal lobe as compared to baseline
  - *The key secondary efficacy null hypothesis is that there is no difference in mean change in ICM volume of the frontal lobe from Part II baseline to the Part III end point between PP and OAP*

11.1.2.2. Disease Modification

In order to demonstrate disease modification, the following results are required:

- At the end point of Part II: Subjects treated with PP for 9 months (early-start group) must demonstrate better outcomes on MCCB than those treated with OAP for 9 months. Similar results for changes in functioning (PSP) and changes in brain anatomy (ICM) will be used to support this finding (ie, treatment effect on disease progression).
- At the end point of Part III: Subjects from Part II who have been treated with PP for 18 months (early-start group) must continue to show better outcomes on MCCB compared with subjects treated with OAP for 18 months (a differential treatment effect is still evident), and compared with subjects treated with OAP for 9 months followed by PP for 9 months (the lead treatment effect remains significant after 9 months); ie, that late initiation of treatment with PP does not allow for achievement of the same level of cognition after 9 months. [(See corresponding null hypotheis below (H_0: $\delta_{31} - \gamma . \delta_{21} \leq 0$)]. Similar results for changes in PSP and ICM will be used to support this finding for disease modification.

For each of the endpoints (MCCB, PSP, and ICM), the following hypotheses will be tested as a function of estimated changes in the Part II endpoint using the observed scores. Let δ_{21} denote the estimated mean differences between treatment groups at the end of Part II for a given endpoint, treatment effect on disease progression. Below, the parameter $\mu_{PP\text{-}PP}$ corresponds to the mean score for a given endpoint following 9 months' of additional PP3M treatment in subjects originally randomized to PP and $\mu_{OAP\text{-}PP}$ corresponds to mean score for 9 months' of delayed-start PP treatment in subjects originally randomized to OAP treatment. Let δ_{31} denote the estimated difference between $\mu_{PP\text{-}PP}$ and $\mu_{OAP\text{-}PP}$, lead treatment effect at the end of Part III. The corresponding null hypotheses for a given endpoint will be listed as:

> H_0: $\delta_{31} - \gamma . \delta_{21} \leq 0$, where γ is a fixed number between 0 and 1 indicating the ratio of treatment effect in Part III compared to the Part II observed differences.

The quantity γ will be determined after Part II database lock and prior to finalization of Part III Statistical Analysis Plan. For γ, the quantities 0.25 and 0.50 will be considered principally. The γ could be different for a different endpoint.

In addition, for each of the endpoints, δ_{32} (delayed-start treatment effect on disease progression) will be tested in Part III using Part III baseline scores. Below, the parameter $\mu_{OAP\text{-}PP}$ corresponds to mean score for 9 months' of delayed-start PP treatment in subjects originally randomized to

OAP treatment and $\mu_{OAP-OAP}$ corresponds to the mean score for a given endpoint following 9 months' of additional OAP treatment in subjects originally randomized to OAP. The corresponding null hypotheses for a given endpoint will be listed as:

$$H_0: \delta_{32} = \mu_{OAP-PP} - \mu_{OAP-OAP} = 0.$$

The quantity δ_{33} represents the cumulative effect on disease progression at the end of Part III following early start for PP compared to continuing OAP after a total of 18 months of treatment. At the conclusion of Part III, the database will again be locked and data analyzed to assess response in variables δ_{31}, δ_{32}, and δ_{33} (overall effect of treatment). Positive results (δ_{33} is significant [a differential treatment effect is still evident] **and** δ_{31} is significant [the lead effect remains significant after 9 months]) will be used to support a conclusion for disease modification.

11.2. Sample Size Determination

The overall primary efficacy null hypothesis is that there is no difference in the distribution of time to treatment failure between the PP and OAP in the treatment of subjects with recent-onset schizophrenia or schizophreniform disorder in Part II. Treatment differences will be compared using a log-rank test. It is assumed that treatment failure rate in Part II is approximately 40% for the OAP group and 20% for the PP group at month 9 with a corresponding hazard ratio of 0.44. It is also assumed that the hazard rates of treatment failure for the two groups are proportional. Additional assumptions made to calculate the expected number of subjects that need to be randomized to obtain the required number of treatment failures are:

- In both treatment groups, 10% of the randomized subjects will be lost-to-follow-up.
- Uniform accrual rate during the 15 month accrual period.

With these assumptions, it is planned to randomize 225 (75 in PP and 150 in OAP group) subjects in a 1:2 ratio to receive either PP or OAP to obtain at least 62 treatment failures to show that PP is significantly different from OAP at the 2 sided significance level of 0.05, with 80% power to detect a hazard ratio of 0.44 using a log rank test.

Blinded surveillance of the total number of events in Part II will be performed during the study to assess the appropriateness of the assumptions. The number of subjects enrolled and the number of subjects who discontinue before entering Part II will be closely monitored.

Assuming 20% attrition rate during the 2-month Run-in period (Part I), the total number of subjects to be enrolled in Part I will be approximately 275.

One of the key secondary efficacy null hypotheses in Part II (see Section 11.5.1) is that there is no difference in mean change from Part II baseline to the Part II end point in the MCCB composite score between PP and OAP in the treatment of subjects with recent-onset schizophrenia or schizophreniform disorder. The corresponding efficacy variable is the change in the MCCB composite score. This variable will be analyzed in Part II using mixed-effects repeated measures analysis of covariance (ANCOVA) model, described later. Similarly, the matching null hypothesis in Part III is that there is no difference in mean change from Part II

baseline to the Part III end point in the MCCB composite score between PP and OAP in the treatment of subjects with recent-onset schizophrenia or schizophreniform disorder.

This is the first study to assess the efficacy of PP on cognition in subjects with recent-onset schizophrenia or schizophreniform disorder. A small study comparing the clinical efficacy of the LAI formulation of risperidone (RLAI) to the oral formulation of risperidone (oral Ris) in the early course of schizophrenia in UCLA Aftercare Research program showed an effect size of 0.46 between the treatment groups in the MCCB composite score (change from baseline) at Month 6 end point. We consider an effect size of 0.3 and above to be clinically meaningful for cognition in a therapeutic area where there are no known effective treatments.

Assuming an effect size of approximately 0.40 for the difference in the mean change from Part II baseline to Part II end point in the MCCB composite score between PP and OAP, with 1:2 randomization ratio, sample sizes of 75 subjects in the PP group and 150 subjects in the OAP group are necessary to provide 80% power based on a two group t-test with a 0.05 two-sided significance level. This computation is also consistent with the time to treatment failure calculations ignoring correlations among these endpoints.

It is assumed that approximately 20% of subjects who entered Part II will not be transitioned to the Part III (Extended Disease Progression and Disease Modification) period in each treatment group. Approximately, a total of 180 subjects will be available at the Part III baseline. Subjects in the OAP treatment arm will be re-randomized in a 1:1 ratio to continued treatment with their oral treatment or to PP (delayed-start PP arm). Subjects previously assigned to treatment with PP in Part II will continue in that treatment in Part III. Thus, approximately 60 subjects will be available for each treatment group at the Part III baseline. Assuming approximately 5% of subjects will be missing either the Part III baseline or all post-baseline MCCB assessments, a sample size of 57 in each group will have 80% power to detect an effect size of 0.53 between PP and OAP in the difference in the mean change from Part II baseline in the MCCB composite score using a two group t-test with a 0.05 two-sided significance level in Part III. The primary objective in Part III is to compare changes in cognition following 18 months' treatment with PP compared to 18 months' treatment with OAP.

11.3. Analysis Populations

Efficacy analyses will be based on the ITT and explanatory intent-to-treat (eITT) analysis sets. All safety analyses will be based on ITT analysis set. As there are different objectives for different periods of this study, separate ITT and eITT populations will be identified for the Part I (Run-in), Part II (Disease Progression), and Part III (Extended Disease Progression and Disease Modification) periods. eITT analysis set will not be included in Part I. The analysis sets are defined below.

Part I (Run-in) Intent-to-Treat Analysis Set

Efficacy and safety summaries for the Part I period will be based on the Part I ITT analysis set, which will include all subjects who receive at least one dose of study medication (or any portion of the dose) in Part I, regardless of their compliance with the protocol.

Part II (Disease Progression) Analysis Sets

Efficacy and safety summaries for the Part II period will be based on the Part II ITT analysis set, which will include all randomized subjects who receive at least one dose of study medication (or any portion of the dose) in Part II, regardless of their compliance with the protocol.

An explanatory ITT (eITT) analysis set will also be defined in Part II. The eITT analysis set will consist of all ITT subjects, as well as their study assessments for the time period between the date of randomization and the eITT end point. The eITT end point for subjects randomized to PP will be defined as the last PP1M injection date +28 days or the last PP3M injection date +84 days. For subjects randomized to OAP treatment, the eITT end point is defined as the last prescription date of the randomized oral medication + the number of days' supply + 1 day. Changes in PSP, CGI-S, CRDPSS, and MSQ scales will also be analyzed using eITT analysis set.

The eITT analysis set for the primary efficacy endpoint in Part II consists of the 1st treatment failure time observed at or prior to the eITT endpoint, for all ITT subjects. For subjects who did not experience any treatment failure at or prior to the eITT endpoint, their 1st treatment failure times would be censored at the eITT end point or the date of last contact, whichever was earlier. For any other efficacy endpoint (PSP, CGI-S, etc.), the eITT analysis set consists of only measures for that endpoint that were taken at or prior to the eITT end point. The eITT analysis set will be used for testing the primary as well as key secondary efficacy hypotheses.

Part III (Extended Disease Progression and Disease Modification) Analysis Sets

Efficacy and safety summaries for the Part III period will be based on the Part III ITT analysis set, which will include all randomized subjects who receive at least one dose of study medication (or any portion of the dose) in Part III, regardless of their compliance with the protocol. On Day 1 of Part III, subjects in the OAP treatment arm will be re-randomized in a 1:1 ratio to continued treatment with their oral treatment or to PP (delayed-start PP arm). Subjects previously assigned to treatment with PP in Part II will continue on that treatment; however, in order to be included in the ITT population, this group must have at least one post-baseline MCCB, ICM, or PSP assessment.

An explanatory ITT (eITT) analysis set will be defined in Part III. The eITT analysis set will consist of all ITT subjects, as well as their study assessments for the time period between the date of randomization and the eITT end point. The eITT end point for subjects randomized to PP will be defined as the last PP1M injection date +28 days or the last PP3M injection date +84 days. For subjects randomized to OAP treatment, the eITT end point is defined as the last prescription date of the randomized (start of Part III) oral medication + the number of days' supply + 1 day. Changes in PSP, CGI-S, CRDPSS, and MSQ scales will be analyzed using the eITT analysis set.

11.4. Subject Characteristics, Disposition, Study Medication

Baseline subject characteristics will be summarized descriptively by study period, and the comparability of treatment groups at Part II and Part III baselines will be assessed using

Chi-square test for categorical variables and Analysis of Variance (ANOVA) for continuous variables. Particular interest will be given to the individual stratification factors for randomization: age, race, duration of previous antipsychotic usage prior to screening, baseline MCCB composite score, baseline PSP score, and substance use history.

Subject disposition including the timing of and reasons for discontinuation will be summarized by phase. Subjects' exposure to study medications will be summarized. Duration of treatment with randomized study medication, defined as the time from subject randomization to discontinuation of the randomized study medication, will be summarized descriptively for the eITT subjects. For eITT subjects, the distribution of the number of injections for PP will be determined and summarized. A descriptive summary of mean daily dose will be presented for each of the randomized OAPs. Mean daily dose for a subject is calculated as the sum of total prescribed daily dose during the treatment period divided by the total number of days covered.

11.5. Efficacy Analyses

11.5.1. Part II: Disease Progression

At the end of Part II, the database will be locked and data analyzed.

Primary Analysis in Part II (Treatment Failure):

Subjects who meet at least 1 of the criteria for treatment failure while on Part II treatment at the time of or before Part II completion will be considered to have had an event. Treatment differences will be compared using a log-rank test. The cumulative distribution function of the time to treatment failure will be estimated by the Kaplan-Meier method. The 95% CIs for the median treatment failure rates, as well as the failure rates at 3 months, 6 months, and at 9 months will be provided. In addition, the estimate of the hazard ratio and its 95% CI will be provided by treatment group based on the Cox proportional hazards model. The reasons for first treatment failure and subsequent treatment failures will be summarized at each visit and end point.

If the log-rank test result is statistically significant (p-value <0.05) in favor of PP, the null hypothesis would be rejected and we would conclude that PP is superior to OAP in delaying time to treatment failure. Hazard ratio and 95% CI will be used to describe reduction in risk treatment failure.

In case of significant missing treatment failure information (ie, >20%), the tipping point analysis will be implemented to assess the robustness and consistency of findings. Subjects in the PP treatment arm with missing data will be assigned a value that inflates the hazard by a known factor. Events will be imputed 1,000 times assuming a Weibull distribution. Results will be combined using standard multiple imputation combining rules. The inflation factor will be increased until the upper limit of 95% confidence interval crosses 1.

Key Secondary Analyses in Part II:

At the end of Part II, changes in MCCB composite score, PSP, and ICM volume will be analyzed to determine if there is an early treatment effect demonstrating disease progression of PP relative to OAP. The early treatment effect is illustrated by δ_{21} in Figure 2.

The change from baseline in MCCB composite score will be analyzed using a mixed model repeated measures (MMRM) ANCOVA model. The analysis will be based on observed data, ie, data collected at each time point without carrying forward previous values. The data points from unscheduled visits will also be included. The response variable will be the change in MCCB total score. The model will include Part II baseline MCCB composite score as a fixed-effect covariate; treatment (PP and OAP) and site as fixed-effect (categorical) factors, time as a regression variable, and the interaction between time and treatment. Using this model, treatment effects at the Month 9 end point will be estimated based on differences between least squares (LS) means. Accompanying 95% CIs for the LS mean differences between PP and OAP will be presented. An unstructured matrix will be used for the covariance of the within-subject repeated measures as a base case. However, the following spatial covariance structures will also be evaluated, SP(POW), SP(GAU), and SP(SPH). Linearity of response over time will be examined. A random intercept and random slope for each subject will also be fitted.

The purpose of this analysis is to examine treatment differences at Month 9 using LS means from the MMRM model. The treatment effect measures the deviation from the hypothesis of equality of means among treatments, "averaged" over the treatment duration. The time effect is a measure of deviation from the hypothesis of constancy of mean response over time for all treatment groups combined after aggregating over subjects. The treatment-by-time interaction tests the hypothesis of parallel response profiles over time in the treatment groups. A significant treatment-by-time interaction means that changes in response over time differ among treatments; in other words, there is a difference among the treatment groups, but the magnitude of the difference varies over time. The interaction will remain in the model, regardless of significance, in order to obtain an estimate of the treatment effect at the Month 9 time point. In the ITT analysis set, the model-based test for the mean treatment group difference will also be examined.

To assess missing data patterns, plots of mean MCCB change score from baseline over time for completers and for subjects who withdraw (by reason for withdrawal) will be generated. To assess normality, diagnostic plots such as normal quantile-quantile plots of residuals will be created. If a high degree of non-normality is suspected, remedies such as rank-based methods will be considered.

The eITT analysis set will also be used to test changes at end point. The eITT analysis set consists of MCCB score assessed at or prior to the eITT end point.

Changes in ICM volume will be analyzed using the same method as the MCCB analysis except the baseline MCCB score will be replaced by the corresponding ICM baseline score.

The analysis of time to 7-point worsening in PSP total score will be similar in methodology to the primary efficacy analysis. At each PSP assessment time point including the last eITT time

point, frequency counts, percentages, and cumulative percentages of subjects reporting each PSP level will be summarized by treatment group for the observed cases and LOCF data. Mean changes in PSP total score will be analyzed using the same method as the MCCB analysis except the baseline MCCB score will be replaced by the corresponding PSP baseline score. Additional PSP analyses include: Time to 10-point worsening; Categorical summary of frequency distribution of PSP total score and domain scores by time point; Shift from baseline scores by time point. Responses for PSP domain scores will also be dichotomized as absent to mild vs. manifest to very severe. The proportion of subjects in each group within domains will be calculated at each visit and compared between treatment groups using a CMH test.

Secondary Analyses in Part II:

Frequency counts, percentages, and cumulative percentages of subjects reporting each CGI-S score, CRDPSS domain scores, and MSQ level will be summarized by treatment group. Difference between treatment groups will be evaluated using the Cochran-Mantel-Haenszel (CMH) mean score test using modified ridit scores. The ordinal repeated measures data will also be evaluated using Generalized Estimation Equations (GEE) for both the ITT and eITT analysis sets. Responses for MSQ will also be dichotomized as Satisfied and Dissatisfied when the observed response on the MSQ scale was between 1 and 4 and between 5 and 7, respectively. The proportion of subjects who were either satisfied or dissatisfied on the MSQ scale will be calculated at each visit and compared between treatment groups using a CMH test.

Continuous efficacy endpoints at each post-baseline time point (LOCF) will also be analyzed using an ANCOVA model including treatment as a fixed design factor and corresponding baseline score as a covariate.

11.5.2. Part III: Extended Disease Progression and Disease Modification

Subjects who complete Part II will be eligible to enter Part III. At the start of Part III, subjects treated with OAP during Part II will be re-randomized in a 1:1 ratio to either continue treatment with OAP (OAP-OAP group) or to switch to PP (OAP-PP or 'Delayed-start PP' group). Subjects treated with PP during Part II will continue the same treatment (PP-PP group). The Part III treatment duration is 9 months.

The *Extended Disease Progression* analyses will focus on comparisons between the OAP-OAP and PP-PP groups; the *Disease Modification* analyses will focus on comparisons between the PP-PP and the OAP-PP groups (ie, subjects who started treatment with PP early vs. subjects who started PP treatment 9 months later).

11.5.2.1. Extended Disease Progression

The cumulative effect on disease progression at the end of Part III is illustrated by the quantity δ_{33} in Figure 2.

The change from Part II baseline in MCCB composite score at the end of Part III will be analyzed using a MMRM ANCOVA model. Changes in ICM volume and PSP total score will be analyzed using the same method as the MCCB analysis. Treatment differences for time to

7-point worsening in PSP score will be compared using a log-rank test, and Hazard Ratio along with 95% CI will be provided.

Categorical summary of frequency distribution of PSP total score and domain scores by time point will be examined. Shifts in PSP total score and domain scores from baseline scores by time point will be provided. Frequency counts, percentages, and cumulative percentages of subjects reporting each CGI-S score, CRDPSS domain scores, and MSQ level will be summarized by treatment group. Difference between treatment groups will be evaluated using the CMH mean score test using modified ridit scores. The ordinal repeated measures data will also be evaluated using GEE for both the ITT and eITT analysis set. Responses for MSQ will also be dichotomized as Satisfied and Dissatisfied when the observed response on the MSQ scale was between 1 and 4 and between 5 and 7, respectively. The proportion of subjects who were either satisfied or dissatisfied on the MSQ scale will be calculated at each visit and compared between treatment groups using a CMH test. Continuous and categorical endpoints at each post-baseline LOCF time point will also be examined.

11.5.2.2. Disease Modification

In order to demonstrate disease modification, the following results are required:

- At the end point of Part II: Subjects treated with PP for 9 months (early-start group) must demonstrate better outcomes on MCCB than those treated with OAP for 9 months. Similar results for changes in functioning (PSP) and changes in brain anatomy (ICM) will be used to support this finding (ie, treatment effect on disease progression).
- At the end point of Part III: Subjects who have been treated with PP for 18 months (early-start group) must continue to show better outcomes on MCCB compared with subjects treated with OAP for 18 months (a differential treatment effect is still evident), and compared with subjects treated with OAP for 9 months followed by PP for 9 months (the lead treatment effect remains significant after 9 months); ie, that late initiation of treatment with PP does not allow for achievement of the same level of cognition after 9 months. [(See corresponding null hypothesis below (H_0: $\delta_{31} - \gamma . \delta_{21} \leq 0$)]. Similar results for changes in PSP and ICM will be used to support this finding for disease modification.

For each of the endpoints (MCCB, PSP, and ICM), the following hypotheses will be tested as a function of estimated changes in the Part II endpoint using the observed scores. Let δ_{21} denote the estimated mean differences between treatment groups at the end of Part II for a given endpoint, treatment effect on disease progression. Below, the parameter $\mu_{PP\text{-}PP}$ corresponds to the mean score for a given endpoint following 9 months of additional PP treatment in subjects originally randomized to PP and $\mu_{OAP\text{-}PP}$ corresponds to mean score for 9 months of delayed-start PP treatment in subjects originally randomized to OAP treatment. Let δ_{31} denote the estimated difference between $\mu_{PP\text{-}PP}$ and $\mu_{OAP\text{-}PP}$, lead treatment effect at the end of Part III. The corresponding null hypotheses for a given endpoint will be listed as:

> H_0: $\delta_{31} - \gamma . \delta_{21} \leq 0$, where γ is a fixed number between 0 and 1 indicating the ratio of treatment effect in Part III compared to the Part II observed differences.

The quantity γ will be determined after Part II database lock and prior to finalization of Part III SAP. For γ, the quantities 0.25 and 0.50 will be considered principally. The γ could be different for a different endpoint.

In addition, for each of the endpoints, δ_{32} (delayed-start treatment effect on disease progression) will be tested in Part III using Part III baseline scores. Below, the parameter $\mu_{OAP\text{-}PP}$ corresponds to mean score for 9 months of delayed-start PP treatment in subjects originally randomized to OAP treatment and $\mu_{OAP\text{-}OAP}$ corresponds to the mean score for a given endpoint following 9 months of additional OAP treatment in subjects originally randomized to OAP. The corresponding null hypotheses for a given endpoint will be listed as:

$$H_0: \delta_{32} = \mu_{OAP\text{-}PP} - \mu_{OAP\text{-}OAP} = 0.$$

The quantity δ_{33} represents the cumulative effect on disease progression at the end of Part III following early start for PP compared to continuing OAP after a total of 18 months of treatment.

At the end of Part III, changes in MCCB composite score, PSP, and ICM volume will be analyzed to assess variables δ_{31}, δ_{32}, and δ_{33} (overall effect of treatment). Positive results (δ_{33} is significant [a differential treatment effect is still evident] **and** δ_{31} is significant [the lead effect remains significant after 9 months]) will be used to support a conclusion for disease modification.

The quantity δ_{31} (lead treatment effect) will be examined as a function of δ_{21} (treatment effect on disease progression) at the end of Part III using Part III baseline scores. The observed differences in MCCB composite score will be analyzed using a MMRM ANCOVA model. The analytical models will account for differences in intercept. Changes in ICM volume and PSP total score will be analyzed using the same method as the MCCB analysis as a function of corresponding δ_{21} value.

The quantity δ_{32} represents the delayed-start effect on disease progression for PP compared to continuing OAP after 9 months of additional treatment. The quantity δ_{33} represents the cumulative effect on extended disease progression at the end of Part III following early start for PP compared to continuing OAP after a total of 18 months of treatment.

The quantity δ_{32} (the delayed-start effect on disease progression) will be examined using change scores from Part III baseline to Part III end point. The differences in scale scores will be analyzed using MMRM ANCOVA models.

One of the objectives of Part I is to identify those subjects who have propensity to discontinue along with collecting and characterizing matching criteria. Patients who cannot tolerate oral paliperidone ER or oral risperidone will be discontinued in Part I. During Part II, patients are allowed to switch their OAP medications or adjust their dose levels in injectable arm. In other words, they are encouraged to stay in trial. These study features should minimize dropouts during Part II. However, there is still a potential that Part III subjects on PP-PP may not be comparable to subjects on OAP-PP or OAP-OAP with differential dropouts in Part II. For this

reason, additional sensitivity analysis using the Marginal Structural Models to describe study results will be considered.

The Disease Modification concept in Part III for each end point will also have corresponding Bayesian data analyses. This work will include all data points starting from Part II baseline and will utilize Bayesian Models with Hierarchy-Based Priors. The standard Markov Chain Monte Carlo methods including Gibbs and Langevin-Metropolis Hasting will be used to compute posterior estimates of $\delta_{21}=\mu_{PP} - \mu_{OAP}$ and $\delta_{31}=\mu_{PP\text{-}PP} - \mu_{OAP\text{-}PP}$. The primary objective of this analysis is to estimate posterior probability of $P(\delta_{31} - \gamma\ \delta_{21} > 0$ given data) accounting for inherent relationships between study visits within each endpoint. The quantity γ will be determined prior to Part III SAP finalization. Posterior median estimates and 90% credible intervals will be provided for μ_{PP}, μ_{OAP}, $\mu_{PP\text{-}PP}$, and $\mu_{OAP\text{-}PP}$. If the $P(\delta_{31} - \gamma\ \delta_{21} > 0$ given data) is greater than 80%, we will conclude that late initiation of treatment with PP does not allow for the same level of recovery after 9 months. In other words, subjects who start PP late do not catch up to those subjects who start PP 9 months earlier.

11.6. Safety Analyses

Safety variables to be analyzed include treatment-emergent adverse event incidence, ESRS-A scores, laboratory parameters, vital signs, ECG measures, physical examination reports, and ISST-Plus. The ITT analysis sets will be used for analyses performed on safety parameters unless otherwise specified. Any statistical tests performed to explore the data will be used only to highlight any comparisons that may warrant further consideration.

Adverse Events

The original terms used in the CRFs by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number of subjects with treatment-emergent adverse events, as well as the total number of events, will be displayed for each event within each phase. In addition, the severity of the event and its relationship to the study drug will be summarized by System Organ Class and preferred term. Incidence, type, timing, and resolution of serious adverse events will be reported. Special attention will be given to those subjects who discontinue treatment due to an adverse event or who experience a severe or a serious adverse event.

Clinical Laboratory Tests

Descriptive statistics will be provided for each laboratory analyte at the respective baseline and at each scheduled assessment time point. The criteria used to define markedly abnormal laboratory values will be defined in the SAP. The incidence of markedly abnormal laboratory values for each treatment group will be provided. A listing of subjects with any laboratory results outside the reference ranges will also be provided.

Electrocardiogram (ECG)

The effects on cardiovascular measurements will be evaluated using descriptive statistics and frequency tabulations. All important abnormalities from the ECG readings will be listed.

Vital Signs and Physical Examination

Changes from baseline in vital signs measurements will be presented descriptively. The percentage of subjects with values beyond clinically important limits will be presented.

Continuous variables such as heart rate, blood pressure, and change from baseline will be summarized at each assessment time point and at end point. Descriptive statistics will be presented at each assessment point and at end point for vital signs, body weight, and BMI. Body mass index will be calculated as weight (kg)/(height [m])^2.

For each of the vital signs parameters, the following categories for treatment-emergent abnormality will be tabulated with percentages by treatment group at each assessment time point and at end point. A treatment-emergent abnormality in vital sign is defined as a post-baseline value and change from baseline that meets any criteria in Table 9 with a normal or missing baseline value (ie, the baseline value must be above [in the case of abnormally low] or below [in the case of abnormally high] the value given in the table or missing). For example, when looking at abnormally low pulse, a normal baseline value would be considered any value >50 bpm. Similarly, when looking at abnormally high systolic blood pressure, a normal baseline value would be considered any value <180 mmHg.

Table 9: Treatment-Emergent Abnormality Categories for Vital Signs

	Post-baseline value outside of normal limit if:	
	Abnormally low	Abnormally high
Pulse (bpm)	A decrease from baseline of ≥ 15 to a value ≤ 50	An increase from baseline of ≥ 15 to a value ≥ 100
Systolic BP (mmHg)	A decrease from baseline of ≥ 20 to a value ≤ 90	An increase from baseline of ≥ 20 to a value ≥ 180
Diastolic BP (mmHg)	A decrease from baseline of ≥ 15 to a value ≤ 50	An increase from baseline of ≥ 15 to a value ≥ 105

BP = blood pressure

For body weight the incidence of increases/decreases from baseline ≥7% will be summarized in a frequency table by treatment group and by time point.

Extrapyramidal Symptom Rating Scale – Abbreviated (ESRS-A)

Descriptive statistics and frequency counts on changes from Part II or III baseline values will be provided for each measurement at each time of evaluation and at the subject's last evaluation in each study period.

InterSePT Scale for Suicidal Thinking-Plus (ISST-Plus)

Descriptive summaries will be provided for each ISST-Plus item score at each assessment time point using both eITT and ITT analysis sets.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For all paliperidone formulations (including oral paliperidone ER, oral risperidone, PP1M, and PP3M formulations), the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure. For all other OAP treatments used in the OAP treatment arm, the expectedness of an adverse event will be determined by whether or not it is listed in the relevant package insert.

Adverse Event Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2.

Anticipated Event

An anticipated event is an adverse event (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease related) or background regimen.

12.1.2. Attribution Definitions

Not Related

An adverse event that is not related to the use of the drug.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Special Reporting Situations

Safety events of interest on a sponsor study drug that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Inadvertent or accidental exposure to a sponsor study drug
- Any failure of expected pharmacologic action (ie, lack of effect) of a sponsor study drug
- Unexpected therapeutic or clinical benefit from use of a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the CRF.

12.3. Procedures

12.3.1. All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure (which may include contact for follow-up of safety). Serious adverse events, including those spontaneously reported to the investigator either at the End-of-Study Visit

or within 3 months after the last injection of study drug for the PP treatment groups, or within 30 days of the last oral dose for the OAP treatment group, whichever is later, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments. Anticipated events will be recorded and reported as described in Attachment 2.

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

For all studies with an outpatient phase, including open-label studies, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number

12.3.2. Serious Adverse Events

All serious adverse events occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site,

and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax).

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.
- Study-designated hospitalizations, such as during the Screening Period.

The cause of death of a subject in a study, whether or not the event is expected or associated with the study drug, is considered a serious adverse event.

12.3.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Pregnancy itself is not an adverse event; however, abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must be promptly withdrawn from the study.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed on the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed on the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

Paliperidone Palmitate

Paliperidone palmitate as a 1-month or a 3-month long-lasting IM formulation (ie, PP1M and PP3M, respectively) will be manufactured and provided under the responsibility of the sponsor.

Medication labels will comply with the legal requirements of each country.

PP1M and PP3M injections will contain paliperidone palmitate aqueous injectable suspension. PP1M dose concentrations will be 78, 117, 156, and 234 mg (50, 75, 100, and 150 mg eq.) and PP3M dose concentrations will be 273, 410, 546, and 819 mg (175, 263, 350, or 525 mg eq.) [as described in Table 3 of this protocol].

Please refer to the Investigator's Brochure for information on the physical and chemical characteristics of paliperidone palmitate, and for a list of excipients.[102]

Oral Antipsychotic Medications (Including Oral paliperidone ER and Oral Risperidone During Part I)

Oral antipsychotic medications (including oral paliperidone ER and oral risperidone during Part I) will not be provided directly by the sponsor.

The investigator will apply feasible doses of each OAP within the approved dose range. The medication will be prescribed for self-administration.

14.2. Packaging

Paliperidone Palmitate

Paliperidone palmitate (PP1M and PP3M; at concentrations listed in Table 3) will be supplied in a carton containing 2 safety needles, instructions for use, and a blistered, pre-filled syringe assembled with a plunger rod. Each carton box and each syringe will be labeled.

Paliperidone palmitate will not be dispensed in child-resistant packaging. Since the study drug will be administered at the investigational site only, access by children will be very unlikely. Investigators will be asked to store medication at a secured place.

14.3. Labeling

All study drugs provided by the sponsor will be labeled. Study drug labels will contain information to meet the applicable regulatory requirements.

14.4. Preparation, Handling, and Storage

All formulations of paliperidone palmitate (PP1M and PP3M) should be stored between 15°C and 30°C (59°F and 86°F respectively). PP1M and PP3M injections will be administered by trained study-site personnel. Prior to administration, it is critical to shake the PP1M and PP3M containing syringes **vigorously** for at least 10 and 15 seconds, respectively.

Please refer to the pharmacy manual for additional guidance on study drug preparation, handling, and storage.

14.5. Drug Accountability

The investigator is responsible for ensuring that all paliperidone palmitate received at the site is inventoried and accounted for throughout the study. For subjects receiving paliperidone palmitate, accountability will be maintained in an injection log.

Paliperidone palmitate must be handled in strict accordance with the protocol and the container label and will be stored in a limited access area or in a locked cabinet under appropriate environmental conditions. Unused paliperidone palmitate must be available for verification by the sponsor’s site monitor during on-site monitoring visits. All paliperidone palmitate syringes, used and unused, returned for destruction will be documented on the Drug Return Form. When

the site is an authorized destruction unit and paliperidone palmitate is destroyed on site, this must also be documented on the Drug Return Form.

Hazardous materials such as used needles and syringes containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes. The immediate destruction of these drug supplies should be documented in the drug accountability records on site.

Paliperidone palmitate should be dispensed under the supervision of the investigator, a qualified member of the investigational staff, or by a hospital/clinic pharmacist. Paliperidone palmitate will be supplied only to subjects participating in the study. Paliperidone palmitate may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense paliperidone palmitate, nor store it, at any site other than the study sites agreed upon with the sponsor.

Oral antipsychotic medications will not be provided directly by the sponsor. At each visit the investigator will provide a voucher and prescription for oral antipsychotic medication to each subject to bring to a local pharmacy to receive his or her medication. As subjects in the OAP treatment group are expected to self-administer their own medications, subjects do not have to return unused study drug to the site. This study seeks to replicate treatment reflective of regular clinical practice and there will be no monitoring of treatment compliance in subjects in the OAP group, and drug accountability of OAPs used or unused by the subject will not be performed.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Blood collection tubes, storage tubes, preprinted labels (or tubes labeled with preprinted labels)
- Urine pregnancy test kits
- Urine collection kits
- Urine drug screen test strip
- eDC Completion Guidelines
- Questionnaires/Rating Scales
- Investigator Brochure for paliperidone
- PI for risperidone, paliperidone ER, PP1M, and PP3M
- Laboratory manual
- IVRS/IWRS Manual
- MRI acquisition manual (for sites participating in MRI acquisition)

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

The potential advantage of PP3M over OAPs is that its administration would require outpatient clinic visits only 4 times a year, and is thus expected to facilitate treatment access and medication adherence among patients with schizophrenia with irregular or sporadic access to treatment. By extension, PP3M could potentially improve the feasibility of coordinating medical care with the patient's primary physician and healthcare team, and ultimately improve the overall economic burden of healthcare costs for patients with schizophrenia.

Additionally, PP3M is supplied in prefilled syringes that do not require refrigeration. These characteristics, together with its long duration of action and 3-monthly dosing interval make this a promising treatment option for patients with limited access to healthcare because they either live in an underserved rural or inner city setting, or simply cannot coordinate biweekly or once-monthly transportation for injection visits.

In any clinical study there is always some risk to removing current psychotropic medications and starting an investigational compound. Only subjects that require treatment with an antipsychotic medication or a change in antipsychotic medication due to lack of efficacy, tolerability, safety issues or investigator/subject preference, will be eligible for the study. Subjects with a prior history of lack of response to oral or LAI risperidone or paliperidone treatment will not be eligible for the study. A screening phase of up to 4 weeks was chosen to allow adequate time for completion of all screening procedures with results available to the investigator before the first dose of oral paliperidone ER, and to allow for washout of the current OAP other than oral risperidone or oral paliperidone ER to occur. All subjects will initially be treated with oral paliperidone ER or oral risperidone during the Part I oral run-in phase, which will allow the investigator to evaluate efficacy and safety of paliperidone or oral risperidone and find an optimal dose. Subjects who find oral paliperidone ER or oral risperidone inadequately efficacious or who wish to change their OAP for reasons other than tolerability may be switched to another protocol-specified OAP. Subjects who find oral paliperidone ER or oral risperidone intolerable will be withdrawn from the study. If the investigator believes that starting PP treatment is not clinically appropriate in a given subject, the subject will be discontinued from the study prior to randomization. After randomization, treatment in the OAP treatment group will be provided in a similar fashion as in a regular practice, ie, switching or add-on of other OAPs is allowed. Seven commonly used OAPs are available to provide option to select the appropriate treatment for subjects. Subjects who switched off oral paliperidone ER or oral risperidone treatment during Part I and II will be eligible to be randomized and continue treatment with OAP

or start treatment with PP when the investigator believes it is clinically appropriate. This approach is justifiable because studies have shown the clinical value of initiating LAI treatment in subjects who have not achieved adequate symptom control with an identical or chemically related oral antipsychotic, despite the similarities in mechanisms of action.[1,46,87,106,111] This result may be explained by the assured knowledge of drug delivery with an LAI formulation. The relatively constant plasma paliperidone concentrations achieved over the dosing interval of 1 to 3 months may also lead to longer sustained efficacy and improved tolerability.

Additional protective measures are incorporated into this protocol to assure safety of study subjects:

- Only those subjects who have the capacity to provide informed consent will be allowed to enroll in the study;
- Subjects will be carefully screened prior to enrollment, and subjects judged to be at high risk for AEs, violence, or self-harm will be excluded;
- For optimal management of symptoms/tolerability, subjects receiving PP3M (during either Part II or Part III) may go back to treatment with PP1M (monthly injections of 78, 117, 156 or 234 mg, flexibly dosed) for further dose adjustment or for the duration of the trial with the approval of the medical monitor;
- Subjects should not be discontinued from their current antipsychotic, if effective, for the sole purpose of entering the study;
- Subjects will receive any new information that may impact the benefit/risk of the investigational product and the subject's willingness to continue in the study, as it becomes available;
- Subjects may withdraw consent at any time and expect to receive regular, quality, conventional therapy;
- Supportive psychotherapy, self-help, and educational programs are permitted to mitigate the potential effects of an ineffective dose of study medication;
- Use of benzodiazepines and other rescue medications, and supplemental antipsychotic medications, are allowed to treat the symptoms that may emerge;
- During the study, subjects will be monitored for any emergent medical and psychiatric illnesses, events, or symptoms that may introduce added health risks;
- Subjects may be withdrawn from the study for any medical reason at the discretion of the investigator;
- MRI uses no radiation. To date, no side effects from the magnetic fields and radio waves have been reported. Any subjects with metal implants that are incompatible with MRI scanning will be excluded from MRI scanning.

Additional risks may arise from the long-acting nature of the study drug. When an OAP is stopped, they are quickly eliminated from the body. This rapid elimination reduces the severity of most TEAEs. With LAI antipsychotics, the plasma concentrations are maintained for many weeks after injection. If a TEAE occurs, there is no effective way to accelerate the elimination.

However, many of the expected adverse effects can be managed with pharmacological intervention (eg, betablockers for akathisia, anticholinergics for EPS).

The total blood volume to be collected (approximately 50 mL) is considered to be less than a standard Red Cross blood donation and will be collected over the course of more than a year.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Approval for the collection of optional DNA samples for research and for the corresponding ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data, or study conduct).

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

16.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorizing such access, including permission to obtain information about his or her survival status, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, and subsequent disease-related treatments, or to obtain information about his or her survival status.

The subject will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

Subjects will be asked for consent to provide optional DNA samples for research (where local regulations permit). After informed consent for the study is appropriately obtained, the subject will be asked to sign and personally date a separate ICF indicating agreement to participate in the optional research component. Refusal to participate in the optional research will not result in ineligibility for the study. A copy of this signed ICF will be given to the subject.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized

disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

16.2.5. Long-Term Retention of Samples for Additional Future Research

DNA samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand paliperidone palmitate or oral antipsychotics, or schizophrenia and schizophreniform disorder. They may also be used to develop tests/assays related to paliperidone palmitate or oral antipsychotics and schizophrenia and schizophreniform disorder. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.2, Withdrawal From the Study (Withdrawal From the Use of Samples in Future Research).

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the

sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (see Contact Information page(s) provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated Clinical Trial Agreement, which includes the financial agreement

- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the CRF: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

In addition, the author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly recorded at the study site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

17.5. Case Report Form Completion

Case report forms are provided for each subject in electronic format.

Electronic Data Capture (eDC) will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, and transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the study site. The electronic file will be considered to be the CRF.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subject's source documentation. All data relating to the study must be recorded in CRFs prepared by the sponsor. Data must be entered into CRFs in English. Study site personnel must complete the CRF as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

All subjective measurements (eg, scales other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible. The investigator must verify that all data entries in the CRFs are accurate and correct.

All CRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool.

If corrections to a CRF are needed after the initial entry into the CRF, this can be done in 3 different ways:

- Study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Site manager can generate a query for resolution by the study-site personnel.
- Clinical data manager (CDM) can generate a query for resolution by the study-site personnel.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, and periodic monitoring visits by the sponsor. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study-site personnel before the start of the study.

The sponsor will review CRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.8. Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study center visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. Findings from this review of CRFs and source documents will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

17.9. Study Completion/Termination

17.9.1. Study Completion

The study is considered completed with the last visit for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject visit at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study drug development

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the CRFs. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding PP1M/PP3M or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomics or exploratory research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of PP1M/PP3M, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain CRF data from all study sites that participated in the study. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of pharmacogenomics or exploratory MRI imaging analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication.

Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

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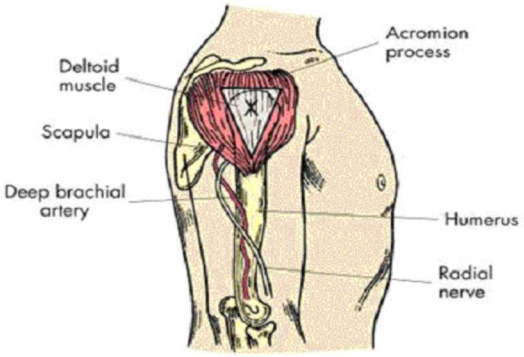
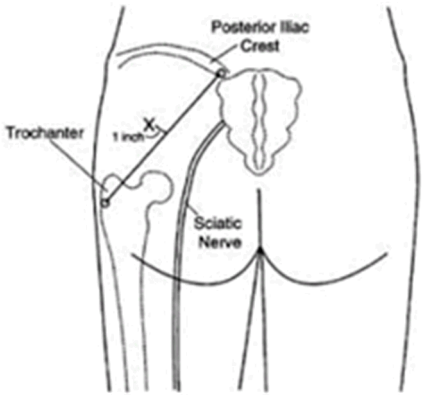
Attachment 1: Injection Site Guidelines

Guidelines for the intramuscular injection of paliperidone palmitate (1-month and 3-month formulations):

- Doses should be given at approximately the same time each day
- Prior to administration, it is critical to shake the PP1M and PP3M containing syringes **vigorously** for at least 10 and 15 seconds, respectively.
- The full content of the syringe should be injected
- Muscle group (deltoid or gluteal) or side (right or left) should be alternated from one injection to the next

Site	Deltoid Injection Site	Gluteal Injection Site
		
Needle sizes for PP1M injections	<200 lbs (90 kg): 1 inch (23 gauge) needle ≥200 lbs (90 kg): 1.5 inch (22 gauge) needle	All injections use 1.5 inch (22 gauge) needle
Needle sizes for PP3M injections	<200 lbs (90 kg): 1 inch (22 gauge) needle ≥200 lbs (90 kg): 1.5 inch (22 gauge) needle	All injections use 1.5 inch (22 gauge) needle
Notes	Insert the needle at a 90 degree angle to the skin with a quick thrust. Insert the needle into the thickest portion of the deltoid muscle - above the level of the axilla and below the acromion.	Palpate the junction of the posterior iliac crest and sacrum. Then imagine drawing a line to the greater trochanter of the femur. Injection is given in the upper outer area bordered by this imaginary triangle.

Attachment 2: Anticipated Events

Anticipated Event

An anticipated event is an adverse event (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease related) or background regimen.

For the purposes of this study the following events will be considered anticipated events:

Schizophrenia
Psychotic disorder
Hallucination, auditory
Hallucination, visual
Hallucination
Paranoia
Delusion
Apathy
Avolition
Drug use

Reporting of Anticipated Events

These events will be captured on the CRF and in the database, and will be reported to the sponsor as described in Section 12.3.1, All Adverse Events. Any event that meets serious adverse event criteria will be reported to the sponsor within the appropriate timeline as described in Section 12.3.2, Serious Adverse Events. These anticipated events are exempt from expedited reporting as individual single cases to health authorities. However, if based on an aggregate review, it is determined that an anticipated event is possibly related to study drug, the sponsor will report these events in an expedited manner.

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Edward Kim, MD

Institution: PPD Janssen Scientific Affairs, LLC.

Signature: PPD _____ Date: 2 Nov. 2017
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.