Janssen Research & Development *

Clinical Protocol

Single-arm, Open-label Extension to a Double-blind, Randomized, Active-controlled, Parallel-group Study of Paliperidone Palmitate 6-Month Formulation

Protocol R092670PSY3016; Phase 3
AMENDMENT 2

R092670 (paliperidone palmitate)

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This study will be conducted under United States (US) Food & Drug Administration (FDA) Investigational New Drug (IND) regulations (21 Code of Federal Regulations [CFR] Part 312).

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

PROTOCOL AMENDMENTS

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	15-Dec-2020
Amendment 1 (COVID-19 Appendix)	23-Apr-2020
Original Protocol	14-Feb-2019

Amendment 2, 15 December 2020

Overall Rationale for the Amendment: To remove text related to anticipated events and to increase the estimated number of subjects to be enrolled in the study.

Section Number and Name	Description of Change	Brief Rationale
Section 12.3.1. All Adverse Events; Attachment 3	Text related to anticipated events has been deleted from Section 12.3.1. Attachment 3 has been removed from the protocol.	Text related to anticipated events has been removed from the protocol to align with (1) the sponsor's current Safety Assessment Committee policy, which does not require review of anticipated events in single-arm, open-label extension studies by a safety committee independent of the study team, and (2) current protocol template text, which does not require a list of anticipated events for single-arm, open-label studies.
Synopsis, Overview of Study Design; Section 3.1. Overview of Study Design	The estimated number of subjects to be enrolled in the study was increased from approximately 100 to approximately 180.	The estimated number of subjects was increased because (1) the number of subjects enrolled in Study R092670PSY3015 was higher than anticipated, (2) the relapse and early withdrawal rates during the double-blind phase of Study R092670PSY3015 were lower than expected, resulting in a higher rate of enrollment in Study R092670PSY3016, and (3) 1 country was added to the list of countries participating in Study R092670PSY3016.
Time and Events Schedule; 3.2. Study Design Rationale	Added the mental status examination to the list of assessments that may be performed at other scheduled or unscheduled visits, as deemed necessary by the investigator.	Text added to clarify that the mental status examination may be performed as needed per the investigator.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted

Amendment 1, 23 April 2020

Overall Rationale for the Amendment: To provide guidance on changes to study conduct and assessments due to restrictions and limitations during the COVID-19 pandemic.

Section Number and Name	Description of Change	Brief Rationale
COVID-19 Appendix	Added a COVID-19 Appendix as guidance on changes to study conduct and assessments due to restrictions and limitations during the COVID-19 pandemic.	To provide guidance on study conduct and assessments during the COVID-19 pandemic.

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SYNOPSIS

Single-arm, Open-label Extension to a Double-blind, Randomized, Active-controlled, Parallel-group Study of Paliperidone Palmitate 6-Month Formulation

Paliperidone, the active metabolite of risperidone, is a monoaminergic antagonist that exhibits the characteristic dopamine type 2 (D_2) combined with predominant serotonin (5-hydroxytryptamine [5HT] type 2A [$5HT_{2A}$]) antagonism of the newer, or second generation, antipsychotic drugs. Paliperidone is currently available for therapeutic use in 3 formulations: an oral extended-release (ER) tablet formulation and two long-acting injectable formulations (paliperidone palmitate 1-month injection [PP1M] and paliperidone palmitate 3-month injection [PP3M]). To support further improvement in adherence and convenience, the sponsor is now developing a third paliperidone palmitate product intended for administration once every 6 months (paliperidone palmitate 6-month injection [PP6M]).

The current study is an open-label extension designed to assess the long-term safety and tolerability of PP6M and to provide medication access to PP6M in subjects with schizophrenia who have previously been treated in a double-blind, randomized, active-controlled study (Study R092670PSY3015). Only a limited number of countries participating in Study R092670PSY3015 will take part in this open-label extension.

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess (in a limited number of countries) the long-term safety and tolerability of PP6M (700 or 1000 mg eq.) and to provide access to PP6M in subjects with schizophrenia completing the R092670PSY3015 study without relapse.	• Safety will be assessed through evaluation of adverse events, mental status examination, clinical laboratory values, vital signs, physical examinations, the Abnormal Involuntary Movement Scale (AIMS), and injection site evaluations. Mandatory assessments will occur at limited time points during the study with additional assessments to be added at the discretion of the investigator if considered necessary. • Proportion of subjects who receive 1, 2, 3, or 4 PP6M injections.
Secondary	
• To assess the long-term efficacy of PP6M based on: – Overall symptom improvement and global severity of the illness – Personal and social functioning – Remission rates	• Efficacy will be assessed based on the change from open-label extension baseline on: – The Clinical Global Impression-Severity (CGI-S) scale. – The Personal and Social Performance (PSP) scale. – The proportion of subjects in remission will be assessed based on the Positive and Negative Syndrome Scale (PANSS) assessment at open-label extension baseline, Month 12, Month 24, and the

Objectives	Endpoints
	End-of-Study/Early Withdrawal visit.
• To continually assess the long-term effectiveness of PP6M on the prevention of relapse by evaluating the data from R092670PSY3015 and R092670PSY3016.	• Effectiveness will be assessed based on relapse, where relapse in the open-label extension is defined as one or more of the following: – Psychiatric hospitalization for schizophrenia (involuntary or voluntary admission to a psychiatric hospital for decompensation of the subject's schizophrenic symptoms); – Emergency Department/Room/Ward visit due to a worsening of the subject's symptoms of schizophrenia, but a psychiatric hospitalization does not occur; – The subject inflicts deliberate self-injury or exhibits violent behavior resulting in suicide, clinically significant injury to him/her self or another person, or significant property damage; – The subject has suicidal or homicidal ideation and aggressive behavior that is clinically significant (in frequency and severity) in the investigator's judgment.
• To evaluate the impact of PP6M on Medical Resource Utilization	• Based on the Healthcare Resource Utilization Questionnaire (HRUQ).

Note: Data from this study may also be used in a future analysis and combined with results from other studies (R092670PSY3015 and R092670SCH4067). If performed, this analysis will be reported separately.

Hypothesis

The primary hypothesis is that long-term treatment with PP6M (700 or 1000 mg eq.) is safe and well tolerated in subjects with schizophrenia who have previously been treated with PP6M for 12 months, or are being switched to PP6M from corresponding doses of PP3M.

OVERVIEW OF STUDY DESIGN

This study is a single-arm, 24-month open-label extension to Study R092670PSY3015, a double-blind, randomized, active-controlled, parallel-group study to evaluate whether the efficacy of PP6M is noninferior to that of PP3M in adults with schizophrenia. Subjects who complete the 12-month Double-blind Phase of R092670PSY3015 in the selected countries without a relapse will be eligible to enter the open-label extension study (R092670PSY3016). Approximately 180 subjects from Study R092670PSY3015 are estimated to be enrolled in the open-label extension.

All subjects will initially complete a screening assessment, during which eligibility will be assessed and informed consent obtained. Subjects who satisfy inclusion criteria will enter the 24-month open-label extension study. Subjects will attend site visits at a minimum of once every 3 months to complete safety, efficacy, and other assessments, with additional visits to be added at the discretion of the investigator as deemed necessary, per usual clinical practice. Subjects who meet criteria for relapse or other criteria for withdrawal during the study will be discontinued; these subjects will complete the End-of-Study

procedures as soon as possible and return for a follow-up assessment 6 months (183 ± 14 days) after their last PP6M injection.

For subjects who do not relapse or withdraw, study participation will be continued for up to a maximum of 2 years, or until PP6M becomes commercially available in the subject's local country, whichever occurs first. Subjects will get access to the medication for a maximum of 2 years. If PP6M becomes available locally before the 2-year endpoint, then subjects will be considered as having completed the open-label extension study and will be switched to a commercially available supply if they wish to continue the PP6M treatment.

SUBJECT POPULATION

The study will enroll adult men and women with Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnosis of schizophrenia who completed the Double-blind Phase of Study R092670PSY3015 without a relapse and who continue to be willing to be treated with PP6M.

DOSAGE AND ADMINISTRATION

All subjects in the open-label extension study will receive treatment with PP6M (700 or 1000 mg eq.), with injections administered once every 6 months. The initial dose of PP6M will be determined based on the dose level ("moderate" or "higher") that the subject was receiving during the Double-blind Phase of Study R092670PSY3015. Investigators will be allowed to change the PP6M dose during the study based on clinical judgment. All PP6M injections will be administered in the gluteal muscle, and will rotate across both sides (left or right) of the body.

EFFICACY EVALUATIONS

Efficacy evaluations include the CGI-S scale, the PSP scale, the PANSS (at limited timepoints, to allow assessment of remission), and relapse.

SAFETY EVALUATIONS

The study's safety evaluations will include assessment of adverse events, mental status examination, clinical laboratory assessments, vital signs, physical examinations, the AIMS, and injection site evaluations. In addition, the Columbia Suicide Severity Rating Scale (C-SSRS) will be performed if suicidal ideation is identified during the mental status examination. Other safety assessments (including but not limited to: 12-lead electrocardiogram [ECG], Barnes Akathisia Rating Scale [BARS], Simpson Angus Scale [SAS], and urine drug screen) may be conducted if deemed necessary by the investigator.

MEDICAL RESOURCE UTILIZATION

Medical resource utilization will be evaluated using the HRUQ.

STATISTICAL METHODS

The sample size will be determined by the number of subjects who complete Double-blind Phase of Study R092670PSY3015 without relapse and are willing to participate in R092670PSY3016.

All subjects who receive at least one dose of study intervention (PP6M) during the open-label extension study will be included in the evaluable analysis population. Descriptive statistics, summaries, tabulations, listings, etc. will be provided for each outcome as appropriate.

TIME AND EVENTS SCHEDULE

A. Open-label Extension Study

	Open-label Extension[a]								
Visit	1[b,c]	2	3	4	5	6	7	8	9/EOS[k]
Day (of Phase)	1[b,c]	92	183	274	365	456	547	638	729
Visit window (Days)		±14	±14	±14	±14	±14	±14	±14	±14
Screening/administrative									
Informed consent (ICF)[d]	X								
Inclusion/exclusion criteria[e]	X								
Pregnancy test[f]	X[g]		X		X		X		X
Concomitant therapy	X[g]	X	X	X	X	X	X	X	X
Study Intervention									
Administer PP6M	X		X		X		X		
Safety assessments[i]									
Adverse events	X	X	X	X	X	X	X	X	X
Mental status examination/clinical assessment[h,i]	X	X	X	X	X	X	X	X	X
Physical examination and vital signs[j]	X[g]				X				X
AIMS[i]	X[g]				X				X
Assessment of the injection site	X		X		X		X		X
Efficacy assessments									
CGI-S[i]	X[g]	X	X	X	X	X	X	X	X
PSP	X[g]				X				X
Full PANSS	X[g]				X				X
Clinical Laboratory Assessments									
Blood for hematology and serum chemistry[i]	X[g]				X				X
Urinalysis[i]	X[g]				X				X
Additional assessments									
HRUQ	X[g]		X		X		X		X

Keys: AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; CGI-S = Clinical Global Impression-Severity; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EOS = End-of-Study (Visit), which may be conducted as an Early Withdrawal Visit when relevant (see Section 10, Subject Completion/Discontinuation of Study Intervention/Withdrawal from the Study); HRUQ = Healthcare Resource Utilization Questionnaire; ICF = Informed Consent Form; PP1M = paliperidone palmitate 1-month (product); PP3M = paliperidone palmitate 3-month (product); PP6M = paliperidone palmitate 6-month (product); PANSS = Positive and Negative Syndrome Scale; PSP = Personal and Social Performance (scale); SAS = Simpson Angus Scale

Footnotes:

a. Subjects will attend study visits every 3 months. Intermediate visits are permitted, as deemed necessary by the investigator.

b. Visit 1 (Day 1) coincides with the End-of-Study visit for Study R092670PSY3015, and will take place immediately after completion of the R092670PSY3015 End-of-Study procedures.

c. There may be a small number of subjects who complete Study R092670PSY3015 before the R092670PSY3016 protocol is approved and implemented in that local country. These subjects may be screened and can enter Study R092670PSY3016 later, provided that: Visit 1 (Day 1) of Study R092670PSY3016 (ie, first dose of PP6M) is scheduled to occur no later than 3 months after the End-of-Study visit of R092670PSY3015, that in the interim period the subject has been treated with PP1M (100 or 150 mg eq.) or PP3M (350 or 525 mg eq.) (PP3M is preferred) and has not experienced a relapse (as defined in Section 9.2.4, Relapse Criteria), and the subject meets other criteria for study entry. For these subjects, Visit 1 (Day 1) of Study R092670PSY3016 will take place at the time of the subject's next scheduled dose of PP1M or PP3M (ie, 30 ±7 days after the last dose of PP1M; or 90 ±14 days after the last dose of PP3M). For these subjects, a screening period of 2 weeks will apply during which the procedures indicated on Visit 1 (Day 1) plus a baseline 12-lead ECG will be performed and laboratory results will need to be available and reviewed prior to dosing.

d. The ICF must be signed before the first study-related activity. Check clinical status again before the first dose of study drug.

e. The minimum criteria for the availability of documentation supporting the eligibility criteria are described in Section 17.4, Source Documentation.

f. The pregnancy test is applicable only to women of childbearing potential. It will be a urine test at all time points (via local testing) and must be confirmed negative before study intervention is administered at the marked visits.
g. Results from the R092670PSY3015 End-of-Study visit may be used, unless the End-of Study visit of R092670PSY3015 and Visit 1 (Day 1) of R092670PSY3016 are more than 4 weeks apart.
h. The mental status examination includes an assessment of suicidal ideation. If present, a C-SSRS is to be performed.
i. In addition to marked visits, assessments may also be performed at other visits, whether scheduled or unscheduled, as deemed necessary by the investigator. These include, but are not limited to: mental status examination, CGI-S, C-SSRS, AIMS, BARS, SAS, hematology labs, chemistry labs, urinalysis, urine drug screen, 12-lead ECG.
j. Physical examinations include body examination, weight, and waist circumference. Body mass index (BMI) will be calculated using the height measurement taken at the screening visit of Study R092670PSY3015.
k. End-of-Study procedures must also be completed for subjects who relapse or meet other criteria for withdrawal from the study. These procedures are to be completed on the day that withdrawal or relapse occurs, or as soon as possible thereafter. Subjects who withdraw or relapse should return for an additional follow-up visit (please refer to the Time and Events Schedule for the Follow-up Phase on the next page).

B. Follow-up Phase (for Subjects Who Discontinue, Withdraw, or Relapse)

Phase	Follow-up Phase
Visit Number (of Study)	Variable
Day	183 days from last study drug injection
Visit Window (Days)	±14
Concomitant therapy	X
Adverse events	X

Note: The Follow-up Phase is applicable only to subjects who relapse or meet other relevant conditions for withdrawal or discontinuation, as described in Section 10.2 (Withdrawal From the Study).

ABBREVIATIONS AND TERMS

Abbreviations

$5HT_{2A}$	5-hydroxytryptamine type 2A
AIMS	Abnormal Involuntary Movement Scale
BARS	Barnes Akathisia Rating Scale
BMI	body mass index
CGI-S	Clinical Global Impression - Severity
C-SSRS	Columbia Suicide Severity Rating Scale
D_2	dopamine type 2
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	electrocardiogram
eCRF	electronic Case Report Form
EPS	extrapyramidal symptoms
ER/PR	extended-release/prolonged-release
F013	a formulation of paliperidone palmitate, used in PP1M
F015	a formulation of paliperidone palmitate, used in PP3M and PP6M
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
G[x]	a general-psychopathology item of the PANSS scale, where x is the number of the item
GCP	Good Clinical Practice
HRUQ	Healthcare Resource Utilization Questionnaire
ICF	Informed Consent Form
ICH	International Conference on Harmonisation / International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LAI	long-acting injectable
MedDRA	Medical Dictionary for Regulatory Activities
mg eq.	(paliperidone palmitate) milligrams equivalent (to paliperidone)
N[x]	a negative-symptom item of the PANSS scale, where x is the number of the item
NIMH	National Institute of Mental Health
P[x]	a positive-symptom item of the PANSS scale, where x is the number of the item
PANSS	Positive and Negative Syndrome Scale
PK	pharmacokinetic(s)
PP1M	paliperidone palmitate 1-month (product)
PP3M	paliperidone palmitate 3-month (product)
PP6M	paliperidone palmitate 6-month (product)
PQC	Product Quality Complaint
PSP	Personal and Social Performance (scale)
SAS	Simpson Angus Scale
TEAE	treatment-emergent adverse event
VAS	Visual Analog Scale

Definitions

study “intervention”	PP6M (previously referred to as study “drug”)

1. INTRODUCTION

Paliperidone, the active metabolite of risperidone, is a monoaminergic antagonist that exhibits the characteristic dopamine type 2 (D_2), combined with predominant serotonin (5-hydroxytryptamine [5HT] type 2A [$5HT_{2A}$]), antagonism of the newer, or second generation, antipsychotic drugs. Paliperidone is currently available for therapeutic use in 3 formulations: an oral extended-release (ER) tablet formulation (INVEGA®) and two long-acting injectable formulations (paliperidone palmitate 1-month injection [PP1M] and paliperidone palmitate 3-month injection [PP3M]). To support further improvement in adherence and convenience, the sponsor is now developing a third paliperidone palmitate product intended for administration once every 6 months (paliperidone palmitate 6-month injection [PP6M]).

The PP6M product has been developed building upon the extensive knowledge collected during the development of the PP1M and PP3M formulations. The PP1M and PP3M formulations (F013 and F015, respectively) contain the same drug substance and similar excipients and are manufactured using the same equipment and process. The main differences between PP3M and PP1M are the suspension strength, particle size, and the fill volume for injection. The PP6M product has the same formulation as the PP3M product (F015). The key differences between the PP3M and PP6M product are that PP6M will be provided as a larger injection volume (and hence larger dose), is administered once every 6 months (as opposed to once every 3 months for PP3M), and, due to the larger volume, it planned to only be delivered in the gluteal muscle. Based on population pharmacokinetic (PK) simulations, it is expected that these changes will enable sustained paliperidone exposures over a 6-month dosing interval.

The current study is an open-label extension designed to evaluate the long-term safety and tolerability of PP6M and to provide medication access to PP6M for subjects with schizophrenia who have previously been treated in a double-blind, randomized, active-controlled study (Study R092670PSY3015). Subjects who complete 12 months of treatment with PP3M or PP6M during the Double-blind Phase of Study R092670PSY3015 without a relapse will be eligible, in a limited number of countries, to enter the current study and will receive PP6M (700 or 1000 mg eq.) during the 24-month open-label extension.

Doses of paliperidone palmitate (PP1M, PP3M, and PP6M) can be expressed in milligrams (mg) of paliperidone palmitate or in milligrams equivalent (mg eq.) to paliperidone. Throughout this document, doses will be described in mg eq. Conversions between paliperidone palmitate products and between units are described in Table 1.

Table 1: Conversions Between Doses and Injection Volumes for the 1-, 3-, and 6-Month Paliperidone Palmitate Products

	F013 Formulation			F015 Formulation					
	PP1M Dose			PP3M Dose[a]			PP6M Dose[b]		
	mg eq.	mg	Volume	mg eq.	mg	Volume	mg eq.	mg	Volume
	25 mg eq.	39 mg	0.25 mL	--	--	--	--	--	--
	50 mg eq.	78 mg	0.50 mL	175 mg eq.	273 mg	0.875 mL	--	--	--
	75 mg eq.	117 mg	0.75 mL	263 mg eq.	410 mg	1.315 mL	--	--	--
Moderate dose[c]	100 mg eq.	156 mg	1.00 mL	***350 mg eq.***	***546 mg***	1.750 mL	***700 mg eq.***	***1092 mg***	3.50 mL
Higher dose[c]	150 mg eq.	234 mg	1.50 mL	***525 mg eq.***	***819 mg***	2.625 mL	***1000 mg eq.***	***1560 mg***	5.00 mL

[a] PP3M dose = 3.5× the patient's previous PP1M dose.
[b] PP6M dose = ≈7× the patient's previous PP1M dose or ≈2× the previous PP3M dose.
[c] Doses shown in ***Bold Italics*** represent the PP3M and PP6M doses evaluated during Double-blind Phase of Study R092670PSY3015.
Key: -- = No corresponding dose level available; mg eq. = (paliperidone palmitate) milligrams equivalent (to paliperidone); PP1M = paliperidone palmitate 1-month product; PP3M = paliperidone palmitate 3-month product; PP6M = paliperidone palmitate 6-month product.

For the most comprehensive nonclinical and clinical information regarding paliperidone and paliperidone palmitate products (including PP6M), refer to the latest version of the Investigator's Brochure for paliperidone/paliperidone palmitate.

The term "study intervention" throughout the protocol, refers to the 6-month paliperidone product (PP6M).

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.

1.1. Background

Nonclinical Studies

Pharmacologic Profile

Paliperidone is a racemic mixture. Binding affinities are similar between risperidone and paliperidone for $5HT_{2A}$ and D_2 receptors, alpha-adrenergic receptor subfamilies Type 1 and 2, and histamine Type 1 receptors. In vitro, paliperidone was equipotent to risperidone in reversing the dopamine-induced suppression of prolactin release from anterior pituitary cells and had similar effects on human platelet function, plasma coagulation, and fibrinolysis. Paliperidone is devoid of antimuscarinic activity.

Toxicology

The nonclinical profile of paliperidone has been extensively evaluated during the development of the approved products. Paliperidone is associated with toxicologic effects that are typical of D_2 receptor antagonists. Two 12-week studies in minipigs indicated that the toxicological profiles of PP1M and PP3M were comparable when tested up to the maximum dose levels for humans (150 mg eq. for PP1M and 525 mg eq. for PP3M).

The sponsor conducted a 6-month local tolerability study in minipigs for PP6M up to a dose of 1060 mg eq. in an injection volume of 5.3 mL, which is more than the highest dose and volume

(1000 mg eq. in 5.0 mL) to be tested in the current clinical study. That 1060 mg eq. in 5.3 mL is administered unilaterally or bilaterally and yields a dose up to 141 mg eq./kg if tested in a (for example) 15-kg minipig, which is approximately 8-fold the highest dose on a mg eq./kg basis that will tested in the current clinical study (1000 mg eq., or 16.7 mg eq./kg in a [for example] 60-kg subject). Results of this 6-month local tolerability study in minipigs (described in the Investigator's Brochure) adequately support the use of PP6M in clinical studies.

Clinical Studies

Paliperidone Palmitate 6-month Product (PP6M)

The currently ongoing Phase 3 study (R092670PSY3015) is the first clinical study to evaluate the efficacy and safety of the PP6M product. Results of this study are not yet available; a brief overview of the study design is provided below.

- Study R092670PSY3015 is a randomized, double-blind, active-controlled, multicenter, interventional, parallel-group study in adults with schizophrenia. The study includes an initial open-label Transition and/or Maintenance Phase followed by a randomized Double-blind Treatment Phase. During the open-label Transition and Maintenance Phases, subjects will be treated with PP1M or PP3M. Subjects who are clinically stable on a moderate or high dose of PP1M (100 or 150 mg eq.) or PP3M (350 or 525 mg eq.) at the end of the Maintenance Phase will be eligible to enter the Double-blind Phase. At entry to the Double-blind Phase, subjects will be randomized in a 1:2 ratio to receive either PP3M (350 or 525 mg eq., every 3 months) or PP6M (700 or 1000 mg eq., every 6 months [with intervening placebo injections]). The dose of PP3M or PP6M for each subject during the Double-blind Phase will be calculated based on the last dose of PP1M or PP3M received during the Maintenance Phase (using the conversion factors as shown in Table 1). It is estimated approximately 549 subjects will be randomized in the Double-blind Phase. The Double-blind Phase will be 12 months in duration. The primary endpoint is time to relapse during the Double-blind Phase, with noninferiority assessed based on the difference in Kaplan-Meier 12-month estimate of survival (ie, percentage of subjects remaining relapse-free) between PP6M and PP3M. Secondary endpoints include evaluation of efficacy (based on changes from baseline in Positive and Negative Syndrome Scale [PANSS], Clinical Global Impression-Severity [CGI-S], and Personal and Social Performance [PSP] scales), safety and tolerability, and PK of PP6M versus PP3M.

Paliperidone Palmitate 1-month and 3-month Products (PP1M and PP3M)

While Study R092670PSY3015 is the first clinical study to evaluate the PP6M product, extensive clinical trial experience is available with the approved oral paliperidone formulation (paliperidone extended-release [ER] [or 'prolonged-release'] tablets) and the approved paliperidone palmitate products (PP1M and PP3M). Up to the most recent clinical cut-off date of 31 December 2017, over 15,000 subjects have received paliperidone ER, over 10,000 subjects have received PP1M, and approximately 1,500 subjects have received PP3M during cumulative clinical trial experience across all studied indications.

Of note, the sponsor has completed 3 registrational clinical studies of PP3M, which has the same formulation as PP6M. A total of 1,191 subjects received at least 1 dose of PP3M (F015) in

1 registrational Phase 1 study (R092670PSY1005) and 2 registrational Phase 3 studies (R092670PSY3011 and R092670PSY3012), with 319 subjects receiving at least 48 weeks of treatment with PP3M in the Phase 3 studies.[3] The combined exposure to PP3M was 567.6 subject-years.[3]

Pharmacokinetics

After injection, paliperidone palmitate dissolves slowly 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), 3 months (PP3M), or now potentially 6 months (PP6M); the duration depends on the particle size, concentration, and injection volume.

The sponsor developed a population PK model to describe the time course of plasma paliperidone concentrations after administration of PP3M, using data from Studies R092670PSY1005 and R092670PSY3012. The model was subjected to external evaluations, extensive model diagnostics, and validations using data from Study R092670PSY3011. The sponsor used this population PK modeling for PP3M to guide dose selection for PP6M (see Section 3.2, Study Design Rationale), which has the same formulation.

Efficacy

Efficacy data are not yet available for the PP6M product. The efficacy of the PP1M product is well established. The efficacy of the PP3M product in the maintenance treatment in adults with schizophrenia was established in two Phase 3 studies:

- Study R092670PSY3012 was a double-blind, placebo-controlled, long-term, randomized withdrawal study designed to determine whether PP3M was more effective than placebo in delaying the time to relapse of the symptoms of schizophrenia. Subjects progressed, as eligible, through a 17-week open-label PP1M treatment period (n=506), a 12-week open-label PP3M maintenance period (n=379), then were randomized to continue PP3M (n=160) or to switch to placebo (n=145) during the double-blind period. Relapses occurred in 3 times as many subjects in the placebo group (29.0%) as in the PP3M group (8.8%). The hazard ratio of relapse of schizophrenia symptoms was 3.81 (95% confidence interval: 2.08 to 6.99) times higher for a subject switching to placebo than for a subject continuing to receive PP3M, indicating a 74% decrease in relapse risk associated with continued PP3M treatment. The time to relapse was significantly different ($p<0.001$) in favor of PP3M over placebo; the median estimated time to relapse was not estimable for subjects in the PP3M group but was 395 days for subjects who switched to placebo. The long time to relapse in subjects who switched from PP3M to placebo, in combination with their PK results, indicates that many subjects had sufficiently therapeutic paliperidone plasma concentrations beyond their last PP3M dose.
- Study R092670PSY3011 was a double-blind, parallel-group, noninferiority study comparing the PP1M and PP3M formulations in subjects with schizophrenia. Subjects progressed, as eligible, through a 17-week open-label PP1M treatment period (n=1,429) and then were randomized to receive PP1M (n=512) or PP3M (n=504) during a 48-week double-blind

period. Relapse rates were low, occurring in 8.1% of PP3M subjects and 9.2% of PP1M subjects. The lower bound of the 95% confidence interval (-2.7%) was greater than the prespecified noninferiority margin of -15%, thus demonstrating that PP3M was noninferior to PP1M.

Overall, the previous efficacy outcomes with PP3M support clinical evaluation of PP6M, with a longer duration of efficacy expected to be provided by higher doses of the same formulation.

Safety

In addition to extensive studies of oral paliperidone and PP1M, the safety profile of PP3M (F015) was established in 3 registrational studies. The head-to-head comparison of PP3M and PP1M in Study R092670PSY3011 showed no clinically meaningful differences in their safety profiles. In particular, results were similar between PP3M and PP1M in the types and incidences of adverse events, adverse drug reactions, and injection site reactions. Across the development program for PP3M, no safety signals were detected that related specifically to the PP3M (F015) formulation.

Neither of the registrational Phase 3 studies of PP3M was designed to assess dose-related safety, since the investigators adjusted doses of PP1M for each subject based on his or her tolerability and efficacy; those flexible doses then were converted to a corresponding dose of PP3M. Therefore, any conclusions about dose-related PP3M safety results during the double-blind periods may be confounded by the ability or inability of individual subjects to tolerate PP1M in the preceding open-label periods. Still, selected exploratory analyses of safety outcomes stratified by optimized PP3M dose levels in the double-blind periods of these studies did not show higher overall rates of adverse events related to extrapyramidal symptoms (EPS) at the highest dose level relative to the lower dose levels, and did not show any evidence for a dose-related effect on the investigators' or subjects' ratings of the injection sites.

Overall, the previous safety and tolerability outcomes with PP3M support the clinical evaluation of PP6M, with acceptable safety and tolerability expected to be possible with higher doses of the same formulation for a longer duration.

1.2. Overall Rationale for the Study

The main rationale for this study is to collect long-term safety and tolerability data with PP6M and to provide access to the PP6M formulation for subjects who complete Study R092670PSY3015 without relapse. This study will be continued for up to a maximum of 2 years for each individual subject, or until PP6M becomes commercially available in a subject’s local country, whichever occurs first. In some countries, additional reimbursement negotiations and central formulary approvals will be needed before PP6M becomes available. In this case, subjects participating in the R092670PSY3016 study can continue to receive PP6M until the PP6M formulation is available in their local country, or for a maximum of 2 years. If PP6M becomes available locally before the 2-year endpoint, then subjects will be considered as having completed the open-label extension study at the end of the most recent 6-month injection cycle and will be switched to a commercially available supply if they wish to continue PP6M

treatment. For these subjects, the End-of-Study visit will be conducted 6 months after the subject's last dose of PP6M.

1.3. Benefit/Risk Assessment

Schizophrenia is a severe and chronic mental disorder. Several oral and long-acting injectable (LAI) antipsychotic medications are available for the treatment of patients with schizophrenia, but the disorder is associated with high rates of nonadherence to oral medications and some patients are not willing or able to attend regular clinic visits to receive their medication, including available LAI injections. The PP6M product offers the potential for patients to receive just 2 antipsychotic injections per year.

Having a LAI antipsychotic that requires injections only twice per year is unique; there is no other antipsychotic on the market with a comparable duration between injections. The combination of assured medication delivery, long-lasting antipsychotic coverage, and the reduced frequency of injections with the PP6M product may offer benefits in terms of improved patient convenience and reduced potential for nonadherence compared with currently available antipsychotics. If approved, PP6M therefore has the potential to improve serious outcomes (eg, hospitalization and/or relapse) associated with poor medication adherence in this population.

There is extensive evidence that paliperidone (the active ingredient of PP6M) is a safe and effective molecule for the treatment of schizophrenia. The currently available data (see Section 1.1, Background) as well as the population PK modeling performed to select the PP6M dose levels (see Section 3.2, Study Design Rationale) provide support for the conduct of this long-term open-label study.

The primary objective of this study is to evaluate the long-term safety and tolerability of the PP6M product (700 and 1000 mg eq., every 6 months) and provide medication access to PP6M in patients who have previously received PP6M or PP3M in Study R092670PSY3015. Only a limited number of countries that participated in Study R092670PSY3015 will take part in this open-label extension. Besides routine safety monitoring and subject management, this study includes several design features to minimize risk to subjects enrolled in this study. Firstly, only those subjects who have completed the Double-blind Phase and demonstrated adequate efficacy (ie, no relapses) and tolerability (ie, no significant adverse events) during 12 months of double-blind treatment with PP3M or PP6M will be eligible to enter the open-label extension study. Therefore, subjects will have already demonstrated a good response and tolerability to paliperidone palmitate LAI prior to entering the open-label extension study. Subjects will either be continuing PP6M at the same dose as they received during the R092670PSY3015 Double-blind Phase, or will be switching from PP3M to a corresponding dose of PP6M. Risks associated with switching from PP3M to PP6M are considered limited, given that both the PP3M and PP6M products have the same formulation (F015). Potential risks and risk mitigation strategies for subjects switching from PP3M are discussed further below:

- Higher dose: The PP6M doses in this study (700 and 1000 mg eq.) are approximately 2-fold higher than the corresponding PP3M doses (350 and 525 mg eq., respectively) (see Table 1).

The sponsor performed population PK simulations to select the chosen PP6M doses, and considered the acceptability of the PP6M exposures based on comparison with paliperidone and risperidone data from previous studies. The results indicated that exposures at the proposed PP6M dose levels are predicted to stay within the range of exposures that were shown to be efficacious and tolerated during clinical trial experience with other paliperidone/risperidone products (see further details in Section 3.2, Study Design Rationale). The maximum exposures predicted with PP6M in this study are therefore expected to be adequately tolerated. In addition, medications commonly used to improve tolerability of antipsychotic medications (eg, anti-EPS medications, benzodiazepines) will be permitted during the study, as needed (see Section 8, Prestudy and Concomitant Medication).

- Larger volume: The injection volumes for the PP6M doses (3.5 mL and 5 mL for the 700 and 1000 mg eq. doses, respectively) are higher than injection volume for the PP3M product (Table 1). The sponsor has consulted nursing guidelines[6] for the acceptability of the proposed PP6M volumes, and these guidelines indicate that volumes of up to 5 mL can be administered in the gluteus. The sponsor has accordingly restricted the administration of PP6M into the gluteal muscle in this study.
- Longer-acting formulation: A concern may be associated with the longer-acting nature of PP6M vs. PP3M. If an adverse event occurs during treatment with an oral antipsychotic, then dosing can be stopped, which results in rapid elimination from the body and often a resolution of the adverse event over a similar time course. If an adverse event occurs during treatment with a LAI antipsychotic, then the plasma concentrations may be maintained for months after the injection; elimination of the drug cannot be accelerated to facilitate resolution of the adverse event. However, many of the expected adverse events can be managed with pharmacological intervention (eg, beta-blockers for akathisia or anticholinergics for EPS). Moreover, eligible study subjects will already have been using LAI formulations before enrolling in the study; the study does not introduce a new risk of this nature, but only extends the duration in which the risk is present.

Overall, the potential benefits associated with an LAI antipsychotic that only requires administration twice a year, in addition to the positive efficacy and safety profile of paliperidone demonstrated in previous clinical studies with the approved paliperidone/paliperidone palmitate formulations, support the evaluation of PP6M in the proposed study. The overall risk-benefit balance for conducting the proposed clinical study is considered favorable.

More detailed information about the known and expected benefits and risks of paliperidone and paliperidone palmitate, including PP6M, may be found in the Investigator's Brochure.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess (in a limited number of countries) the long-term safety and tolerability of PP6M (700 or 1000 mg eq.) and to provide access to PP6M in	• Safety will be assessed through evaluation of adverse events, mental status examination, clinical laboratory values, vital signs, physical examinations, the Abnormal Involuntary

Objectives	Endpoints
subjects with schizophrenia completing the R092670PSY3015 study without relapse.	Movement Scale (AIMS), and injection site evaluations. Mandatory assessments will occur at limited time points during the study with additional assessments to be added at the discretion of the investigator if considered necessary. • Proportion of subjects who receive 1, 2, 3, or 4 PP6M injections.
Secondary	
• To assess the long-term efficacy of PP6M based on: – Overall symptom improvement and global severity of the illness – Personal and social functioning – Remission rates	• Efficacy will be assessed based on the change from open-label extension baseline on: – The Clinical Global Impression-Severity (CGI-S) scale. – The Personal and Social Performance (PSP) scale. – The proportion of subjects in remission will be assessed based on PANSS assessment at open-label extension baseline, Month 12, Month 24, and the End-of-Study/Early Withdrawal visit.
• To continually assess the long-term effectiveness of PP6M on the prevention of relapse by evaluating the data from R092670PSY3015 and R092670PSY3016.	• Effectiveness will be assessed based on relapse, where relapse in the open-label extension is defined as one or more of the following: – Psychiatric hospitalization for schizophrenia (involuntary or voluntary admission to a psychiatric hospital for decompensation of the subject's schizophrenic symptoms); – Emergency Department/Room/Ward visit due to a worsening of the subject's symptoms of schizophrenia, but a psychiatric hospitalization does not occur; – The subject inflicts deliberate self-injury or exhibits violent behavior resulting in suicide, clinically significant injury to him/her self or another person, or significant property damage; – The subject has suicidal or homicidal ideation and aggressive behavior that is clinically significant (in frequency and severity) in the investigator's judgment.
• To evaluate the impact of PP6M on Medical Resource Utilization	• Based on the Healthcare Resource Utilization Questionnaire (HRUQ).

Refer to Section 9 (Study Evaluations) for evaluations related to endpoints.

Note: Data from this study may also be used in a future analysis and combined with results from other studies (R092670PSY3015 and R092670SCH4067). If performed, this analysis will be reported separately.

2.2. Hypothesis

The primary hypothesis is that long-term treatment with PP6M (700 or 1000 mg eq.) is safe and well tolerated in subjects with schizophrenia who have previously been treated with PP6M for 12 months, or are being switched to PP6M from corresponding doses of PP3M.

3. STUDY DESIGN AND RATIONALE

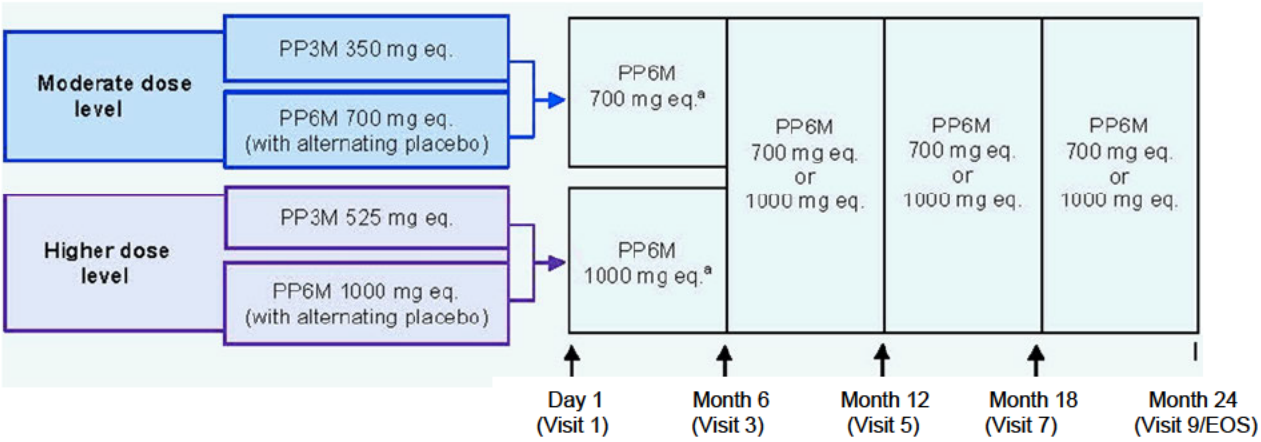
3.1. Overview of Study Design

This study is a single-arm, 24-month open-label extension to Study R092670PSY3015, a double-blind, randomized, active-controlled, parallel-group study to evaluate whether the efficacy of PP6M is noninferior to that of PP3M in adults with schizophrenia. Subjects who complete the 12-month Double-blind Phase of R092670PSY3015 in the selected countries without a relapse will be eligible to enter the open-label extension study (R092670PSY3016). Approximately 180 subjects from Study R092670PSY3015 are estimated to be enrolled in the open-label extension.

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

Figure 1: Schematic Overview of the Study

Study R092670PSY3015	Study R092670PSY3016 (Open-Label Extension)
Double-blind, Active-Controlled Phase	Open-label Extension
12 months (injections every 3 months)	24 months (injections every 6 months)



[a] The initial dose of PP6M in this study will be determined based on the dose level ("moderate" or "higher") that the subject was receiving during the Double-blind Phase of R092670PSY3015. The PP6M dose level may be adjusted (to 700 or 1000 mg eq.) later in the study, based on clinical judgment. However, the long-acting nature of PP6M should be taken into consideration. Any dose change will take many months to become apparent.

Key: ↑=PP6M injection; EOS=End of Study PP3M=paliperidone palmitate 3-month product; PP6M=paliperidone palmitate 6-month product.

All subjects will initially complete a screening assessment, during which eligibility will be assessed and informed consent obtained. Subjects who satisfy inclusion criteria will enter the 24-month open-label extension study.

The initial dose of PP6M received during the open-label extension (ie, at Visit 1) will be determined based on the subject's dose level (moderate or higher) during the Double-blind Phase of Study R092670PSY3015, as summarized below. Since treatment assignment (ie, to PP6M vs PP3M) during the Double-blind Phase of R092670PSY3015 will remain blinded when Visit 1 occurs, dosing will be fixed for all subjects at this visit to ensure that those subjects treated with PP3M during the Double-blind Phase of R092670PSY3015 will initiate treatment with PP6M at an equivalent dose:

- Subjects receiving a "moderate" dose in Study R092670PSY3015 (ie, receiving a PP3M dose of 350 mg eq. or PP6M dose of 700 mg eq.) will receive **PP6M 700 mg eq.** as an initial dose during the open-label extension.
- Subjects receiving a "higher" dose in Study R092670PSY3015 (ie, receiving a PP3M dose of 525 mg eq. or PP6M dose of 1000 mg eq.) will receive **PP6M 1000 mg eq.** as an initial dose during the open-label extension.

Flexible dosing will be permitted for subsequent PP6M injections at Visits 3, 5, and 7, such that the dose may be increased to 1000 mg eq. or decreased to 700 mg eq., based on the investigator's

judgment. However, given the slow rate of change in paliperidone blood levels expected over time with PP6M, it may take weeks or months for the desired effect of a dose change to occur.

The duration of exposure to study drug and the duration of study participation in the open-label extension study are intended to be a maximum of 2 years (ie, four PP6M injection cycles). Subjects will attend site visits at a minimum of once every 3 months to complete safety, efficacy, and other assessments according to the Time and Events Schedule, with additional visits to be added at the discretion of the investigator as deemed necessary, per usual clinical practice. Subjects who meet criteria for relapse (as defined in Section 9.2.4, Relapse Criteria) or other criteria for withdrawal during the study will be discontinued (see Section 10.2, Withdrawal From the Study); these subjects will complete the End-of-Study procedures as soon as possible and return for a follow-up assessment 6 months (183 ± 14 days) after their last PP6M injection.

For subjects who do not relapse or withdraw, study participation will be continued for up to a maximum of 2 years, or until PP6M becomes commercially available in the subject's local country, whichever occurs first. In some countries, additional reimbursement negotiations and central formulary approvals will be needed before PP6M becomes available. In this case, subjects participating in the R092670PSY3016 study can continue to receive PP6M until the PP6M formulation is available in their local country, or for a maximum of 2 years. Subjects will get access to the medication for a maximum of 2 years. If PP6M becomes available locally before the 2-year endpoint, then subjects will be considered as having completed the open-label extension study at the end of the most recent 6-month injection cycle and will be switched to a commercially available supply if they wish to continue PP6M treatment. For these subjects, participation may continue as described in the Time and Events Schedule and the End-of-Study visit will be conducted 6 months after the subject's last dose of PP6M.

3.2. Study Design Rationale

Subject selection criteria

This study will recruit adult subjects (men and women) with schizophrenia who completed the Double-blind Phase of R092670PSY3015 without a relapse and who continue to be willing to receive PP6M during the open-label extension. Subjects will be required to meet selection criteria (see Section 4, Subject Population) and must voluntarily consent and be able and willing to fulfill all study requirements.

Study design

This is a single-arm, open-label study in which all subjects will receive PP6M. Open-label treatment design is considered suitable for the collection of long-term safety and tolerability data and is more consistent with real-world clinical practice. As such, this study will strive to be pragmatic, with minimal mandated assessments.

Subjects will be entering the open-label extension study after completing the 12-month Double-blind Phase of Study R092670PSY3015. Therefore, subjects will either be continuing treatment with PP6M or will be switching from PP3M to PP6M. The inclusion of subjects switching from

PP3M to PP6M will allow for intrasubject comparison between PP3M and PP6M treatment and enable collection of additional data regarding the switch from stable PP3M treatment to PP6M, which is consistent with the proposed use of PP6M in clinical practice.

During this study, subjects will attend site visits at a minimum of once every 3 months according to the Time and Events Schedule. Additional study visits may be added at the discretion of the investigator, as deemed necessary, per usual practice. Concomitant psychotropic medications can be used during the study as required (eg, for concomitant conditions [eg, insomnia, anxiety], extrapyramidal symptoms), with some limitations (refer to Section 8, Prestudy and Concomitant Medications, for details).

Selection of efficacy and safety evaluations

The full lists of efficacy and safety assessments for this study are described in Section 9, Study Evaluations.

The primary objective of this study is to collect long-term safety and tolerability information for PP6M and to provide access to PP6M for patients who successfully completed the Double-blind Phase of Study R092670PSY3015 without a relapse. At each study visit, adverse events will be assessed and investigators will evaluate the subject's mental status (including an assessment of suicidality). In addition, an assessment of the injection site will be performed after each PP6M injection. Clinical laboratory values, physical examinations (including body weight/body mass index [BMI]), vital signs, and the AIMS will be assessed at limited time points during the study, with additional assessments to be added at the discretion of the investigator. Paliperidone palmitate may cause increases in serum prolactin levels; therefore, prolactin levels will be measured as part of the clinical laboratory safety assessment. If clinically warranted, investigators may perform additional evaluations as needed during the study, including but not limited to: the mental status examination, Columbia Suicide Severity Rating Scale (C-SSRS), Barnes Akathisia Rating Scale (BARS), Simpson Angus Scale (SAS), 12-lead electrocardiogram (ECG), urine drug screen.

Efficacy and effectiveness of PP6M will be assessed as secondary objectives, and will be evaluated based on changes from baseline in CGI-S, PANSS, and PSP scales as well as assessment of relapse and remission. The CGI-S was chosen to assess efficacy as it is a well-known and widely accepted scale to assess the severity of symptoms of schizophrenia. Additionally, the PSP will be utilized as a tool to assess the impact that treatment has on subjects' personal and social functionality because of the vital importance of improvement in these domains. The relapse criteria used in this study (listed in Section 9.2.4) have been adapted from the criteria that were used in the R092670PSY3015 study and other registrational clinical studies that were conducted to support approval of PP1M and PP3M. The criteria selected for this open-label study more closely resemble typical indicators of relapse in real-world clinical practice.

Dose selection rationale

The PP6M dose levels evaluated in this open-label extension study (and in the Double-blind Phase of Study R092670PSY3015), 700 and 1000 mg eq., were selected based on the results of population PK simulations. Both PP3M and PP6M are the F015 formulation; that is, PP3M and PP6M differ in the mass and volume of each dose, but not in the formulation of paliperidone palmitate. Therefore, the population PK model that was developed for PP3M is expected to be suitable for the dose selection of PP6M.

The population PK model that describes the time course of plasma paliperidone concentrations after PP3M administration was developed by using data from a Phase 1 study (R092670PSY1005) and a Phase 3 study (R092670PSY3012).[3] This model was internally and externally evaluated, not only by performing extensive model diagnostics at the model building stage, but also by successfully validating the model using data from another Phase 3 study (R092670PSY3011). Using that previously developed and validated population PK model for PP3M, new population PK simulations were performed to project the optimal dose levels for PP6M that would correspond to similar trough paliperidone concentrations of the PP3M dose levels of 350 and 525 mg eq., while remaining at or below the recommended maximum 5.0-mL volume for aqueous intramuscular injections.[6] The results indicated that investigational PP6M dose levels should be 700 and 1000 mg eq.

Population PK modeling was used to compare the investigational PP6M dosages against the highest and lowest approved dosages of other products that contain paliperidone or risperidone.

- The higher investigational PP6M dosage is 1000 mg eq. The highest approved dosage of oral risperidone in the United States and some other countries is 16 mg/day (as 8 mg twice a day).[a] The maximum plasma concentration of paliperidone associated with PP6M as 1000 mg eq. was calculated to be lower than the maximum plasma concentration of active moiety associated with oral risperidone 16 mg/day (as 8 mg twice a day), and in line with the maximum plasma concentration associated with oral risperidone 6 mg/day (as 3 mg twice a day).
- The lower investigational PP6M dosage is 700 mg eq. The lowest approved dosage of the oral paliperidone extended-release/prolonged-release (ER/PR)[b] formulation in the United States and some other countries is 3 mg/day.[c] The minimum plasma concentration of PP6M as 700 mg eq. was calculated to be higher than the minimum plasma concentration of oral paliperidone ER/PR formulation as 3 mg/day.

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[a] RISPERDAL® [United States Prescribing Information]. Titusville, NJ: Janssen Research & Development. www.accessdata fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020272. Accessed 28 December 2018.

[b] The terminology for ER versus PR varies by country; therefore, both terms are used together in this protocol.

[c] INVEGA® [United States Prescribing Information]. Titusville, NJ: Janssen Research & Development. www.accessdata fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021999. Accessed 28 December 2018.

Medical Resource Utilization Data Collection

The Healthcare Resource Use Questionnaire will be included in order to collect medical resource utilization data that will inform future schizophrenia treatment cost analyses. Data collected from this study will be analyzed together with results from other studies; the economic analyses may be conducted and reported separately from this study.

4. SUBJECT POPULATION

Screening assessment for eligible subjects will be performed on Day 1 (Visit 1), prior to the first dose of study intervention administered in the open-label extension study.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

4.1. Inclusion Criteria

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

1. Completed the Double-blind Phase of Study R092670PSY3015 without relapse and continue to be willing to be treated with PP6M.

   Note: There may be a small number of subjects who complete Study R092670PSY3015 before the R092670PSY3016 protocol is approved and implemented in that local country. These subjects may be screened and can enter Study R092670PSY3016 later, provided that: Visit 1 (Day 1) of Study R092670PSY3016 (ie, first dose of PP6M) is scheduled to occur no later than 3 months after the End-of-Study visit of R092670PSY3015, that in the interim period the subject has been treated with PP1M (100 or 150 mg eq.) or PP3M (350 or 525 mg eq.) (PP3M is preferred) and has not experienced a relapse (per criteria in Section 9.2.4, Relapse Criteria), and the subject meets other criteria for study entry.

2. Must, in the opinion of the investigator, be able to continue treatment at the same dose level (moderate or higher dose) as used during the Double-blind Phase of Study R092670PSY3015 at the time of screening for this study.

3. A woman of childbearing potential must have a negative urine pregnancy test on Day 1.

4. Use contraception consistent with local regulations for subjects participating in clinical studies. Before receiving study intervention, a woman must be either:

   a. Not of childbearing potential, defined as being either postmenopausal or permanently sterile, as follows:
      - Postmenopausal: A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to

confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy, however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

- Permanently sterile: Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

b. Of childbearing potential, but meeting the contraception requirements as follows:
   - Practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly). Examples of highly effective contraceptives include the following:
     - User-independent methods: Implantable progestogen-only hormone contraception associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system; vasectomized partner; sexual abstinence (sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention; the reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject).
     - User-dependent methods: combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, and transdermal; progestogen-only hormone contraception associated with inhibition of ovulation: oral and injectable.

     Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

   - Agree to remain on a highly effective method throughout the study and for at least 12 months after the last dose of study intervention. A woman using oral contraceptives should use an additional birth control method (see inclusion criterion text in the sub-bullet above).

Note: If the childbearing potential changes after start of the study or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout this inclusion criterion. If reproductive status is questionable, additional evaluation should be considered.

5. A man must agree that during the study and for a minimum of 12 months after receiving the last dose of study intervention, his female partner(s) will use a highly effective method of contraception as described above, and:

   a) He must, if being sexually active with a woman of childbearing potential, use a barrier method of contraception (eg, condom with spermicidal foam/gel/film/cream/suppository).

   b) He must, if being sexually active with a woman who is pregnant, use a condom.

   c) He must agree not to donate sperm.

6. Sign an informed consent form (ICF) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study; and must be able to provide his or her own consent (ie, consent cannot be provided by a legal representative of the subject).

7. In the opinion of the investigator, the patient would be able to participate for the duration of this study.

4.2. Exclusion Criteria

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

1. Has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

2. Completed R092670PSY3015 while presenting adverse events deemed clinically relevant by the investigator, and which may interfere with safety and well-being of the patient.

3. If a man, has plans to father a child while enrolled in this study or within 12 months after the last dose of study intervention. Must not, if a woman, have plans to become pregnant while enrolled in this study or within 12 months after the last dose of study intervention.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions, Restrictions, and Strong Recommendations

Prohibitions and Restrictions

Potential 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:

1. Refer to Section 8, Prestudy and Concomitant Therapy, for details regarding prohibited and restricted therapy during the study.

2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

3. If a woman of childbearing potential, continue using an appropriate method of contraception, as described in Section 4.1 (Inclusion Criteria), during participation in the study and for at least 12 months after the last dose of study intervention. (Women who have a positive pregnancy test during the study will be withdrawn from the study.)

4. If a man, continue using the measures described in Section 4.1 (Inclusion Criteria) to prevent women from being exposed to his sperm or conceiving his child during the study and for 12 months after receiving the last dose of study intervention.

Strong Recommendations

Potential subjects should also be willing and able to adhere to the following strong recommendations (which are not strict prohibitions or restrictions) during the course of the study:

1. Should not donate blood during the study and for at least 6 months after completion of the study.

2. Should not participate in an investigational drug study during the study and for at least 6 months after completion of the study.

3. Should not use alcohol, illicit substances, or recreational marijuana (even where legal) during the entire study. (Recreational marijuana is a strong recommendation, but medical marijuana is a prohibition; see Section 8, Prestudy and Concomitant Therapy).

4. Should not eat before blood laboratory full panel sampling. (Nonfasting exceptions should be noted; fasted states are overnight or for at least 8 hours).

5. INTERVENTION ALLOCATION AND BLINDING

Intervention Allocation

Randomization will not be used in this study. All subjects will receive PP6M during the open-label extension; the PP6M starting dose will be allocated as described in Section 6, Dosage and Administration.

Blinding

As this is an open study, blinding procedures are not applicable.

6. DOSAGE AND ADMINISTRATION

All subjects in the open-label extension study will receive treatment with PP6M. Two PP6M dose levels are available: 700 and 1000 mg eq. Subjects will receive up to 4 injections of PP6M during the 24-month treatment period.

- For subjects who enter the open-label extension immediately after completing Study R092670PSY3015: Day 1 of Study R092670PSY3016 is intended to take place on the same day as the End-of-Study visit in R092670PSY3015, immediately after completion of the R092670PSY3015 End-of-Study procedures. This visit coincides with the timing of when PP6M may be administered relative to the subject's last dose of PP6M (if randomized to PP6M treatment in Study R092670PSY3015) or PP3M (if randomized to PP3M treatment in Study R092670PSY3015). For these subjects, the initial dose of PP6M will be selected based on the unblinded dose level ("moderate" or "higher") that the subject was receiving during the Double-blind Phase of Study R092670PSY3015; ie, subjects in the "moderate" dose level will receive PP6M 700 mg eq., and subjects in the "higher" dose level will receive PP6M 1000 mg eq. during the open-label extension. The blind in R092670PSY3015 does not need to be broken for purposes of treatment assignment.
- For subjects who enter the open-label extension later (up to 3 months after they complete R092670PSY3015): In a small number of subjects, the Day 1 visit of R092670PSY3016 may occur up to 3 months after the R092670PSY3015 End-of-Study visit, and these subjects may be receiving poststudy treatment with PP3M or PP1M (PP3M is preferred). For these subjects, the Day 1 visit of the open-label extension study will be scheduled to coincide with the subject's next dose of PP3M or PP1M (ie, 90 ± 14 days after the last dose of PP3M, or 30 ± 7 days after the last dose of PP1M). Only those subjects on a moderate or higher dose of PP3M (350 or 525 mg eq.) or PP1M (100 or 150 mg eq.) will be eligible to enter the open-label extension. For these subjects, the initial dose of PP6M (700 or 1000 mg eq.) in the open-label extension study will be calculated based on the subject's previous dose of PP1M or PP3M, using the conversion factors summarized in Table 1.

For all subjects, study intervention (PP6M) during the open-label extension will be administered once every 6 months. Investigators will be allowed to change the dose at Visits 3, 5, and 7 (increase or decrease, to 700 or 1000 mg eq.) based on clinical judgment. However, given the slow rate of change in paliperidone blood levels expected over time with PP6M, it may take weeks or months for the desired effect of a dose change to occur.

All PP6M injections will be administered in the gluteal muscle, and will rotate across both sides (left or right) of the body. For each dose, a study-site personnel member must shake the syringe vigorously with the tip facing up and with a loose wrist for at least 15 seconds to ensure a homogeneous suspension. The shaken dose must then be administered within 5 minutes after shaking. If more than 5 minutes pass after shaking but before injection, then a study-site personnel member must shake the syringe vigorously again for at least 15 seconds to resuspend the dose. The full content is to be administered in one injection, using only the supplies provided in the study drug kit. See Attachment 1 for more details about administration.

Study intervention administration must be captured in the source documents and the electronic Case Report Form (eCRF).

Treatment After the Study

See Section 10.3 (Antipsychotic Therapy After the Study) for further recommendations regarding poststudy treatments. Such treatments are nonstudy treatments and therefore are not described here.

7. INTERVENTION COMPLIANCE

The study intervention administrator will administer the injections throughout the study and will record the date/time of dosing as well as the injection site (right or left side, gluteal muscle only) in the eCRF.

8. PRESTUDY AND CONCOMITANT THERAPY

All medications (prescriptions, over-the-counter, herbal remedies) other than the study intervention that were either continued at the start, or begun during, the open-label extension study are to be documented in the eCRF. For subjects treated with PP1M or PP3M before entering this study (and after completion of study R092670PSY3015), all interim doses of PP1M or PP3M are to be documented in the eCRF as well. The sponsor is to be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

8.1. Prestudy Medical Therapy and Psychotherapy

Except for the prohibited concomitant medications described in Section 8.3, Prohibited Concomitant Medications, any medications that are ongoing and stable at screening may be allowed to continue thereafter into the open-label extension study. Ongoing psychotherapy and other psychosocial interventions are allowed to continue. For psychiatric medications of special interest at study entry:

- Other psychiatric medications: Other medications taken for the treatment of psychiatric conditions are allowed at screening and to continue thereafter.

It is preferable that no changes have been made to any treatments (for psychiatric or other medical conditions) in the 30 days before screening.

8.2. Concomitant Therapy

Concomitant therapies must be recorded throughout the study beginning with start of the first dose of study intervention.

Except for the prohibited concomitant medications described below, concomitant medications may be initiated during the study for medical or psychiatric reasons. New psychotherapies and psychosocial treatments may be started.

- Anti-EPS medications: The use of anti-EPS medications should be re-evaluated at regular intervals, and investigators and subjects should work together to lower and discontinue doses if clinically indicated.
- Benzodiazepines: For the control of agitation, anxiety, akathisia, etc, lorazepam is the preferred benzodiazepine because of its low potential for drug-drug interactions and its relatively short half-life. However, use of other benzodiazepines is permitted.
- Sleep aids: For insomnia or sleep-related difficulties, subjects may use zolpidem, zaleplon, zopiclone, or eszopiclone at dosages in accordance with the locally approved prescribing information. Sleep aid medications should not be used in the 8 hours preceding any scheduled efficacy assessment or rating scale.

- Oral Antipsychotic Supplementation: Since this study attempts to be pragmatic, supplementation with oral antipsychotics during the study will be allowed. The duration and dose of antipsychotic supplementation should be linked to symptom exacerbation, per the investigator's judgment.

  The maximum duration that oral antipsychotics can be co-administered with PP6M is 2 weeks, at which point the subject must be assessed clinically for relapse criteria. Within a single 6-month injection cycle, if the subject does not meet relapse criteria (as defined in Section 9.2.4, Relapse Criteria), then an additional 2 weeks of oral antipsychotic can be administered continuously for a maximum of 4 weeks. During later injection cycles, oral supplementation can also be administered using this same approach. If oral risperidone or paliperidone ER/PR are used for supplementation, doses higher than those listed in Table 2 below are not recommended. If, in the investigator's judgment, there is a clinical need for oral antipsychotic supplementation for more than 4 continuous weeks, the study intervention is to be discontinued and the subject is to be withdrawn (see Section 10.2, Withdrawal from the Study). The suggested antipsychotic medications and corresponding doses are provided in Table 2; use of oral antipsychotic medications other than those listed below is prohibited.

Table 2: Supplemental Oral Antipsychotic Dosage Chart

	Oral Risperidone	Oral Paliperidone ER/PR
Moderate Dose (700 mg eq. PP6M)	1-2 mg/day	1.5 – 3 mg/day
High Dose (1000 mg eq. PP6M)	1-3 mg/day	1.5 – 6 mg/day

8.3. Prohibited Concomitant Medications

The concomitant medications described below may not be used during the study.

- Concomitant oral and injectable antipsychotics are prohibited (other than as described in Section 8.2, Concomitant Therapy).
- Medicinal products known to prolong the QT interval - such as Class IA antiarrhythmics (eg, disopyramide, quinidine, or procainamide) and Class III antiarrhythmics (eg, amiodarone or sotalol); some antihistamines; some antibiotics (eg, fluoroquinolones like moxifloxacin or ciprofloxacin); some antimalarials (eg, mefloquine); tricyclic antidepressants, and some antipsychotics (eg, chlorpromazine or ziprasidone) - are prohibited.
- Inducers of proteins involved in the metabolism of paliperidone (ie, cytochrome P450 3A4) or the excretion of paliperidone (ie, p-glycoprotein) - such as rifampicin, carbamazepine, oxcarbazepine, barbiturates, phenytoin, troglitazone, and St. John's Wort - are prohibited.
- Systemic antifungals are prohibited.
- Antineoplastic agents are prohibited.
- Medical marijuana is prohibited.
- Dopamine agonists, including, but not limited to: ropinirole, pramipexole, pergolide, cabergoline, lisuride, and amantadine.

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

9. STUDY EVALUATIONS

9.1. Study Procedures

Overview

The Time and Events Schedule summarizes the frequency and timing of efficacy, safety, and other measurements applicable to this study. Actual dates and times of assessments will be recorded in the source documentation and eCRF.

Additional site visits may be performed at any time during the open-label extension study as determined necessary by the investigator. 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 participation in the study.

Efficacy and safety procedures are described in Section 9.2 and Section 9.3, respectively. Medical resource utilization data will also be collected (see Section 9.4).

The total blood volume to be collected from each subject is expected to be less than 400 mL, based on the clinical laboratory samples indicated in the Time and Events Schedule. Repeat or unscheduled samples may be taken at the discretion of the investigator (eg, for safety reasons or for technical issues with the samples).

Screening/Day 1 (Visit 1)

Day 1 (Visit 1) of the open-label extension study is intended to coincide with the End-of-Study visit of R092670PSY3015, and will take place immediately after completion of the End-of-Study assessments. At this visit, subject eligibility will be assessed and informed consent obtained. Eligible subjects will then receive their first open-label injection of PP6M, as described in Section 6, Dosage and Administration.

There may be a small number of subjects who complete the End-of-Study visit for Study R092670PSY3015 before the R092670PSY3016 protocol is approved. These subjects may be screened and can enter Study R092670PSY3016 later, provided that: Day 1 (Visit 1) of Study R092670PSY3016 (ie, first dose of PP6M) occurs no later than 3 months after the End-of-Study visit of R092670PSY3015, that in the interim period the subject has been treated with PP1M or PP3M (PP3M is preferred) and has not experienced a relapse (as defined in Section 9.2.4, Relapse Criteria), and the subject meets other criteria for study entry. For these subjects, Day 1 (Visit 1) of Study R092670PSY3016 will take place at the time of the subject's next scheduled dose of PP1M or PP3M (ie, 30 ±7 days after the last dose of PP1M; or 90 ±14 days after the last dose of PP3M).

For subjects who attend their first study visit of the open-label extension study (Day 1/Visit 1) more than 4 weeks after the R092670PSY3015 End-of-Study visit, a screening period of 2 weeks will apply during which the baseline procedures described in the Time and Events Schedule for Day 1/Visit 1 will need to be conducted. In addition, a baseline 12-lead ECG assessment should be performed and laboratory results will need to be available and reviewed prior to dosing.

For subjects who attend the first study visit the same day or within 4 weeks after the R092670PSY3015 End-of-Study visit, the assessments performed for the R092670PSY3015 End-of-Study visit may be used as the baseline for the open-label extension study, where appropriate (see further details in the Time and Events Schedule).

Subsequent Study Visits

After the first study visit, subjects will attend site visits at a minimum of once every 3 months. Additional in-person or telephone visits may be added at the discretion of the investigator, if deemed necessary (eg, to monitor adverse events or symptom worsening, or if a relapse is suspected), per usual clinical practice.

If a relapse is detected at a scheduled or unscheduled visit (as described in Section 9.2.4, Relapse Criteria), then the subject will be withdrawn from the study and the completion of End-of-Study procedures and arrangements for poststudy treatment are to occur as soon as possible (see Section 10, Subject Completion/Discontinuation of Study Intervention/ Withdrawal from the Study).

Subjects who do not relapse or meet other criteria for withdrawal during the study will participate in the study for up to 2 years. However, if PP6M becomes commercially available in the subject's local country before the 2-year endpoint, then the subject will be considered as having completed the open-label extension study at the end of the most recent 6-month injection cycle and will be switched to a commercially available supply if they wish to continue PP6M treatment (see Section 10, Subject Completion/Discontinuation of Study Intervention/ Withdrawal from the Study). For these subjects, the End-of-Study visit will be conducted 6 months after the subject's last dose of PP6M.

Follow-up Phase

Subjects who relapse or meet other relevant conditions for withdrawal will return for a follow-up visit 6 months (183 ± 14 days) after their last dose of PP6M. At this visit, information regarding post-study/concomitant medication as well as adverse event data will be collected.

The Follow-up Phase, when applicable, is supplementary after study completion. For relevant subjects, participation in the Follow-up Phase is encouraged but not required. No protocol deviations or violations are applicable during this phase. The Follow-up Phase is designed to be as low-burden and noninvasive as possible, in order to encourage participation by the affected subjects while still collecting minimal safety data.

9.2. Efficacy Evaluations

The clinically assessed efficacy evaluations include the CGI-S, the PSP scale, the PANSS, and relapse criteria as described further in the sections below.

9.2.1. Clinical Global Impression - Severity

The CGI-S rating scale[7] 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 (extremely severe). This scale permits a global evaluation of the subject's condition at a given time.

The CGI-S is included in the Early Clinical Development Evaluation Unit Assessment Manual that was published by the US National Institute of Mental Health (NIMH).[7] This study uses a version of the CGI-S that is slightly modified from the original (to be more specific to psychosis, not general for mental illness), as was done in the sponsor's other studies.[4,5] This modified CGI-S poses a single question to the investigator, to consider his or her total clinical experience with this particular population, and to rate the severity of the subject's psychotic disorder on a scale from 1 = not ill to 7 = extremely severe, as shown in the Manual of Assessments. A CGI-S score should be recorded at the time points indicated in the Time and Events Schedule, and at any clinic visit associated with a suspected or impending relapse.

9.2.2. Personal and Social Performance Scale

The PSP scale assesses the degree of difficulty a subject exhibits over a 7-day period within 4 domains of behavior: a) socially useful activities, b) personal and social relationships, c) self care, and d) disturbing and aggressive behavior. The results of the assessment are converted to a numerical score from 1 to 100 points, which can be interpreted in 10-point intervals as excellent functioning (91 to 100 points), good functioning (81 to 90 points), mild difficulties (71 to 80 points), etc, as shown in the Manual of Assessments. Scores from 31 to 70 points indicate varying degrees of difficulty, and scores below 30 points indicate functioning so poor that intensive support or supervision is needed. Individual domain items of the PSP will be collected and recorded in the eCRF.

9.2.3. Positive and Negative Syndrome Scale

The neuropsychiatric symptoms of schizophrenia will be assessed using the 30-item PANSS scale,[9] which provides a total score (sum of the scores for all 30 items) and scores for 3 subscales: the 7-item positive-symptom (P) subscale, the 7-item negative-symptom (N) subscale, and the 16-item general-psychopathology symptom (G) subscale. Each item is rated on a scale from 1 (absent) to 7 (extreme). A trained clinician experienced in the treatment of subjects with schizophrenia will administer the PANSS. An example of a full PANSS is provided in the Manual of Assessments. A full PANSS score should be administered at the time points indicated in the Time and Events Schedule. The full PANSS may be administered using the Structured Clinical Interview (SCI-PANSS) format, or using an equivalent structured interview format to be provided by the sponsor, at the discretion of the investigator.

9.2.4. Relapse Criteria

The criteria for relapse used in R092670PSY3015 were modified for this open-label extension study to reflect the change of the trial setting and a pragmatic approach.

Relapse during the open-label extension study will be defined as 1 or more of the following:

- Psychiatric hospitalization for schizophrenia (involuntary or voluntary admission to a psychiatric hospital for decompensation of the subject's schizophrenic symptoms);
- Emergency Department/Room/Ward visit due to a worsening of the subject's symptoms of schizophrenia, but a psychiatric hospitalization does not occur;
- The subject inflicts deliberate self-injury or exhibits violent behavior resulting in suicide, clinically significant injury to him/her self or another person, or significant property damage;
- The subject has suicidal or homicidal ideation and aggressive behavior that is clinically significant (in frequency and severity) in the investigator's judgment.

A relapse event will be recorded on the first date that a subject meets at least one of the above criteria. Unlike in the R092670PSY3015 study, an increase in PANSS score is not a criterion for relapse; therefore, if an increase in PANSS is noted, a second PANSS assessment to confirm the increase is not necessary.

9.3. Safety Evaluations

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF. 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 evaluations of safety and tolerability as described below and according to the time points provided in the Time and Events Schedule.

9.3.1. Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12 (Adverse Event Reporting).

9.3.2. Mental Status Examination/Clinical Assessment

At each visit, the investigator will perform a mental status examination per usual care. Aspects of the examination are to be documented on the Mental Status Examination Form for R092670PSY3016, which was developed as a data collection tool for this study. At a minimum, the mental status examination performed must include the domains identified on the Mental Status Examination Form. These domains include: General Appearance and Behavior, Mood, Affect, Thought Process, Thought Content, Perceptions, and Insight. If suicidal ideation is present, a C-SSRS (see Section 9.3.8, Columbia Suicide Severity Rating Scale) must also be performed at the visit.

9.3.3. Clinical Laboratory Tests

Blood samples for serum chemistry and hematology and urine samples for urinalysis will be collected. The investigator must review the laboratory results, document this review, and record

any clinically relevant changes occurring during the study in the adverse event section of the eCRF. The laboratory reports must be filed with the source documents.

The tests below will be performed by a local laboratory. The local laboratory should have local country approval and/or recognition for processing of human samples. For full panels, subjects should be in fasted state overnight or for at least 8 hours (and nonfasting exceptions should be noted). To permit standardization, reference and outlier ranges for each local lab will be collected.

- **Hematology Panel**
  - hemoglobin
  - hematocrit
  - platelet count
  - red blood cell count
  - white blood cell count with differential
  - hemoglobin A1c

- **Serum Chemistry Panel**
  - sodium
  - potassium
  - chloride
  - bicarbonate
  - blood urea nitrogen
  - creatinine
  - glucose
  - aspartate aminotransferase
  - alanine aminotransferase
  - gamma-glutamyltransferase
  - bilirubin
  - alkaline phosphatase
  - creatine phosphokinase
  - lactic acid dehydrogenase
  - uric acid
  - calcium
  - phosphate
  - albumin
  - total protein
  - magnesium
  - lipid panel (total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglycerides).
  - prolactin
  - thyroid stimulating hormone.

- **Urinalysis**

Dipstick	Sediment (performed if dipstick result is abnormal)
- specific gravity	- red blood cells
- pH	- white blood cells
- glucose	- epithelial cells
- protein	- crystals
- blood*	- casts
- ketones	- bacteria
- bilirubin	- any other findings
- urobilinogen	
- nitrite*	
- leukocyte esterase*	

*If the dipstick result is abnormal, then flow cytometry or microscopy 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.

- **Additional Tests**
  - For women of childbearing potential, urine pregnancy tests (via local testing) will be conducted at the timepoints indicated in the Time and Events Schedule.
  - To facilitate confirmation of postmenopausal status as described in Section 4.1 (Inclusion Criteria), study-site personnel may order an FSH test if desired (per clinical judgment). For postmenopausal status, the FSH test can only be confirmatory, and cannot replace the associated requirement for 12 months of amenorrhea.
  - Urine drug screen (for illicit substances, including marijuana, even where legal) and alcohol breath tests may be performed at the discretion of the investigator. Alcohol and illicit substances are strongly discouraged but are not exclusionary and are not cause for withdrawal from the study.
  - For subjects who enter the open-label extension study more than 4 weeks after the R092670PSY3015 End-of-Study visit, blood samples for serum chemistry, hematology, and urine samples for analysis should be collected and results should be reviewed by the investigator before the first dose of PP6M.

9.3.4. Vital Signs

Vital signs include temperature, pulse/heart rate, respiratory rate, and blood pressure. Vital signs should be recorded before any invasive tests, such as blood draws. Blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

At each scheduled time point, blood pressure and pulse/heart rate measurements will be assessed in the supine position (after at least 5 minutes rest) with a completely automated device. Pulse/heart rate will be measured for a full minute to minimize the effects of variability. The automated device should consist of an inflatable cuff and an oscillatory detection system. All values should be registered on a built-in recorder so that measurements are observer-

independent. Manual techniques will be used only if an automated device is not available. Whether automated or manual, appropriately-sized blood pressure cuffs should be used for accurate reading of blood pressure.

Orthostatic vital signs may also be performed, at investigator's discretion. If a subject is unable to stand up or is unable to remain standing for 2 minutes, then the blood pressure should be measured immediately after standing is discontinued, while the subject is in a sitting or supine position. Attendants should protect subjects from falling during the evaluations.

All vital sign measurements will be recorded on the eCRF.

9.3.5. Physical Examinations

Physical examinations at the time points designated in the Time and Events Schedule include body examination, and measurements of weight and waist circumference. The height measurement taken at the screening visit of Study R092670PSY3015 will be used to calculate body mass index (BMI: weight/height^2 as kg/m^2).

9.3.6. Extrapyramidal Symptom Rating Scales

The Abnormal Involuntary Movement Scale (AIMS) will be performed at the timepoints indicated in the Time and Events schedule. Additional AIMS assessments may be performed at any time if deemed necessary by the investigator.

Other scales to assess EPS (BARS for akathisia, and the SAS for parkinsonism), may be performed if deemed necessary by the investigator. These 2 scales can be performed at any time, at the discretion of the investigator.

Abnormal Involuntary Movement Scale

The AIMS is included in the Early Clinical Development Evaluation Unit Assessment Manual from the US NIMH.[7] The AIMS rates 9 items about dyskinesia on scale as 0 = none, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe. It rates 1 item about the subject's awareness of abnormal movements as 0 = no awareness; 1 = aware, no distress; 2 = aware, mild distress; 3 = aware, moderate distress; and 4 = aware, severe distress. It has 2 yes/no questions about dental status. An example of the AIMS is provided in the Manual of Assessments.

Barnes Akathisia Rating Scale

The BARS assesses akathisia via 1 objective rating and 2 subjective ratings (awareness of restlessness and reported distress related to restlessness); each is scored from 0 to 3 points.[2] It also assesses akathisia via 1 global clinical rating scored from 0 to 5 points. For all items, anchors are provided for each value and higher scores indicate worse akathisia. An example of the BARS is provided in the Manual of Assessments.

Simpson Angus Scale

The SAS is led by signs (rather than by symptoms) to measure drug-induced parkinsonism.[12] This study uses a version of the SAS that is slightly modified from the original (where the "head

dropping" item was changed to "head rotation," to avoid injury to the cervical spine), as was done in the sponsor's other studies.[4,5] This modified SAS contains 10 items: 6 items for rigidity (arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, and head rotation); 1 compound item for gait (incorporating gait, posture, and loss of arm swing), and 3 items for tremor, glabellar tap, and salivation. An example of the SAS is provided in the Manual of Assessments.

9.3.7. Evaluations of the Injection Site

9.3.7.1. Injection Site Evaluations by Subjects

The Visual Analog Scale (VAS) to measure pain has been widely used in diverse adult populations. The VAS is a continuous scale on a horizontal or vertical line, usually 100-mm long, and anchored by 2 verbal descriptors (1 for each symptom extreme). The instructions, time period for reporting, and verbal descriptor anchors have varied widely in the literature depending on the intended use of the scale. In some settings, test-retest reliability and ability to detect change have been demonstrated.[8]

In this study, subjects will be asked about the pain associated with the injection by means of a 100-mm VAS, scaled from "no pain at all" to "unbearably painful." (Similar VAS assessments were used in previous studies of PP3M.[4,5]) The VAS-Acute will assess pain once within 30 minutes after each injection; the subject does not complete a VAS at the End-of-Phase Visit. The VAS is scored by measuring the distance (in millimeters) from the left (indicating no pain) to the place mark made by the subject.

9.3.7.2. Injection Site Evaluations and Follow-up by Investigators

Investigators or subinvestigators (but not other study-site personnel) will evaluate the injection sites for tenderness, erythema/redness, and induration/swelling after each PP6M injection, plus at the End-of-Study visit or at the time of early withdrawal. The characteristics will be scored as 0=absent, 1=mild, 2=moderate, or 3=severe, in accordance with the anchor points that are provided in the Manual of Assessments. For erythema/redness, a score of 0 is used for a measurement of <2.5 cm, a score of 1 is used for 2.5-5 cm, a score of 2 is used for 5.1-10 cm, and a score of 3 is used for >10 cm. Two dimensions of induration/swelling are assessed: measurement and impact on function. The dimension yielding the higher score will be the one selected for this assessment. Measurement scores are the same as those used for erythema/redness (ie, 0 = <2.5 cm, 1 = 2.5-5 cm, 2 = 5.1-10 cm, 3 = >10 cm). Functional scores are as follows: 0 and 1 = no interference with the subject's usual activities, 2 = interferes with (but does not prevent) one or more of the subject's usual activities, 3 = prevents one or more of the subject's usual activities. Tenderness ratings are as follows: 0 = no tenderness, 1 = mild discomfort to touch, 2 = discomfort with movement, 3 = significant discomfort at rest. The scales and anchors are a hybrid from the sponsor's previous studies of PP3M,[4,5] and from a US FDA

guidance.[d] The results will be recorded on the eCRF. The investigator/subinvestigator should complete these assessments within 30 minutes after the injection; for any characteristic still rated mild, moderate, or severe at the last marked visit, the investigator/subinvestigator should add assessments at subsequent visits (even if not marked) until all of the characteristics are rated absent. Clinical sites should make efforts to have the same individual perform all injection site evaluations for a particular subject. This individual should not review the subject's VAS rating of the injection site pain.

If a subject has an injection site adverse event that is rated as moderate or severe (see Section 12.1.3 [Severity Criteria]) and that is accompanied by objective findings (eg, tenderness, erythema/redness, and induration/swelling), then the clinical site should perform or refer for ultrasonography of the injection site and should refer the subject to a specialist for further evaluation.

- For ultrasonography, the goal is to identify phlegmonous processes that might evolve to overt abscesses of the gluteus and to differentiate real granulomatous reactions from less relevant topical reactions.
- For referrals, considerations are as follows:
  - Suspected cellulitis or abscess should be referred to a dermatologist or surgeon for consideration of incision and drainage procedure along with tissue microbiological samples.
  - Nodule, fibroma, furuncle or other noninfectious reaction with a severity assessment of either moderate or severe should be referred to a dermatologist or surgeon for consideration of fine needle aspiration and/or tissue biopsy.

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

9.3.8. Columbia Suicide Severity Rating Scale

The C-SSRS must be performed at any visit where suicidal ideation is detected during the mental status examination (see Section 9.3.2, Mental Status Examination/Clinical Assessment). Additional assessments may be performed at any time during the study, at the discretion of the investigator.

The C-SSRS is a low-burden measure of the spectrum of suicidal ideation and behavior that was developed in a US NIMH study to assess severity and track suicidal events through any treatment, and is the prospective counterpart to the system developed by Columbia University investigators for the US FDA in their analysis of the association between suicidality and medication.[11] The C-SSRS is a clinical interview providing a summary of both ideation and

[d] US FDA. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf. Issued September 2007. Accessed 28 December 2018.

behavior that can be administered during any evaluation or risk assessment to identify the level and type of suicidality present. It can also be used during treatment to monitor for clinical worsening. The C-SSRS Baseline Version assesses suicidal behavior and ideation over a lifetime, and the C-SSRS "Since Last Visit" Version assesses those parameters over an interval. An example of the C-SSRS is provided in the Manual of Assessments.

9.3.9. Electrocardiograms

Since this study aims to approach real-world conditions, regular collection of 12-lead ECGs are not mandated. Instead ECGs can be collected at any time based on the judgment of the investigator. Electrocardiograms will be obtained locally. If possible, the same ECG machine and reader should be used at each collection. The ECG reader should be locally licensed and have approval to interpret ECGs. Relevant interval measurements (PR, QRS, QT, etc) will be collected, and an overall assessment of clinically relevant rhythm abnormalities will be recorded on the eCRF. The overall assessment of clinical relevance will be up to the judgment of the investigator.

A copy of the 12-lead ECG shall be printed and kept as part of the local source documentation. The paper speed should be set to 25 mm/second and the gain setting of (10 mm/1 mV). Suggested electrode placement is provided in Attachment 2.

For subjects who enter the open-label study more than 4 weeks after the R092670PSY3015 End-of-Study visit, a baseline 12-lead ECG should be performed before the first dose of PP6M.

During the collection of ECGs, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

9.4. Medical Resource Utilization

Healthcare Resource Utilization Questionnaire

Medical resource utilization data will be collected using the HRUQ. This questionnaire was designed to assess utilization of the following resources: hospitalization (refers to ≥1 night stay), emergency room visits without hospitalization, day or night clinic stays, outpatient treatment, as well as daily living conditions and productivity of the subject.[10] The questionnaire will be used in this study as an exploratory tool and has been modified with recall periods appropriate to the study. Study-site personnel will administer the questionnaire. If possible, for a given subject, the same person should administer this scale at all visits. The subject will be the primary provider of the information, but additional outside information should also be included as available, including information from any caregivers. Any resource utilization that is required by the protocol should not be captured on the questionnaire. An example of the HRUQ is provided in the Manual of Assessments.

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY INTERVENTION/ WITHDRAWAL FROM THE STUDY

10.1. Completion

A subject will be considered to have completed the study if he or she completes the 24-month open-label treatment phase and completes the End-of-Study assessments at Day 729.

A subject will also be considered as having completed the study if PP6M becomes commercially available locally during the study. For these subjects, the End-of-Study assessments should be performed 6 months (183 ± 14 days) after the subject's last dose of PP6M, at which time he or she may be switched to a commercially available PP6M supply, if they wish to continue PP6M treatment.

Subjects who prematurely discontinue study intervention for any other reason before completion of the open-label extension will not be considered to have completed the study.

10.2. Withdrawal From the Study

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

- Lost to follow-up
- Withdrawal of consent
- Death
- Noncompliance (defined as a subject being more than 4 weeks late for their scheduled PP6M injection).
- Discontinuation of study intervention for any reason. A subject's study intervention will be automatically discontinued if:
    - The investigator or sponsor believes (eg, that for safety or tolerability reasons (eg, adverse event) it is in the best interest of the subject to discontinue study intervention
    - The subject becomes pregnant
    - Supplemental oral antipsychotics are used for more than 4 continuous weeks
    - Relapse

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 eCRF and in the source document. The study drug assigned to the withdrawn subject may not be assigned to another subject. If subjects withdraw from the study, additional subjects will not be entered. If a subject discontinues study intervention and withdraws from the study before the end of the open-label extension, End-of-Study assessments should be obtained.

If the reason for withdrawal from the study is withdrawal of consent then no additional assessments are allowed.

10.3. Antipsychotic Therapy After the Study

After discontinuation, withdrawal, or completion of the open-label extension study, investigators may choose to continue treatment with paliperidone palmitate, switch to treatment with a different LAI antipsychotic treatment, or switch to oral antipsychotic treatment. At the End-of-Study Visit/Early Withdrawal visit and thereafter, the poststudy treatment is at the discretion of the subject's physician and is not a study intervention.

By the end of the study, PP6M may be available commercially in most countries, if approved. Otherwise, subjects will have to option to receive PP3M since it is (or may be) approved in most of the participating countries by the end of R092670PSY3016.

Given the duration of activity expected from PP6M, recommendations (not requirements) for poststudy treatment schedules are summarized below.

- It is recommended that poststudy LAI antipsychotic medication (paliperidone palmitate or other LAI antipsychotic) should not be started within 6 months after the last PP6M injection. This is to avoid the risk of accumulation of the overall antipsychotic concentration that could be caused by PP6M providing systemic concentrations of paliperidone over a period of 6 months.
- If, at any time within 6 months from the last injection, the investigator/treating physician feels it is necessary to prescribe oral antipsychotic treatment, medication selection should be based on clinical judgment, knowledge of each subject's ability to tolerate and respond to other antipsychotic medications, and the presumption of persisting exposure to PP6M (if supplementation within this 6-month time period will be with oral risperidone or oral paliperidone, Table 2 [Supplemental Oral Antipsychotic Dosage Chart] may be used to guide dose selection; for oral risperidone or oral paliperidone dose selection guidance after this 6-month time period, see Table 3).
- Treatment with PP1M, PP3M, or PP6M may be resumed no earlier than 6 months from the last PP6M injection:
    - If resuming with PP1M, then a monthly regimen may be used immediately; the Day 1 and Day 8 initiation pair is not needed. The first PP1M injection should be administered in the deltoid muscle, and then subsequent injections may be administered in either the deltoid or gluteal muscles. The first PP1M dose should be 100 or 150 mg eq., based on whether the subject was on a PP6M dose of 700 or 1000 mg eq., respectively (see Table 3).
    - If resuming with PP3M, then the first PP3M injection may be administered in either the deltoid or gluteal muscles. The first PP3M dose should be 350 or 525 mg eq., based on whether the subject was on a PP6M dose of 700 or 1000 mg eq., respectively (see Table 3).

  - If resuming with PP6M, which may be possible if PP6M is commercially available, then dosing should be performed in accordance with the local prescribing information.

- Suggested starting doses for post-study oral or LAI paliperidone or oral risperidone are summarized in Table 3.

Table 3: Switching Conversion Table (Oral and LAI Paliperidone)

Last dose during Open-label Extension:	Suggested Post-study Antipsychotic Medication Starting Dose:				
	PP6M (if commercially available)	PP1M	PP3M	Oral Risperidone	Oral Paliperidone
PP6M 700 mg eq.	700 mg eq	100 mg eq	350 mg eq	3-4 mg/day	9 mg/day
PP6M 1000 mg eq.	1000 mg eq	150 mg eq	525 mg eq	5-6 mg/day	12 mg/day
Note: this provides a suggested starting dose of oral medications. The timing of the last injection must be taken into account, and oral dose adjusted as clinically warranted.					

11. STATISTICAL METHODS

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

11.1. Subject Information

Results will be summarized using the evaluable population, defined as all subjects who receive at least 1 dose of study intervention during the open-label extension study.

11.2. Sample Size Determination

No formal sample size determination was performed for this study. The sample size will be determined by the number of subjects who complete Double-blind Phase of Study R092670PSY3015 without relapse and are willing to participate in R092670PSY3016.

11.3. Efficacy Analyses

All efficacy analyses will be carried out using the evaluable population.

Descriptive statistics (mean, standard deviation, median, range [minimum and maximum]) will be provided for CGI-S, PSP, and PANSS over time, including all assessment time points from the baseline of the Double-blind Phase of Study R092670PSY3015 to the End-of-Study/Early Withdrawal visit of the open-label extension study. Descriptive statistics of the change from baseline (open-label extension baseline and the baseline of the Double-blind Phase of Study R092670PSY3015) will also be provided.

- **Relapse:** The relapse rate at Month 12, Month 24, and at the End-of-Study/Early Withdrawal visit will be summarized.

- **Remission**: For single observations, transitory symptomatic remission is defined as having a simultaneous score of mild or less (≤3 points) on the following 8 items from the PANSS: the positive-symptom items P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior); the negative-symptom items N1 (blunted affect), N4 (social withdrawal), and N6 (lack of spontaneity); and the general-psychopathology items G5 (mannerisms/posturing) and G9 (unusual thought content).[1] The number and percentage of subjects achieving symptomatic remission at Month 12, Month 24, and at the End-of-Study/Early Withdrawal visit will be presented. In addition, the number and percentage of subjects by remission status at each time point will be presented for those subjects who were in remission at Open-label baseline.

11.4. Safety Analyses

Adverse Events

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Intervention-emergent adverse events are adverse events with onset during the intervention phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported adverse events will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue study intervention due to an adverse event, or who experience a severe or a serious adverse event. Analyses of the adverse events of special interest (including EPS-related TEAEs, potentially prolactin-related TEAEs, and suicidality-related TEAEs) will be described in the Statistical Analysis Plan.

Mental Status Examination

The results of the mental status examination will be summarized descriptively at each time point.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test.

Vital Signs

Descriptive statistics of vital sign values and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with values beyond clinically important limits will be summarized.

Physical Examinations

Physical examination findings will be summarized at each scheduled time point. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point.

Extrapyramidal Symptom Rating Scales

The AIMS data will be summarized descriptively.

Other EPS scales (SAS and BARS) are not mandatory but may be performed at the investigator's discretion. Any SAS and BARS data collected during the study will be summarized descriptively.

Evaluations of the Injection Sites

The results of the evaluations by the subjects and by the investigators will be summarized descriptively.

Columbia Suicide Severity Rating Scale

The C-SSRS will only be performed if suicidal ideation is detected on the mental status examination. For those subjects who undergo C-SSRS assessment, suicide-related thoughts and behaviors based on the C-SSRS will be summarized descriptively.

Electrocardiograms

Electrocardiograms are not mandatory but may be performed at the investigator's discretion. Any ECG data collected during the study will be summarized descriptively. Clinically relevant ECG abnormalities will be listed.

The effects on cardiovascular variables will be evaluated by means of descriptive statistics and frequency tabulations. These tables will include observed values and changes from baseline values.

The ECG variables that will be analyzed include heart rate, PR interval, QRS interval, QT interval, and corrected QT (QTc) interval.

Descriptive statistics of QTc intervals and changes from baseline will be summarized. The criteria for abnormal QTc interval values will be based on the classification from the relevant ICH guideline[e] (normal as ≤450 milliseconds, or elevated as >450, >480, or >500 milliseconds). Similarly, the percentage of subjects with increases in QTc of normal as ≤30 milliseconds or elevated as 30 to 60 milliseconds or >60 milliseconds will also be summarized at each time point.

All clinically relevant abnormalities in ECG waveform that are changes from the baseline readings will be reported.

[e] ICH. ICH Harmonized Tripartite Guideline E14: Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E14/E14_Guideline.pdf . Dated 12 May 2005. Accessed 28 December 2018.

11.5. Medical Resource Utilization

The HRUQ data will be summarized.

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 intervention. 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 PP6M, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure.

Adverse Event Associated With the Use of the Intervention

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

12.1.2. Attribution Definitions

Not Related

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

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 intervention. 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 intervention. 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 intervention that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study intervention
- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study intervention, eg, name confusion)
- Exposure to a sponsor study intervention from breastfeeding
- Exposure to a sponsor study intervention during pregnancy; see Section 12.3.3 (Pregnancy).

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

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 within 6 months after the last dose of study intervention, 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.

All adverse events, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source document and the eCRF. 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 eCRF 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
- Any other information that is required to do an emergency breaking of the blind

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 intervention 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 eCRF). 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.

The cause of death of a subject in a study, whether or not the event is expected or associated with the study intervention, 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. 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 and discontinue further study intervention. If a subject becomes pregnant during the study, a determination regarding study intervention discontinuation must be made by the investigator in consultation with the sponsor.

Because the effect of the study intervention on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported as noted above.

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 in 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 in the Contact Information page(s), which will be provided as a separate document.

14. STUDY INTERVENTION INFORMATION

14.1. Physical Description of Study Intervention

The study intervention (previously referred to as “study drug”) (PP6M) will be supplied in prefilled syringes, as follows:

- 700 mg eq. (1092 mg) in 3.5 mL
- 1000 mg eq. (1560 mg) in 5.0 mL

The study intervention will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a list of excipients.

Oral supplementation medication (risperidone and paliperidone) will not be supplied as part of study medications. Instead locally available commercial supply should be used and recorded.

14.2. Packaging

The study intervention will be packaged in individual subject kits. Each kit will consist of a safety needle, instructions for use, and a foam insert containing a prefilled syringe assembled with a plunger rod.

14.3. Labeling

Labels will contain blanks for the subject's identification number and the investigator's name. These will be filled in when the study intervention is dispensed to a subject.

Study interventions labels will contain information to meet the applicable regulatory requirements.

14.4. Preparation, Handling, and Storage

All study intervention must be stored at controlled temperatures as instructed by the clinical label.

14.5. Intervention Accountability

The investigator is responsible for ensuring that all study intervention received at the site is inventoried and accounted for throughout the study. The study intervention administered to the subject must be documented on the intervention accountability form. All study intervention will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study intervention containers.

Study intervention must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study intervention must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study intervention will be documented on the intervention return form. When the study site is an authorized destruction unit and study intervention supplies are destroyed on-site, this must also be documented on the intervention return form.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for intervention accountability purposes.

Study intervention should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study intervention will be supplied only to subjects participating in the study. Returned study intervention must not be dispensed again, even to the same subject. Study intervention may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study intervention from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following materials:

- Documentation:
    - Investigator's Brochure

- Manuals:
  - For assessments (ie, questionnaires and scales)
  - For electronic data capture completion guidelines
- Study-site investigational product binder

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 current study will enroll subjects who have completed the Double-blind Phase of Study R092670PSY3015 and who continue to be willing to receive PP6M treatment. The primary ethical concern for this study is that subjects who were receiving PP3M during the Double-blind Phase of R092670PSY3015 will be switched to an investigational product, PP6M. This concern is considered limited given that the PP3M and PP6M products share the same formulation (F015). Therefore, a switch from PP3M to PP6M represents an increase in the dose/volume of study intervention, rather than a switch in active substance. As discussed further in Section 1.3, Benefit/Risk Assessment, and Section 3.2, Study Design Rationale, the increased dose of PP6M compared with PP3M is expected to result in sustained efficacy and acceptable tolerability during a 6-monthly dosing schedule. Because of the larger injection volume of PP6M, all injections will be administered in the gluteus. In addition, medications commonly used to improve tolerability of antipsychotic medications (eg, anti-EPS medications, benzodiazepines) and oral antispychotics (with some limitations) will be permitted during the study, as needed.

The volume of blood to be collected in this study is not considered to pose an ethical concern or a special risk. The total blood volume to be collected will be limited and is considered to be an acceptable amount of blood to be collected over this time period from the population in this study, as it will be left to the clinical judgment of the investigator according to local standards.

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, unless required locally), 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.

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 intervention

- 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, where required.

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. It also denotes that the subject agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed.

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.

If the subject is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject is obtained.

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.

Exploratory research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

16.2.5. 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 if the need for the product persists, 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 IEC/IRB (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 listed in the Contact Information page(s), which will be provided as a separate document. 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 eCRF 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 intervention 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 age at initial informed consent. In cases where the subject is not enrolled into the study, the date seen and age at initial informed consent 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 documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: 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; intervention receipt/dispensing/return records; study intervention administration information; and

date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If the electronic source system is utilized, references made to the eCRF in the protocol include the electronic source system but information collected through the electronic source system may not be limited to that found in the eCRF. Data in this system may be considered source documentation.

17.5. Electronic Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each subject in electronic format. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct. The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documents. Data must be entered into eCRF in English. The eCRF must be completed 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, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the eDC tool. If corrections to a eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

- Investigator and 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).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and 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 eCRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review eCRF 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 eCRF 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 use a combination of monitoring techniques (central, remote, or on-site monitoring) to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records); a sample may be reviewed. The nature and location of all source

documents will be identified to ensure that all sources of original data required to complete the eCRF 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 documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review 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 documents 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 (End of Study)

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, or earlier if PP6M is commercially available in the local country. 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 intervention 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. 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 PP6M 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 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 PP6M, 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 data from all study sites that participated in the study as per protocol. 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 for the study. Results of 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 18 months after study end date, 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 International Medical Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

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

REFERENCES

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7. Guy W. ECDEU (Early Clinical Development Evaluation Unit) Assessment Manual for Psychopharmacology. Rockville, MD: US Department of Health and Human Services; 1976.
8. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain. Arthritis Care Res. 2011;63(Suppl 11):S240-S252.
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10. Leal A, Rosillon D, Mehnert A, Jarema M, Remington G. Healthcare resource utilization during 1-year treatment with long-acting, injectable risperidone. Pharmacoepidemiol Drug Saf. 2004;13:811-816.
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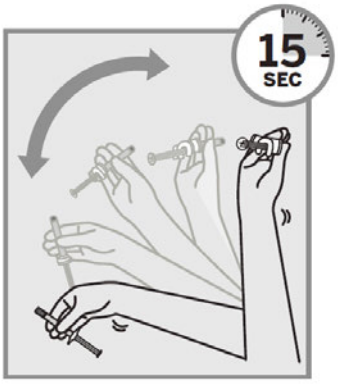
ATTACHMENTS

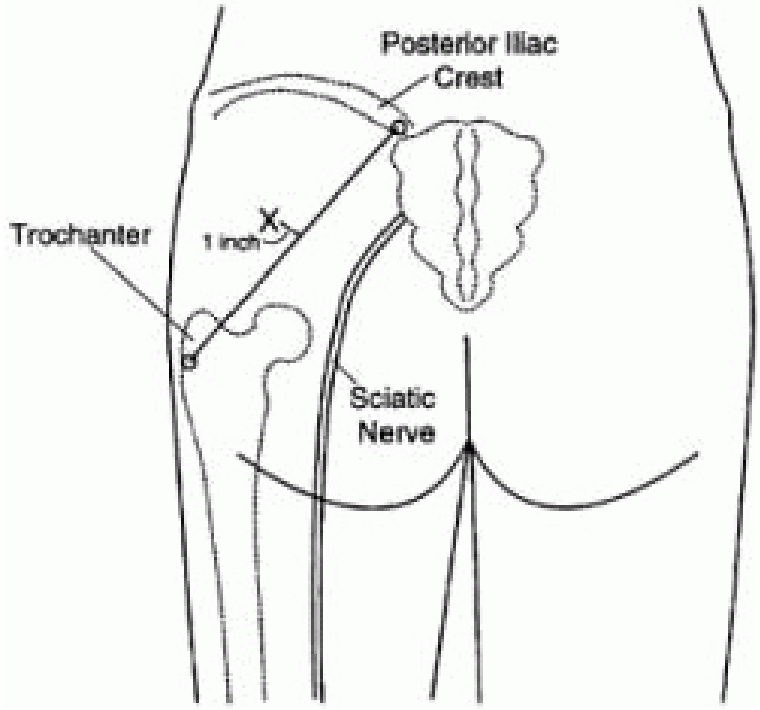
Attachment 1: Guidelines for the Intramuscular Injection of Paliperidone Palmitate 6-month Injection



For each dose, a study-site personnel member must shake the syringe vigorously with the tip facing up and with a loose wrist for at least 15 seconds to ensure a homogeneous suspension. The shaken dose must then be administered within 5 minutes after shaking. If more than 5 minutes pass after shaking but before injection, then a study-site personnel member must shake the syringe vigorously again for at least 15 seconds to resuspend the dose.

The full content of the syringe should be injected, slowly.

Injections will rotate across sides of the body (left or right), but the image below shows landmarks for only 1 side as an example.

Figure	
Needle	1.5-inch, 20-gauge, thin-walled needle
Notes	Palpate the junction of the posterior iliac crest and sacrum. Then imagine drawing a line to the greater trochanter of the femur. Administer the injection in the upper-outer area bordered by this imaginary triangle. Injections should be administered in the dorso-gluteal injection site only. Ventrogluteal injections are not permitted.

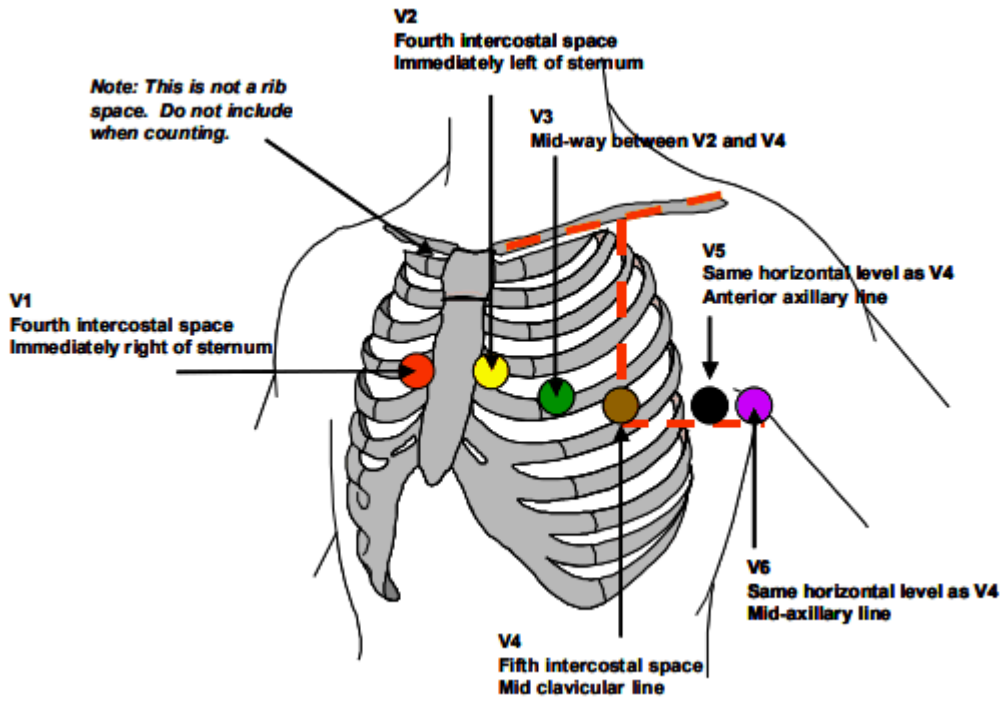
Attachment 2: Standard Placement of ECG Electrodes

Limb Leads

- Right Arm: right forearm proximal to wrist
- Left Arm: left forearm proximal to wrist
- Left leg: left lower leg proximal to ankle
- Right leg: right leg proximal to ankle

Precordial Leads

- V1 Fourth intercostal space at the right sternal edge
- V2 Fourth intercostal space at the left sternal edge
- V3 Midway between V2 and V4
- V4 Fifth intercostal space in the mid-clavicular line
- V5 Left anterio axillary line at the same horizontal level as V4
- V6 Left mid-axillary line at the same horizontal level as V4 and V5



Source: Clinical Guidelines by Consensus: Recording a Standard 12-lead Electrocardiogram: An Approved Methodology. British Cardiovascular Society. Feb 2010. https://www.bcs.com/documents/consensus_guidelines.pdf

INVESTIGATOR AGREEMENT

R092670 (paliperidone palmitate)
Clinical Protocol R092670PSY3016 Amendment 2

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): PPD

Institution: PPD & Development

Signature: _____ Date: 17 DEC 2020
(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.

CONFIDENTIAL – FOIA Exemptions Apply in U.S. 70
Status: Approved, Date: 15 December 2020

Janssen Research & Development *

Clinical Protocol

COVID-19 Appendix

Single-arm, Open-label Extension to a Double-blind, Randomized, Active-controlled, Parallel-group Study of Paliperidone Palmitate 6-Month Formulation

Protocol R092670PSY3016; Phase 3
AMENDMENT 1

R092670 (paliperidone palmitate)

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the Sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen Pharmaceutica NV; Janssen, Inc; Janssen Sciences Ireland UC; or Janssen Research & Development, LLC. The term "Sponsor" is used throughout the protocol to represent these various legal entities; the Sponsor is identified on the Contact Information page that accompanies the protocol.

This study will be conducted under United States (US) Food & Drug Administration (FDA) Investigational New Drug (IND) regulations (21 Code of Federal Regulations [CFR] Part 312).

EudraCT Number: 2018-004532-30

Status: Approved
Date: 23 April 2020
Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-RIM-43675, 1.0

Local: EDMS-ERI-177701234, 1.0

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

PROTOCOL AMENDMENTS

DOCUMENT HISTORY	
Document	**Date**
Amendment 1 (COVID-19 Appendix)	23-Apr-2020
Original Protocol	14-Feb-2019

Amendment 1, 23 April 2020

Overall Rationale for the Amendment: To provide guidance on changes to study conduct and assessments due to restrictions and limitations during the COVID-19 pandemic.

Section Number and Name	Description of Change	Brief Rationale
COVID-19 Appendix	Added a COVID-19 Appendix as guidance on changes to study conduct and assessments due to restrictions and limitations during the COVID-19 pandemic.	To provide guidance on study conduct and assessments during the COVID-19 pandemic.

COVID-19 APPENDIX

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, social distancing, self-isolation/quarantine by participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidances to address the potential impact of COVID-19 on the conduct of clinical trials, the sponsor is providing options for study related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgment of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's safety is considered to be at risk, study intervention will be discontinued, and study follow-up will be conducted. In addition, the measures outlined in this Appendix are temporary, while access to sites is restricted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible in person at the subject's home/remotely/virtually or delayed within the allowed visit window. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up. Modifications to protocol-required assessments may be permitted after consultation between the participant and investigator, and with the agreement of the sponsor. Missed assessments/visits will be captured in the clinical trial management system as protocol deviations. Discontinuations of study interventions and withdrawal from the study due to COVID-19 should be documented in the case report form (CRF).

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a participant has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical monitor to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic will be summarized in the clinical study report.

GUIDANCE SPECIFIC TO THIS PROTOCOL:

- **Subject Visits/Assessments:** If a subject cannot visit the research site in person, the sponsor recommends that any assessments that may be captured remotely for that particular visit be collected. This collection should be performed remotely by trained, delegated site staff. These remote assessments could be conducted via telephone (or videoconference, eg, Facetime, Skype, if possible) with subjects in their homes. Please ensure that the remote method is allowable per local regulations. Assessments that could be completed include a review of adverse events, concomitant medications, clinical interviews such as the Mental Status Examination (including the Columbia Suicide Severity Rating Scale if suicidal ideation is identified during the Mental Status Examination), evaluation of relapse criteria, safety assessments deemed necessary by the investigator, and questionnaires. Please note, the visit windows included in the Time and Events Schedule are still applicable.
  - *Administration of study intervention:* If a subject cannot visit the research site in person for administration of study intervention (eg, for Visit 1, Visit 3), trained delegated staff may conduct the visit at the subject's home in accordance with local regulations.
    - Study intervention transport and administration:
      - The investigational product is injectable and will require qualified, trained delegated site staff to transport the product and administer it in the subject's home.
      - Depending on local regulations, the investigator must either administer the study intervention or supervise administration if PP6M is considered a controlled substance in that country.
      - It will be the investigator's responsibility to ensure that the investigational product will be maintained at the appropriate allowed temperature (15-30°C) during transit to the subject's home.
      - If local regulations allow a home health service to deliver and/or administer the study intervention in the subject's home, the sponsor may assist site staff with utilizing this option.
      - Efforts should be made to administer the study intervention within one hour after delivery by the pharmacy.
      - The administration of study intervention at the subject's home instead of at the study site will be documented in the subject's file and in the CRF.
  - *Study assessments:*
    - Relapse assessment: A relapse assessment should be performed based on the criteria outlined in Section 9.2.4. If deemed necessary per the judgment of the investigator, a remote Positive and Negative Syndrome Scale for Schizophrenia (PANSS) evaluation may be performed.
    - Evaluation of secondary and exploratory endpoints (Personal and Social Performance scale, Clinical Global Impression - Severity, Columbia Suicide Severity Rating Scale, Healthcare Resource Utilization Questionnaire): Many of the

assessments for evaluation of secondary and exploratory endpoints may be collected remotely. Please collect as much information as possible.

- Physical examinations, vital signs, scales to assess extrapyramidal symptoms (Abnormal Involuntary Movement Scale, Barnes Akathisia Rating Scale, Simpson Angus Scale), electrocardiograms, collection of pharmacokinetic/blood samples, pregnancy tests, and laboratory assessments may not be possible to collect as part of the remote visit. However, if permitted by local regulations, these assessments could be performed in the subject's home by trained, delegated site staff or home health service staff. If blood samples are shipped to a laboratory other than the local laboratory typically used by the site, appropriate documentation of the reference and outlier ranges used by the laboratory would also be required.
- It must be documented in the CRF if a visit occurs remotely due to COVID-19.

– *Missed assessments/protocol deviations:*

- Missed assessments will be captured in the clinical trial management system as protocol deviations. All protocol deviations will be recorded as either major or minor protocol deviations in the clinical trial management system using the current Major Protocol Deviation Criteria document.
- Remote visits, missed visits, out of window visits, and missing assessments due to COVID-19-related issues will be recorded as minor protocol deviations.

- **Early Withdrawal:** If a subject is lost to follow-up or unwilling to have any remote assessments performed, then he/she would be considered an early withdrawal. Please attempt to contact the subject via telephone, text message, email or through a relative, if possible. Consider certified mail as an option to contact a subject before declaring him/her as being lost to follow-up.
- **COVID-19 Illness in Subjects:**
  - If a subject in this study becomes symptomatic, the sponsor suggests that Coronavirus infection be confirmed with reverse transcriptase polymerase chain reaction (RT-PCR) using diagnostic test kits. This should be performed using locally approved laboratory kits and reported to the local health authorities as required.
  - Positive test results for Coronavirus as well as any associated symptoms should be recorded as adverse events, and if the subject is hospitalized, the event should be captured as a serious adverse event. Similarly, hospitalization should be recorded on the Healthcare Resource Utilization Questionnaire (HRUQ) form at the next applicable visit.
  - Please notify the treating physician of the subject's participation in Study R092670PSY3016 and details of the study treatment.
- **Source Data Verification/Monitoring:** On-site monitoring visits may not be possible due to local regulations, restrictions and guidance. In these cases, the Site Manager will arrange to conduct site monitoring visits and activities remotely.

INVESTIGATOR AGREEMENT

R092670 (paliperidone palmitate) Clinical Protocol R092670PSY3016 Amendment 1
COVID-19 Appendix

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): PPD

Institution: PPD esearch & Development

Signature: _____ Date: PPD
(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.

CONFIDENTIAL – FOIA Exemptions Apply in U.S. 6
Approved, Date: 23 April 2020