Janssen Research & Development *

Clinical Protocol

A Double-blind, Randomized, Active-controlled, Parallel-group Study of Paliperidone Palmitate 6-Month Formulation

Protocol R092670PSY3015; Phase 3

Amendment 3

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.

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	28 August 2017
Amendment 1	21 March 2018
Amendment 2	28 September 2018
Amendment 3	11 February 2019

Amendments below are listed beginning with the most recent amendment.

Amendment 3 (11 February 2019)

The overall reason for the amendment: To limit the duration of the Double-blind Phase to 12 months by eliminating the double-blind extension period, which is currently of a variable length of 12-24 months; and to increase the estimated number of subjects entering the Transition/Maintenance Phases from a target sample size of 765 to 840.

Applicable Section(s)	Description of Change(s)

Rationale: The rationale for limiting the Double-blind Phase to a fixed duration of 12 months is to align it with the primary endpoint, ie, time to relapse during the Double-blind Phase which is based on the Kaplan-Meier estimate of percentage of subjects who remain relapse-free at Month 12.

Synopsis:

Secondary Endpoints	Removed the greater than or equal to sign '≥' to reflect that secondary endpoints beyond 12 months of the Double-blind Phase are no longer applicable.
OVERVIEW OF STUDY DESIGN	Removed text related to subjects participating in additional double-blind treatment of variable duration beyond the 12-month Double-blind Phase. Removed text related to study procedures beyond the 12 months of the Double-blind Phase. Deleted text stating that the Follow up Phase will end at 6-month time points thereafter if the subject has already participated past the first 12 months of the Double-blind Phase. Revised the text to state that that the longest expected duration is ~19 months and not >31 months for subjects who complete the study without relapse as the variable duration of double-blind phase beyond the first 12 months has been removed.
Dosage: Double-blind Phase	Deleted text describing treatment beyond the first 12 months of the Double-blind Phase
Time and Events Schedules C	Deleted the original Time and Events Schedule C. Double-blind Phase (After the First 12 Months) in its entirety as the Double-blind Phase is limited to 12 months per this amendment.
Time and Events Schedule C (originally Time and Events Schedule D)	In the EOP column, removed "18 or 24" months after the subject's first double-blind injection; removed text "(or at 6-Month Time Points Thereafter, if Applicable)"; deleted text in the footnote describing an example of Follow up Phase visits for a subject who withdraws from the study in the Double-blind Phase beyond the 12 months. Also deleted text stating "… or at 6-month time points thereafter if the subject has already participated past the first 12 months of the Double-blind Phase".

Time and Events Schedule D: Keys and Footnotes (for All Time and Events Schedules) (originally Time and Events Schedule E)	Deleted footnote "aa" in Amendment 2 as it no longer applies with the elimination of variable double-blind phase beyond the 12 months.
2.1.2.3. Secondary Endpoints	Removed secondary endpoints beyond the 12-month Double-blind Phase. Removed the greater than or equal to sign '≥' to reflect that secondary endpoints beyond 12 months of the Double-blind Phase are no longer applicable.
3.1 Overview of Study Design	Removed text related to subjects participating in additional double-blind treatment of variable duration beyond the 12-month Double-blind Phase. Removed text related to study procedures beyond the 12 months of the Double-blind Phase. Deleted text stating that the Follow up Phase will end at 6-month time points thereafter if the subject has already participated past the first 12 months of the Double-blind Phase. Revised text to reflect that the length of the Double-blind Phase is 12 months and a subject could have 19 months of participation with exposure to paliperidone palmitate for subjects without relapse.
Figure 1	Limited the length of Double-blind Phase to 12 months only to align with the primary endpoint. Footnote d: Removed text describing treatment during Double-blind Phase beyond 12 months and revised text on study closure to account for possibilities of the last subject randomized being lost to follow-up or withdrawing consent. Note: Deleted text stating that the Follow up Phase will end at 6-month time points thereafter if the subject has already participated past the first 12 months of the Double-blind Phase.
3.2. Study Design Rationale Study Phases	Deleted text stating that the Follow up Phase will end at 6-month time points thereafter if the subject has already participated past the first 12 months of the Double-blind Phase.
6.1.2. Transition Phase: Figure 2	Limited the length of Double-blind Phase to 12 months only to align with the primary endpoint.
6.1.3. Maintenance Phase: Figure 3 and Figure 4	Limited the length of Double-blind Phase to 12 months only to align with the primary endpoint.
6.1.4. Double-blind Phase	Deleted text describing treatment beyond the first 12 months of the Double-blind Phase.
6.2.2. Administration During the Double-blind Phase: Table 5	Deleted last column of Table 5 that is related to pattern of injection sites beyond the first 12 months of the Double-blind Phase.

9.1. Study Procedures: Double-blind Phase	Deleted text related to study procedures beyond the first 12 months of the Double-blind Phase.
10.2. Discontinuation of Study Drug/Withdrawal From the Study	Removed potential scheduled assessments beyond the 12-month Double-blind Phase (ie, Visits beyond Visit 33a). Removed text describing a scenario of withdrawal in which a subject has not entered the Double-blind Phase when the Sponsor terminates the study.
10.3. Antipsychotic Therapy After the Study or in the Follow-up Phase: Figure 5	Removed Double-blind Time Point that is beyond 12-month (last column). (Note: section numbering has been updated as the original section 10.3 Withdrawal From the Use of Research Samples is now deleted.)
10.4. Process for Planned Study Closure	Removed odd-numbered injections (5th, etc.) that are beyond the 12-month Double-blind Phase. Revised text on study closure to account for possibilities of the last subject randomized being lost to follow-up or withdrawing consent

Rationale: To increase the estimated number of subjects entering the Transition and Maintenance Phases from approximately 765 to 840 to match current dropout/enrollment rates and to meet the randomization target of 549 subjects in the Double-blind Phase. Current enrollment rates project that the number of subjects entering the Transition/Maintenance Phases will exceed the previous target. The increase in the estimated number needed to achieve the randomization target is primarily due to an increased dropout rate during Transition and Maintenance Phases.

3.1 Overview of Study Design; 11.2. Sample Size Determination	Specified that the number of subjects entering the Transition/Maintenance will be approximately 840.

Rationale: To indicate data collection for "Concomitant substance testing and questions" at Visit 13 during the Double-blind Phase for consistency with footnote e and f of Time and Events Schedule B and with the text in section 9.4.2.

Time and Events Schedule B	Added a time point for data collection at Visit 13 in the row of Concomitant substance testing and questions.

Rationale: To remove ECG collection at Visit 4 of the Maintenance Phase as routine ECG monitoring at this timepoint is not expected to enhance safety monitoring for subjects who are continuing the same medications in the Maintenance Phase.

Time and Events Schedule Ai	Removed ECG data collection at Visit 4.
Time and Event Schedule Aii	Removed ECG data collection at Visit 4.

Rationale: To provide guidance on the timing of EOP after relapse confirmation.

Time and Events Schedule D, footnote f 9.1. Study Procedures	Added text to state that the EOP visit is to occur as soon as possible after relapse confirmation (preferably the same day).

Rationale: To remove the EOP Visit from the Follow-up Phase to minimize potential confusions with the EOP visit at the Double-blind Phase (33a) and at the end of the Maintenance Phase (7a).

Time and Events Schedule C (Originally Time and Events Schedule D)	Deleted the EOP Visit column from the Follow-up Phase.
Time and Events Schedule D (Originally Time and Events Schedule E)	Deleted footnote "bb" in Amendment 2
Figure 1	Deleted text related to the EOP Visit of the Follow-up Phase in Footnote d.
Section 10 .4	Deleted text related to the EOP Visit of the Follow-up Phase

Rationale: To clarify that in inclusion criterion 11, the method of contraception referred to above (ie, criterion 10) is for the female partner(s) of male subjects.

4.1 Inclusion Criteria	Modified inclusion criterion 11 to clarify that a male subject must agree that his female partner(s), rather than himself, use method of contraception as described in criterion 10.

Rationale: To remove the introduction sentence under Exclusion Criteria for clarity.

4.2 Exclusion Criteria	Deleted the introduction sentence under Exclusion Criteria

Rationale: To clarify that the excluded injectable formulations of neuroleptic drugs are long-acting injectable formulations.

4.2. Exclusion Criteria	Added "long-acting" to exclusion criterion 6 to state excluded injectable formulation of neuroleptic drugs as long-acting formulations.

Rationale: To clarify that the full content of the study drug should be administered as a single injection**.**

6.2. Administration	Added text to state that the full content is to be administered in one injection, using only the supplies provided in the study drug kit.

Rationale: To add text to instruct the site of the first injection during the Maintenance Phase.

6.2.1. Administration During the Open-label Phases	Added a note to state Day 1 injection should not be administered at the same site as the last injection during the Maintenance Phase.

Rationale: To add tricyclic anti-depressants, known to prolong QT interval, to the list of Prohibited Concomitant Medications; to minimize the risk of concomitant amantadine use, it is now explicitly cited as an example of a dopamine agonist; to add non-antipsychotic dopamine antagonists to the list of Prohibited Concomitant Medications to minimize risk of EPS and akathisia.

8.3. Prohibited Concomitant Medications	Added tricyclic antidepressants, amantadine, and nonantipsychotic dopamine antagonists to the list of Prohibited Concomitant Medications.

Rationale: To provide additional details for injection site assessments.

9.4.8.2. Injection Site Evaluations and Follow-up by Investigators	Added anchor point scores for injection site evaluations regarding tenderness, erythema/redness, and induration/swelling.

Rationale: To provide investigators with detailed information on antipsychotic treatment options after the study or in the Follow-up Phase.

10.3. Antipsychotic Therapy After the Study or in the Follow-up Phase	Diagram in Figure 5 replaced with the Post Study Medication Algorithm; added Table 7, Timing of Resumption of PP1M/PP3M after the Double-blind Study or in Follow-Up Phase; added Table 8, Switching Conversion Table (Oral and LAI Paliperidone and oral risperidone).

Rationale: With a fixed duration of 12 months for the Double-blind Phase, there will be fewer relapse events than anticipated to detect a biomarker signal that could reliably predict relapse events. Therefore, collection of blood biomarkers is now removed from the protocol.

Time and Events Schedules A.i., A.ii. and B	Removed text related to blood biomarkers under Collection of biofluids
Time and Events Schedule D: Keys and footnotes (Originally Time and Events Schedule E)	Under footnote f, removed text related to blood biomarker sample collections. Removed footnote "r" in Amendment 2 which was related to sample collections for blood biomarkers.
2.1.1 Objectives Exploratory Objectives	Removed text related to the exploratory objective to measure blood-based biomarkers.
3.2. Study Design Rationale	Removed the Biomarkers subsection.
4.5. Prohibitions, Restrictions, and Strong Recommendations	Removed text related to strong recommendations for blood biomarker sample collections.
9.1. Study Procedures	Removed text related to blood sample collections for biomarkers.
9.6. Biomarker Evaluations	Removed original section 9.6 Biomarker Evaluations.
10.3. Withdrawal From the Use of Research Samples	Deleted the entire original section 10.3 that was related to biomarker research samples.
11.7. Biomarker Analysis	Removed original section 11.7. Biomarker Analysis.
15. STUDY SPECIFIC MATERIALS	Removed text related to biomarkers under "Documentations" and "Supplies".
16.2.4. Privacy of Personal Data	Removed text related to exploratory biomarker research.
16.2.5. Long-term Retention of Samples for Additional Future Research	Removed the entire original section 16.2.5. that was related to biomarkers.
17.11. Use of Information and Publication	Removed text related biomarker research data analysis and report.

Rationale: To add secondary endpoints in Synopsis and section 2.1.2.3. Secondary Endpoints of the protocol to align secondary endpoints with section 9 Study Evaluations related to secondary endpoints to maintain consistency throughout the protocol.	
Synopsis; 2.1.2.3. Secondary Endpoints	Listed additional secondary endpoints as described in section 9 of the protocol.
Rationale: To include an additional trade name of risperidone LAI.	
6.1.2. Transition Phase	Listed the trade name of risperidone LAI in certain countries.
Rationale: To include a list of Investigational Medicinal Products (IMPs) and Noninvestigational Medicinal Products (NIMPs) used in the study to facilitate protocol review.	
Abbreviations and Terms	Listed IMPs and NIMPs used in the study
Rationale: Minor errors were noted/	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 2 (28 September 2018)

The overall reasons for the amendment:

- To revise the number of prerandomization injections of PP1M from a total of 6 (ie, 5-month duration) to a total of 5 (ie. 4-month duration) required before subjects are randomized to either PP3M or PP6M treatment group in the Double-blind Phase. This change applies to subjects in the study's Open-label phases being treated with PP1M after the PP3M prerandomization target has been met, since these subjects will be randomized directly from PP1M treatment. The change aligns with the minimum of 4-month treatment with PP1M prior to the initiation of PP3M in previously completed pivotal PP3M trials and the approved posology for PP3M.
- To update and clarify supporting text, figures, and tables for consistency and corrects conflicting portions of the protocol that inadvertently increased the minimum duration of PP1M treatment from 4 months to 5 months
- To remove text related to optional salivary biomarkers research since the sample size for this portion of the study is expected to be too low to generate conclusive results.
- Other changes to the protocol are also made for clarity, consistency, or operational feasibility. (Note: in this table, newly added text to the protocol is in bold font and deleted text is in strikethrough.)

Applicable Section(s)	Description of Change(s)
Rationale: To revise the minimum number of PP1M injections from 6 (ie,5 months) to 5 (ie, 4 months) prior to random assignment to treatment with either PP6M or PP3M in the Double-blind Phase. This is to realign the protocol with the intended design in which subjects receive a minimum of 4-month treatment with PP1M in order to determine dose stability and to maintain clarity and consistency throughout the protocol.	
6.1.2 Transition Phase, Figure 2, Table 3	Revised Figure 2 and Table 3 (which now becomes Table 3 and Table 4 to illustrate the Dosage and Administration Schedule for PP1M During the Transition Phase before and after meeting the PP3M prerandomization target, respectively) to specify the minimum numbers of PP1M injections prior to randomization before or after the PP3M prerandomization target has been met. (Footnote f of Table 3 and 4 is revised so the interval from the last prestudy PP1M injection is now 30±7 days to align with section 6.1.3).
6.1.2. Transition Phase: Subjects Previously Treated With Oral Antipsychotics	The following text was added to explain and clarify the changes to the visit schedule after the PP3M prerandomization target is met: "**After the PP3M prerandomization target is met, these subjects will skip Visit 2e and proceed to Visit 2f if the subject is eligible to enter the Maintenance Phase (see Section 4.3, Criteria for Entry Into the Maintenance Phase). If not eligible to enter the Maintenance Phase, the subject will be withdrawn from the study.**"

6.1.2. Transition Phase: Subjects Previously Stabilized on Injectable Risperidone (Biweekly – Risperdal CONSTA™ formulation)	The following text was added: "**After the PP3M prerandomization target is met, these subjects will skip Visit 2e and proceed to Visit 2f, if eligible to enter the Maintenance Phase (see Section 4.3, Criteria for Entry Into the Maintenance Phase). If not eligible to enter the Maintenance Phase, the subject will be withdrawn from the study."**
6.1.2. Transition Phase: Subjects Previously Initiated (But Not on a Stable Regimen) With Moderate or Higher Doses of PP1M (Invega Sustenna ™ or Xeplion ™ formulation)	The following text was added: "**After the PP3M prerandomization target is met, subjects previously initiated on PP1M (but not on a stable regimen) who enter the study at Visit 2c or 2d will skip Visit 2e and proceed to Visit 2f, if eligible to enter the Maintenance Phase (see Section 4.3, Criteria for Entry Into the Maintenance Phase). Subjects with ≥4 prestudy PP1M injections with the last 2 doses being the same strength will enter the study at Visit 2f. Subjects with ≥4 prestudy PP1M injections with the last 2 doses being different (ie, do not have dose stability) will enter the study at Visit 2e. If not eligible to enter the Maintenance Phase, the subject will be withdrawn from the study."**
6.1.3. Maintenance Phase, Figure 4	Revised Figure 4 to reflect the minimum number of PP1M injections during the Transition Phase from a total of 5 to a total of 4. (A footnote was also updated to reflect that the prerandomization targets of PP3M and PP1M groups were changed to approximately one-half from each group.)
Time and Events Schedules, A.ii.	Added the footnote cc for Visit number 2e of Transition Phase to state "**After the PP3M prerandomization target is met, subjects who entered the study at Visits 2a, 2b, 2c, or 2d, will skip Visit 2e and proceed to Visit 2f if the subject is eligible to enter the Maintenance Phase (see Section 4.3, Criteria for Entry Into the Maintenance Phase). If not eligible to enter the Maintenance Phase, the subject will be withdrawn from the study. Visit 2e remains available for subjects with ≥4 prestudy PP1M injections but do not have dose stability."**

Rationale: To update the visit window for Visits 8, 21, 34, and 43 to avoid overlaps with the window of their respective previous visit.

Time and Events Schedules, B and C	Changed visit window for Visits 8, 21, 34, and 43 from ± 1 to -1 to +3.

Rationale: To update footnotes in Time and Event Schedule, E to align with text in section 6.1.3.

Time and Events Schedules, E	Revised footnote g so that the intervals from the last prestudy PP1M and PP3M injections are now 30±7 days and 90±14 days, respectively. Revised footnote w to indicate that the interval from the last prestudy PP1M injection is now 30±7 days and "Table 3" is changed to "Tables 3 and 4".

Rationale: To achieve greater balance between the prerandomization proportions of each medication group.

3.1. Overview of Study Design	The following text was revised as follows: "Of subjects entering the Double-blind Phase, the prerandomization targets are approximately **one-half** ~~one quarter to one third~~ entering from a PP3M group, and **one-half** ~~three quarters to two thirds~~ entering from a PP1M group.

6.1.3. Maintenance Phase	Similar changes were also made to reflect the approximately one-half pre-randomization target from PP1M and PP3M groups. In addition, text was added to the number of PP3M entering the study if needed to maintain the approximate balance of PP1M and PP3M prerandomization targets: **"In order to appropriately balance the number of PP1M and PP3M subjects in the Maintenance Phase and to complete the study in a timely manner, the pathway to study enrollment that includes subjects who enter the study with previous PP3M stability will be open for only a limited time. The Sponsor will inform the sites when this pathway has closed to enrollment."**
Figure 3	Figure 3 updated so that the appearance and position of the box containing the "Low- dose exclusion groups" are aligned with those in Figure 1. A footnote was also updated to reflect the approximately one-half prerandomization target for the PP1M and PP3M group.

Rationale: To simplify the sequence of procedures to be performed so that non-invasive safety assessments are completed before invasive tests to avoid influencing results and the sequence of procedures that is critical to quality is kept.

9.1. Study Procedures	The Time and Events Schedules summarize the frequency and timing of measurements applicable to this study. If multiple assessments are scheduled for the same visit, then **ECG and vital signs should be collected prior to blood sample collections (eg, PK, biomarkers, and/or laboratory tests) and blood sample collections should be collected prior** to ~~procedures should be performed in the following sequence: subject reported efficacy or exploratory scales; ECG; vital signs; sample collection for PK, biomarkers, and/or laboratory tests; clinical assessments of efficacy and safety;~~ study drug injection. **Evaluations of the injection site occur after study drug injection, as described in Section 9.4.8.** ~~and then assessments of injection sites.~~ Actual dates and times of assessments will be recorded in the source documentation.

Rationale: To clarify the need to maintain the same dose level for eligibility, whether continuing PP1M or switching to PP3M.

4.3. Criteria for Entry Into the Maintenance Phase	The following text was modified in criterion for entry into the Maintenance Phase #2 **2. Criterion modified per Amendment 2** **2.1**. For subjects proceeding from the Transition Phase to the Maintenance Phase, the PP1M dose **prior to entering the Maintenance Phase must have been 100 or 150 mg eq. and, in the investigator's judgment, the subject should continue on the same dose level (ie, either the equivalent PP3M dose [before the PP3M prerandomization target is met] or the same PP1M dose [after the PP3M prerandomization target is met]).** ~~must not be planned for adjustment in the foreseeable future and must have been 100 or 150 mg eq. for the last 2 doses~~

Rationale: To ensure a subject has dose stability to enter the DB Phase.

10.2. Discontinuation of Study Drug/Withdrawal From the Study	The following text is added: • **For subjects in the Maintenance Phase:** o **If the dose at Visit 2f is different from the preceding dose or is not a dose equivalent of the preceding dose**

Rationale: To remove text related to optional saliva biomarkers as the sample size for this optional portion of the study is expected to be too low to generate conclusive results.

Time and Events Schedules A.i.	Removed text related to saliva biomarkers for the Optional ICF under Screening/Administrative. Removed text related to optional saliva biomarkers under Collection of biofluids
Time and Events Schedules A.ii.	Removed text related to saliva biomarkers for the Optional ICF under Screening/Administrative. Removed text related to optional saliva biomarkers under Collection of biofluids
Time and Events Schedule B and C	Removed text related to optional saliva biomarkers under Collection of biofluids
Time and Events Schedule E: Keys and footnotes	Under footnote g, removed text related to optional saliva biomarker sample collections.
2.1.1 Objectives Exploratory Objectives	Removed text related to optional saliva based biomarkers.
3.2. Study Design Rationale	Removed text related to sample collections for optional saliva biomarkers under the Biomarkers subheading.
4.1. Inclusion Criteria	Deleted Inclusion Criterion 15 which is related to signing the ICF for the optional saliva biomarkers.
4.5. Prohibitions, Restrictions, and Strong Recommendations	Removed text related to sample collections for optional saliva biomarkers.
9.1. Study Procedures	Removed text related to sample collections for optional saliva biomarkers.
9.6. Biomarker Evaluations	Removed text related to sample collections for optional saliva biomarkers.
10.3. Withdrawal From the Use of Research Samples	Deleted text related to the optional saliva biomarker research samples.
15. STUDY SPECIFIC MATERIALS	Deleted text related to optional saliva sample collections.
16.2.2. Independent Ethics Committee or Institutional Review Board	Removed text related to approval for the collection of optional saliva samples for research and for the corresponding ICF.
16.2.3. Informed Consent	Removed text related to signing the ICF for the optional saliva biomarker research.

Rationale: To explicitly state that rescreening may be considered for some subjects who were withdrawn during the Transition or Maintenance Phases.	
4. SUBJECT POPULATION	Added the following text: **"Rescreening is permitted with the medical monitor's approval for subjects who were withdrawn during the Transition Phase or Maintenance Phase due to an incomplete injection or an unintended dosing or administration of a study drug**."
4.3. Criteria for Entry Into the Maintenance Phase	Added the following text: "**If withdrawal is due to an incomplete injection or an unintended dosing or administration of a study drug, rescreening is permissible with the medical monitor's approval.**"
4.4. Criteria for Entry Into the Double-blind Phase	Added the following text: "**If withdrawal is due to an incomplete injection or an unintended dosing or administration of a study drug, rescreening is permissible with the medical monitor's approval.**"
Rationale: To minimize the risk of confusion related to the process of study closure.	
9.1. Study Procedures	Under the Double-blind Phase subtitle, removed text that may be confusing and instead provide a reference to section 10.5 where the process for study closure is described in detail.
Rationale: To monitor for appropriate eligibility on the basis of exclusionary medications and for correct timing and dosing of study injections with respect to prestudy PP1M and PP3M injections, where applicable.	
8.2. Concomitant Therapy	Text revised to include that therapies from 90 days prior to the study are also to be recorded.
Rationale: To state that although the form used to record concomitant substances use includes alcohol, nicotine, and illicit substances, only nicotine data will be analyzed.	
9.7.3. Concomitant Substances Questions	Removed "alcohol" and "illicit substances" from analysis.
Rationale: To clarify the approximate number of subjects entering the Transition/Maintenance Phases	
3.1. Overview of Study Design	Revised the following text as follows: "The approximate participation targets are 903 subjects entering the Screening Phase, 765 subjects entering the **Transition**/Maintenance Phase**s**, and 549 subjects entering the Double-blind Phase."
11.2. Sample Size Determination	Revised the following text as follows: "Given these assumptions for discontinuation, the study targets approximately 765 subjects to enter the **Transition**/Maintenance Phase**s**."
Rationale: To include measurements of thyroid stimulating hormone to the Serum Chemistry Panel	
9.4.2. Clinical Laboratory Tests	Added thyroid stimulating hormone to the Serum Chemistry Panel.
Rationale: Improvements in the conduct of the protocol.	
Throughout the protocol	Changes for consistency between sections and for clarification were made that had no impact on safety.

Amendment 1 (21 March 2018)

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

The overall reasons for the amendment:

- to clarify which version of the Columbia Suicide Severity Rating Scale (C-SSRS) will be used at the screening and baseline visits, and all other visits;
- to update the visit window for Visit 3 to avoid overlap with Visit 2;
- to clarify that an alcohol breath test, and not a saliva test, will be performed to test for concomitant substances;
- Figure 1 was updated;
- to clarify that vital signs to be collected every 3 months (Q3) during double-blind (DB) phase;
- to minimize risk of fetal exposure to study drug;
- to remove renal insufficiency as part of exclusion criterion #7;
- to prevent unnecessary exclusion of patients with gaps in historical medical documents;
- to include exclusion criterion #26 as per Food and Drug Administration (FDA) request for clarification;
- to maximize patient safety, exclude clinically unstable patients, and align with the R092670PSY3011 protocol;
- the first 3 bullets in Section 2.1.2.2 (Relapse Criteria) were previously in a different order and are now included in Section 4.3 (Criteria For Entry Into the Maintenance Phase) and in Section 4.4 (Criteria For Entry Into the Double-blind Phase);
- to include risperidone 3 mg/day as a valid alternative at an equivalent dose in countries for which the paliperidone extended-release (ER)/prolonged-release (PR) formulations are not available;
- to include additional text to the section subtitle, to clarify the frequency of prestudy Risperdal injections, and to clarify that subjects taking branded long-acting injectables (LAI) of risperidone or paliperidone palmitate will be permitted to enter this phase of the study;
- to clarify that the actual dates and times of electrocardiogram (ECG) and laboratory tests are not recorded in electronic case report form (eCRF);
- to update text in the protocol for clarity and consistency with Time and Events Schedules;
- to provide clearer guidance on timing of the end-of-phase (EOP) visit;
- to clarify text to include an accurate description of the Satisfaction With Participation in Social Roles Short Form 8a (SPSR), and to allow flexibility for regions to begin enrollment despite lack of translation availability;
- to modify text to prevent the risk of unblinding study treatment while collecting prolactin samples for clinical laboratory testing;
- to update Attachment 1 with clear instructions regarding the administration of injection;
- to remove controlling stratification by the maintenance dose level in the primary efficacy analysis; and
- to add a formula to clarify the calculation of percent change of total PANSS score.

Applicable Section(s)	Description of Change(s)

Rationale: To clarify which version of the C-SSRS will be used at the screening and baseline visits, and all other visits.

Applicable Section(s)	Description of Change(s)
Synopsis, Safety Evaluations; Time and Events Schedules – Section A.i. Subjects with prestudy PP1M or PP3M stability; Section A.ii. Subjects without prestudy PP1M or PP3M stability; Section E. Keys and Footnotes (for All Time and Events Schedules)	In Sections A.i. (Subjects with prestudy PP1M or PP3M stability), A.ii. (Subjects without prestudy PP1M or PP3M stability), and E (Keys and Footnotes [for All Time and Events Schedules]), the following footnote was modified for C-SSRS (strikethrough text deleted): m. ~~The C-SSRS is administered as the "Baseline" version during screening and as the "Since Last Visit" version at all other visits.~~ At the patients first study visit, the C-SSRS Baseline/Screening Form will be used; for all other visits, the C-SSRS Since Last Visit Form will be used. Removed the other visits in this row (Sections A.i and A.ii) and X, once before first dose (Section A.ii). In Sections A.i. and A.ii., the Suicidality (C-SSRS)[f,m] row has been changed to Suicidality (C-SSRS Baseline/Screening)[f,m], and added a row to include Suicidality (C-SSRS Since Last Visit)[f,m] for all other visits. The following text was modified in the Synopsis (Safety Evaluations)(bold text added): The study's standard safety evaluations will be physical examinations, vital signs, adverse events, electrocardiograms (ECGs), the Columbia Suicide Severity Rating Scale (C-SSRS **Baseline/Screening and C-SSRS Since Last Visit**), the Abnormal Involuntary Movement Scale (AIMS), the Barnes Akathisia Rating Scale (BARS), the Simpson Angus Scale (SAS), clinical laboratory assessments (in full [including prolactin] at some time points, or for prolactin only at other time points), and injection site evaluations.
Rationale: To update the visit window for Visit 3 to avoid overlap with Visit 2.	
Time and Events Schedules – Section A.i. Subjects with prestudy PP1M or PP3M stability	In the Time and Events Schedules (Section A.i, For Subjects with prestudy PP1M or PP3M stability), the visit window was changed from ±2 days to -1 to +2 days for Visit 3.
Rationale: To clarify that an alcohol breath test, and not a saliva test, will be performed to test for concomitant substances.	

Applicable Section(s)	Description of Change(s)
Time and Event schedule- Section E- Keys and Footnotes; 9.1. Study Procedures; 9.4.2. Clinical Laboratory Tests; 15. Study Specific Materials	The following text was modified in footnote e (bold text added; deleted text strikethrough): e. These tests for concomitant substances (both a**n** ~~saliva test for~~ **alcohol breath test** and a urine drug screen for illicit substances), including marijuana (even where legal). Alcohol and illicit substances are strongly discouraged but are not exclusionary and are not cause for withdrawal from the study. The following text was modified in footnote f (bold text added; deleted text strikethrough): f. In addition to the indicated visits, suspected relapses during the Double-blind Phase should prompt all of the following assessments at all associated clinic visits, even if not designated on these schedules: a pharmacokinetics (PK) sample, the biomarker samples (plasma and serum for all subjects, and saliva for subjects who are participating in that optional part of the study), a full PANSS assessment, a CGI-S assessment, a C-SSRS assessment, and testing for concomitant substances (both a**n** ~~saliva test for~~ **alcohol breath test** and a urine drug screen for illicit substances). In Section 9.1 (Study Procedures), the following bullet point text was modified (bold text added; deleted text strikethrough): Testing for concomitant substances (both a**n** ~~saliva test for~~ **alcohol breath test** and a urine drug screen for illicit substances), per Section 9.4.2 (Clinical Laboratory Tests). In Section 9.4.2 (Clinical Laboratory Tests), the following bullet point text was modified (bold text added; deleted text strikethrough): Urine drug screen kits (for illicit substances, including marijuana, even where legal) and alcohol ~~saliva test kits~~ **breath tests** will be provided for local use at the time points specified in the Time and Events Schedules. In Section 15 (Study Specific Materials), the following bullet point text was modified (bold text added; deleted text strikethrough): **Alcohol breath test**~~Saliva alcohol test kit~~
Rationale: Figure 1 was updated.	
3.1. Overview of Study Design	Replaced Figure 1 with a new figure.
Rationale: To clarify that vital signs to be collected Q3 during DB phase.	
Time and Events Schedules, Section B. Double-blind Phase (First 12 Months); Section C. Double-blind Phase (After the First 12 Months)	In the Time and Events Schedules, vital signs measurements (body weight and waist circumference) were added to Visit 13 (Section B, Double-blind Phase [First 12 Months]), and also to Visit 39 (Section C, Double-blind Phase [After the First 12 Months]).
Rationale: To minimize risk of fetal exposure to study drug.	

Applicable Section(s)	Description of Change(s)
4.1. Inclusion Criteria	The note following inclusion criterion #10 was modified (bold text added; deleted text strikethrough): **10. Criterion modified per Amendment 1** **10.1…** 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 sexually active) a woman must ~~begin~~ **consent to starting** a highly effective method of contraception ~~as described throughout this inclusion criterion~~ **after a negative pregnancy test.** ~~**If reproductive status is questionable, additional evaluation should be considered.**~~ **If the subject declines consent for start of a highly effective method of contraception, the subject must be withdrawn from the study.**
Rationale: To remove renal insufficiency as part of exclusion criterion #7.	
Synopsis, Subject Population; 4.2. Exclusion Criteria	The following text was modified in the Synopsis (Subject Population) and under exclusion criterion #7 (bold text added; deleted text strikethrough): **7. Criterion modified per Amendment 1** **7.1** Must not have a clinically significant and unstable medical illness in history or at screening, including (but not limited to) cardiac arrhythmias or other cardiac disease, hematologic disease, coagulation disorders (including any abnormal bleeding or blood dyscrasias), significant pulmonary disease including bronchospastic respiratory disease, diabetes mellitus (poorly controlled or requiring insulin), ~~renal or~~ hepatic insufficiency, thyroid disease (poorly controlled based on recent thyroid stimulating hormone [TSH] level),
Rationale: To prevent unnecessary exclusion of patients with gaps in historical medical documents.	
4.2. Exclusion Criteria	The following text was modified in exclusion criterion #12 (bold text added; strikethrough text deleted): **12. Criterion modified per Amendment 1** **12.1** Must not have a history of treatment resistance, defined as failure to respond to 2 adequate trials with adequate doses of different antipsychotic medications (where an adequate trial is defined as a minimum of 4 weeks at a therapeutic dosage)~~.~~**, based on the available medical records. Final determination of eligibility is based on investigator judgment.**
Rationale: To include exclusion criterion #26 as per FDA request for clarification.	
4.2. Exclusion Criteria	The following bullet point text was added to exclusion criterion #26: Must not have moderate to severe renal impairment (ie, creatinine clearance, as estimated by the Cockcroft-Gault method, of <60 mL/min).
Rationale: To maximize patient safety, exclude clinically unstable patients, and align with the R092670PSY3011 protocol.	

Applicable Section(s)	Description of Change(s)
4.2. Exclusion Criteria; 8.3. Prohibited Concomitant Medications	The following bullet point text was included in exclusion criterion #27: Subjects must not have the following: -Electroconvulsive therapy (ECT) within 60 days before screening -Nonselective/irreversible monoamine oxidase inhibitors (MAOI) antidepressants within 30 days prior to screening. -Other antidepressants unless at a stable dosage for 30 days before screening (If the dosage has been stable for less than 30 days and the subject does not require the antidepressant, it can be washed out by the baseline visit; if the dosage has been stable for less than 30 days and the subject requires antidepressant treatment, the subject should not be included in this study). The following bullet point text was included in exclusion criterion #28: Must not be concomitantly treated with mood stabilizers including lithium, or valproate, or other antiepileptics/anticonvulsants within 14 days of the first screening visit. The exclusion criterion #29 was added: Must not have been treated with a dopamine agonist (eg, ropinirole or pramipexole) within 90 days of the first screening visit. The following bullet point text was included in Section 8.3 (Prohibited Concomitant Medications): - Mood stabilizers and anticonvulsants including, but not limited to: lithium, valproate, lamotrigine, carbamazepine, phenytoin, and gabapentin. - Antidepressants not taken at a stable dosage for 30 days before screening, and all nonselective/irreversible MAOIs. Throughout the study, an antidepressant (other than a nonselective MAOI) may be initiated in rare circumstances only after consultation with the Medical Monitor. - Any prescription, herbal, or over-the-counter agents with psychotropic actions including any substances with stimulant and cognitive-enhancing properties. - Dopamine agonists, including, but not limited to: ropinirole, pramipexole, pergolide, cabergoline, and lisuride.
Rationale: The first 3 bullets in Section 2.1.2.2 (Relapse Criteria) were previously in a different order and are now included in Section 4.3 (Criteria For Entry Into the Maintenance Phase) and in Section 4.4 (Criteria For Entry Into the Double-blind Phase).	

Applicable Section(s)	Description of Change(s)
4.3. Criteria For Entry Into the Maintenance Phase; 4.4. Criteria For Entry Into the Double-blind Phase	The following text was modified in Section 4.3 (Criteria For Entry Into the Maintenance Phase)(bold text added; strikethrough text deleted): 3. For subjects proceeding from the Transition Phase to the Maintenance Phase, they must not have **during the Transition Phase**: ~~met any of the first 3 bullet points in Section 2.1.2.2 (Relapse Criteria) during the Transition Phase~~ **a. required psychiatric hospitalization (involuntary or voluntary admission to a psychiatric hospital for decompensation of the subject's schizophrenic symptoms), or** **b. inflicted deliberate self-injury or exhibited violent behavior resulting in suicide, clinically significant injury to him/her self or another person, or significant property damage, or** **c. had suicidal or homicidal ideation and aggressive behavior that is clinically significant (in frequency and severity) in the investigator's judgment** The following text was modified in Section 4.4 (Criteria For Entry Into the Double-blind Phase)(bold text added; strikethrough text deleted): 5. Subjects must not have **during the Maintenance Phase:** ~~met any of the first 3 bullet points in Section 2.1.2.2 (Relapse Criteria) during the Maintenance Phase~~ The sub-bullet points presented in Section 4.3 (Criteria For Entry Into the Maintenance Phase) are also presented in Section 4.4 (Criteria For Entry Into the Double-blind Phase).
Rationale: Paliperidone ER/PR are not available in all study countries. Risperidone 3 mg/day is a valid alternative at an equivalent dose.	
6.1.1. Screening Phase	The following text was modified in Section 6.1.1 (Screening Phase) (bold text added; strikethrough text deleted): **To demonstrate oral tolerability, p**~~P~~paliperidone ER/PR 6 mg tablets **or risperidone 3 mg/day (dose may be divided)** will be given during the Screening Phase for 4 to 6 consecutive days with the last dose swallowed on or before Day -1. **The recommended dose is paliperidone ER/PR of 6 mg/day or risperidone 3 mg/day (dose may be divided), but higher doses of paliperidone or risperidone may be used if clinically indicated, based on investigator judgment.**
Rationale: To include additional text to the section subtitle, to clarify the frequency of prestudy Risperdal injections, and to clarify that subjects taking branded LAI of risperidone or paliperidone palmitate will be permitted to enter this phase of the study.	

Applicable Section(s)	Description of Change(s)
6.1.2. Transition Phase	The following subtitle was modified (bold text added): Transition Phase: Subjects Previously Stabilized on Injectable Risperidone **(Biweekly – Risperdal CONSTA™ formulation)** The following subtitle was modified and text was included (bold text added): Transition Phase: Subjects Previously Initiated (But Not on a Stable Regimen) With Moderate or Higher Doses of PP1M **(Invega Sustenna ™ or Xeplion ™ formulation)** In the Transition Phase, subjects who entered the study on PP1M as 100 or 150 mg eq., but who do not yet meet criteria for stabilization with those doses, are treated with additional doses of PP1M during the Transition Phase, as shown in Table 3. **Owing to potential differences in release characteristics, only subjects who are taking Invega Sustenna ™ or Xeplion ™ PP1M formulations will be permitted to enter this phase of the study. Subjects who are taking non-branded formulations of once monthly paliperidone LAI or other once monthly LAIs will not be permitted to enter this phase.**
Rationale: Actual dates and times of ECG and laboratory tests are not recorded in eCRF. This information would be recorded by CROs.	
9.1. Study Procedures	The following text was modified in Section 9.1 (Study Procedures, Overview) (strikethrough text deleted): Actual dates and times of assessments will be recorded in the source documentation. ~~and eCRF~~
Rationale: Text was updated in the protocol for clarity and consistency with Time and Events Schedule.	
Time and Events Schedule, Section D. Follow-up Phase; 11.5.7. Columbia Suicide Severity Rating Scale	The following text was added to the Time and Events Schedule (Section D, Follow-up Phase) (bold text added): 12**, 18 or 24** Months after the Subject's First Double-blind Injection (or at 6-Month Time Points Thereafter, if Applicable) The following text was added to Section 11.5.7 (Columbia Suicide Severity Rating Scale) (bold text added): **C-SSRS Baseline/Screening Form will be used at screening. C-SSRS Since Last Visit Form will be used at other visits, as per Time and Events Schedules.** Suicide-related thoughts and behaviors based on the C-SSRS scale will be summarized by treatment group in incidence and shift tables.
Rationale: To provide clearer guidance on timing of the EOP visit.	

Applicable Section(s)	Description of Change(s)
Time and Events Schedule, Section C. Double-blind Phase (After the First 12 Months); Section E. Keys and Footnotes (for All Time and Events Schedules)	In Section C, the visit window of the EOP visit was changed from "Variable" to "±7[bb]". The following text was modified in Section E, footnote aa (bold text added; strikethrough text deleted): After completing the first 12 months of the Double-blind Phase, subjects who cannot proceed further in the Double-blind Phase (eg, if the study is closed) will complete the EOP Visit as an End-of-Study Visit. For subjects who can proceed to further treatment in the Double-blind Phase, Visit 33a is the same as Visit 33b, with the addition of another dose of study drug. Thereafter, subjects continue with this schedule until the Sponsor informs the sites that the study is closing, at which time subjects should be asked to return ~~as soon as possible~~ to the site for an EOP Visit, which becomes the End-of-Study Visit. The planned closure will be 12 months after the last subject has been randomized in the Double-blind Phase. **Refer to section 10.4 (Antipsychotic Therapy After the Study or in the Follow-up Phase) and 10.5 (Process for Planned Study Closure) for more information.** Footnote bb was added: bb. For EOP visits occurring during study closure (ie, not a result of withdrawal or relapse), the visit window is specified as ±7 days. In the event of study withdrawal or relapse, a visit window (in days) for the EOP visit is not specified but is to occur as soon as possible.
Rationale: Text was updated to include an accurate description of the SPSR Short Form 8a, and to allow flexibility for patient enrollment to begin in regions where translations are not yet available.	
Time and Events Schedules, Section E. Keys and Footnotes; Synopsis, Efficacy Evaluations; 9.2.5. Satisfaction With Participation in Social Roles	In Section E, footnote u, the following text was added: For subjects that require translation of the SPSR into their local language, the collection of the SPSR is optional until the final, approved translation is available. The following text was modified in the Synopsis (Efficacy Evaluations) (bold text added; deleted text strikethrough): Subject-reported efficacy evaluations include the Satisfaction With Participation in Social Roles ~~scale~~ **Short Form 8a** (SPSR) and the abbreviated 9-item Treatment Satisfaction Questionnaire for Medication (TSQM-9). The following text was modified in Section 9.2.5 (Satisfaction With Participation in Social Roles) (bold text added; deleted text strikethrough): The Patient-Reported Outcomes Measurement Information System (PROMIS) group developed and evaluated the Satisfaction With Participation in Social Roles ~~scale~~ **Short Form 8a** (SPSR) with funding from the US National Institutes of Health (NIH) and other academic and research grants.[15] A study in a diverse clinical population demonstrated the SPSR's responsiveness to change.[15] The SPSR asks subjects to consider the past 7 days and to rate ~~14~~ **8** items on 5-point Likert scales with higher scores representing higher satisfaction. An example of the SPSR is provided in the Manual of Assessments. **Note: For subjects that require translation of the SPSR into their local language, the collection of the SPSR is optional until the final, approved translation is available.**

Applicable Section(s)	Description of Change(s)
Rationale: To prevent the risk of unblinding study treatment while collecting prolactin samples for clinical laboratory testing.	
9.4.2. Clinical Laboratory Tests	The following text was modified in Section 9.4.2 (Clinical Laboratory Tests) (strikethrough text deleted): -prolactin, which will be blinded to the study-site personnel and Sponsor ~~except by request due to an adverse event~~; some samples will be for prolactin only (not the other analytes listed above), as designated in the Time and Events Schedules
Rationale: Because the choice of dose level in the maintenance was determined on the appropriate dose that subjects had been stabilized on, and which the investigators consider as appropriate from both efficacy and safety point of view, the KM curves analysis by treatment group is thus by regimen and not by individual dose level. This is consistent with the previous registration studies (R092670PSY3001, R092670PSY3011, and R092670PSY3012).	
11.3.1.1.2. Primary Efficacy Analyses	The following sentence was removed in Section 11.3.1.1.2 (Primary Efficacy Analyses): The tests above are adjusted by the stratification factor used during randomization (for moderate or higher dose).
Rationale: To update Attachment 1 with clear instructions regarding the administration of injection.	
Attachment 1	The following text was added to the Notes of the figure in Attachment 1: Injections should be administered in the dorso-gluteal injection site only. Ventrogluteal injections are not permitted.
Rationale: To add a formula to clarify the calculation of percent change of total PANSS score.	
Attachment 2	A formula for calculating percent change of total PANSS score was added.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

A Double-blind, Randomized, Active-controlled, Parallel-group Study of Paliperidone Palmitate 6-Month Formulation

Paliperidone is a monoaminergic antagonist that exhibits the characteristic dopamine Type 2 and serotonin Type 2A antagonism of the newer, or second-generation, atypical antipsychotic medications. Paliperidone is the active metabolite of risperidone and is available as a daily-dose oral formulation. Paliperidone palmitate is an ester of paliperidone, and is available for intramuscular injection in the paliperidone palmitate 1-month (PP1M) product as the F013 formulation and the paliperidone palmitate 3-month (PP3M) product as the F015 formulation. To further improve adherence and convenience, a paliperidone palmitate 6-month (PP6M) product is now under development. CCI [redacted] (ie, PP3M may be administered into either the deltoid or the gluteal muscle, but the larger volume associated with a PP6M dose requires injection into the larger gluteal muscle).

Doses can be expressed in milligrams of paliperidone palmitate or in milligrams equivalent (mg eq.) to paliperidone. Conversions between products and between units are described in the table below.

Conversions Between Doses of the 1-, 3-, and 6-Month Formulations of Paliperidone Palmitate; Study R092670PSY3015

	PP1M Dose		PP3M Dose		PP6M Dose	
	mg	**mg eq.**	**mg**	**mg eq.**	**mg**	**mg eq.**
Lowest-dose groups [a]	78 mg	50 mg eq.	Not used in this study		- - - - Not available - - - -	
Lower-dose groups	117 mg	75 mg eq.	Not used in this study		- - - - Not available - - - -	
Moderate-dose groups	156 mg	100 mg eq.	546 mg	350 mg eq.	1092 mg	700 mg eq.
Higher-dose groups	234 mg	150 mg eq.	819 mg	525 mg eq.	1560 mg	1000 mg eq.

Key: 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).

[a] Some countries may also have an ultralow dose of PP1M (below the lowest dose stated here), but the ultralow dose is not used in this study.

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

Objectives

Primary Objective

- The primary efficacy objective is to demonstrate that injection cycles consisting of a single administration of PP6M (700 or 1000 mg eq.) are not less effective than 2 sequentially administered injections of PP3M (350 or 525 mg eq.) for the prevention of relapse in subjects with schizophrenia previously stabilized on corresponding doses of PP1M (100 or 150 mg eq.) or PP3M (350 or 525 mg eq.).

Secondary Objectives

- To evaluate the safety and tolerability of PP6M (700 or 1000 mg eq.) in subjects with schizophrenia who have switched from corresponding doses of PP1M (100 or 150 mg eq.) or PP3M (350 or 525 mg eq.).
- To assess the pharmacokinetic (PK) profile of PP6M (700 or 1000 mg eq.) administered in the gluteal muscle in subjects with schizophrenia who have switched from corresponding doses of PP1M (100 or 150 mg eq.) or PP3M (350 or 525 mg eq.).
- To evaluate the clinically assessed efficacy of PP6M (700 or 1000 mg eq.) versus PP3M (350 or 525 mg eq.) in maintaining symptom control, functioning personally and socially, and achieving or

sustaining remission in subjects with schizophrenia who were previously stabilized on corresponding doses of PP1M (100 or 150 mg eq.) or PP3M (350 or 525 mg eq.).

- To evaluate the subject-reported efficacy outcomes of PP6M (700 or 1000 mg eq.) or PP3M (350 or 525 mg eq.) compared with treatment with previous oral antipsychotics in terms of satisfaction with medication and with participation in social roles.

Exploratory Objectives

Exploratory objectives are also defined in the full protocol, but are excluded from this synopsis for brevity.

Endpoints

Primary Endpoint

The primary endpoint is time to relapse during the Double-blind Phase. This noninferiority primary endpoint will be based on the difference in Kaplan-Meier 12-month estimate of survival (ie, percentage of subjects remaining relapse-free) between PP6M and PP3M.

Relapse Criteria

Relapse is defined as 1 or more of the following:

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

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

Secondary Endpoints

The secondary efficacy endpoints include the changes from baseline during the 12-month Double-blind Phase in the following scales: the PANSS total score and subscale scores, the Clinical Global Impression - Severity (CGI-S), and the Personal and Social Performance (PSP) scale. Additionally, the proportion of

subjects during the Double-blind Phase who meet criteria for symptomatic remission will be summarized; the definition of remission is provided in the full protocol.

The secondary PK endpoint is plasma paliperidone exposure.

The secondary endpoints for satisfaction with medication and with participation in social roles are abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) and Satisfaction with Participation in Social Roles (SPSR), respectively.

The secondary endpoints that measure safety and tolerability include physical examinations, vital signs, adverse events, electrocardiograms (ECGs), the Columbia Suicide Severity Rating Scale (C-SSRS Baseline/Screening and C-SSRS Since Last Visit), the Abnormal Involuntary Movement Scale (AIMS), the Barnes Akathisia Rating Scale (BARS), the Simpson Angus Scale (SAS), clinical laboratory assessments (in full [including prolactin] at some time points, or for prolactin only at other time points), and injection site evaluations.

Hypothesis

The primary hypothesis is that the efficacy of PP6M is noninferior to PP3M for preventing relapse in subjects with schizophrenia who were previously stabilized on corresponding doses of PP1M or PP3M.

SUBJECT POPULATION

Eligibility criteria are presented as a detailed list in the full protocol. A few important highlights are presented here in the synopsis:

- Must be 18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place) to 70 years of age, inclusive, at the time of informed consent.
- Must meet the diagnostic criteria for schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) for at least 6 months before screening.
- Must be receiving treatment with paliperidone palmitate (as either the PP1M or PP3M formulation), or injectable risperidone, or any oral antipsychotic.
    a. If the treatment is paliperidone palmitate, then:
        1) The dose strength must be PP1M as 100 or 150 mg eq. or PP3M as 350 or 525 mg eq.
        2) The dose timing must fit the study schedule. The next injection must be due within 28 days of the first screening (or first rescreening) visit.
    b. If the treatment is injectable risperidone, then the dose strength must be 50 mg, the dosing cycle must be every 2 weeks, the efficacy and tolerability must have been established as adequate with the same strength and frequency for at least 3 injection cycles before screening, and the subject must have a preference for a longer-acting injectable medication.
    c. If the treatment is an oral antipsychotic, then the subject must have a valid reason to discontinue the previous treatment, such as problems with efficacy, safety, or tolerability, or preference for a long-acting injectable medication.
- Criterion modified per Amendment 1
- 7.1 Must not have a clinically significant and unstable medical illness in history or at screening, including (but not limited to) cardiac arrhythmias or other cardiac disease, hematologic disease, coagulation disorders (including any abnormal bleeding or blood dyscrasias), significant pulmonary disease including bronchospastic respiratory disease, diabetes mellitus (poorly controlled or requiring insulin), hepatic insufficiency, thyroid disease (poorly controlled based on recent thyroid

stimulating hormone [TSH] level), neurologic or other psychiatric disease (except schizophrenia), infection, cancer, or any other illness that the investigator considers should exclude the subject or that could interfere with the interpretation of the efficacy or safety measurements.

If a subject does not meet all inclusion criteria (is a screen failure) with respect to dose level, dose duration, or dose timing of prestudy treatment with paliperidone palmitate or injectable risperidone, but at some point in the future is expected to meet these inclusion criteria, then the subject may be rescreened on 1 occasion. If a subject meets any exclusion criteria (is a screen failure) with respect to safety parameters, then rescreening is not allowed.

OVERVIEW OF STUDY DESIGN

This is a randomized, double-blind, active-controlled, multicenter, interventional, parallel-group study. All eligible subjects who progress without relapse will participate in a Screening Phase (of up to 28 days), a Maintenance Phase that includes 1 injection cycle with either PP1M or PP3M (yielding a phase duration of 1 or 3 months, accordingly), and a Double-blind Phase (of 12 months). The Double-blind Phase is designed to include 2 injection cycles of PP6M (investigational drug with alternating placebo) or 4 injection cycles of PP3M (active control). In addition to standard participation as described above, further conditional/additional participation is possible as follows:

- Before the Maintenance Phase, some subjects will participate in a Transition Phase, with 1 to 5 injections of PP1M, if they entered the study on an oral antipsychotic, on injectable risperidone, or on PP1M previously initiated but not yet stabilized.
- The planned closure will be 12 months after the last subject has been randomized in the Double-blind Phase.
- If a subject has already received at least 1 dose of double-blind study drug but then has relapsed or has met other relevant conditions for withdrawal or discontinuation, then the subject should enter a Follow-up Phase. The Follow-up Phase ends 12 months after the subject's first double-blind injection. The Follow-up Phase collects supplementary poststudy data from willing affected subjects, in an effort to document minimum safety information (ie, adverse events) and minimum efficacy information (ie, relapse status). The Follow-up Phase is designed to be as low-burden and noninvasive as possible, in order to encourage participation by the affected subjects.

The duration of exposure to study drug (ie, the number of injections) and the duration of study participation are variable based on a subject's flow through treatment types, on participation in conditional phases or parts as described in the 3 bullet points above, and on whether a subject experiences a relapse during the study.

For subjects who complete the study without relapse, the longest expected duration is ~19 months and the shortest expected duration is ~13 months, as described in the full protocol. For subjects who complete the study with relapse, the duration of exposure and participation depend on the timing of the relapse, and could even be (for example) only ~2 months of injections with a variable duration of assessments thereafter, as described in the full protocol.

DOSAGE AND ADMINISTRATION

Dosage: Screening Phase

During the Screening Phase, subjects must have already been receiving PP1M at 100 or 150 mg eq., PP3M at 350 or 525 mg eq., injectable risperidone at 50 mg, or an oral antipsychotic at any dosage with a reason to change, as described in the inclusion criteria.

Dosage: Transition Phase

The Transition Phase is applicable only to subjects who entered the Screening Phase without previous PP1M or PP3M stability. These subjects may have been previously treated with oral antipsychotics, injectable risperidone, or a moderate or higher dose of PP1M with previous initiation but without previous stabilization (where stabilization is defined is at least 3 months of injections with the last 2 doses being the same strength). A table in the full protocol provides further information about the PP1M administration schedule for subjects who participate in the Transition Phase.

Dosage: Maintenance Phase

For all subjects, the Maintenance Phase includes only 1 dose of PP1M as 100 or 150 mg eq. or PP3M as 350 or 525 mg eq. Each subject's Maintenance Phase dose will be matched by straightforward progression (PP1M to PP1M, or PP3M to PP3M) or will be matched by established conversion (PP1M to PP3M) to the same dose that they had been receiving during the Screening Phase or at the end of the Transition Phase. Progression versus conversion will depend on prestudy treatment types and on the need to balance the PP1M and PP3M groups in the Maintenance Phase, as described in the full protocol.

Dosage: Double-blind Phase

The PP1M and PP3M dose levels that were administered in the Maintenance Phase will be converted to PP3M or PP6M dose levels for the Double-blind Phase as follows:

- For the active control group,
  - The open-label PP1M doses (100 or 150 mg eq.) will be converted to double-blind PP3M doses (350 or 525 mg eq.) in accordance with the approved prescribing information for PP3M.
  - The open-label PP3M doses (350 or 525 mg eq.) will continue at the same double-blind dose level.
- For the investigational drug group,
  - The open-label 100 mg eq. PP1M and 350 mg eq. PP3M doses will be converted to double-blind 700 mg eq. PP6M doses.
  - The open-label 150 mg eq. PP1M and 525 mg eq. PP3M doses will be converted to double-blind 1000 mg eq. PP6M doses.

To maintain the blind, the subjects who are assigned to treatment with PP6M will receive injections of placebo at the 3-month time points between their 6-month doses of investigational drug. The placebo is 20% Intralipid® (200 mg/mL) injectable emulsion. Therefore, the Double-blind Phase should include a total of 4 doses at 3-month intervals, no matter which treatment group.

Administration

During the Transition Phase and Maintenance Phase, injections will be in the deltoid or gluteal muscles in accordance with the prescribing information for PP1M or PP3M, and will use injection kits equivalent to commercially available kits. During the Double-blind Phase, injections will be in the gluteal muscles only, will use study-specific injection kits, and will rotate across sides of the body as described in the full protocol.

PHARMACOKINETIC AND PHARMACODYNAMIC EVALUATIONS

Venous blood samples of approximately 4 mL will be collected to obtain approximately 2 mL of plasma, for measurement of plasma concentrations of paliperidone (and on selected samples, paliperidone palmitate). The aim of the PK evaluations will be to characterize the time course of plasma paliperidone concentrations and PK parameters such as maximum and minimum plasma concentrations and timing.

Therefore, 3 PK samples are scheduled weekly around the expected paliperidone peak at approximately 1 month after the PP6M dose, and 6 PK samples are scheduled weekly when approaching the end of the 6-month dosing interval. For paliperidone palmitate, PK evaluations will be performed on samples collected 2 days after the injections indicated in the Time and Events Schedules, to check for any prodrug in the bloodstream from possible partial intravascular injections.

In addition to PK sampling time points indicated in the Time and Events Schedules, sites should collect unscheduled PK samples associated with important efficacy or safety events, as described in the full protocol.

EFFICACY EVALUATIONS

The clinically assessed efficacy evaluations include the PANSS (full and abbreviated), the CGI-S, the PSP scale, and other relapse criteria as described above. Subject-reported efficacy evaluations include the Satisfaction With Participation in Social Roles Short Form 8a (SPSR) and the abbreviated 9-item Treatment Satisfaction Questionnaire for Medication (TSQM-9).

SAFETY EVALUATIONS

The study's standard safety evaluations will be physical examinations, vital signs, adverse events, electrocardiograms (ECGs), the Columbia Suicide Severity Rating Scale (C-SSRS Baseline/Screening and C-SSRS Since Last Visit), the Abnormal Involuntary Movement Scale (AIMS), the Barnes Akathisia Rating Scale (BARS), the Simpson Angus Scale (SAS), clinical laboratory assessments (in full [including prolactin] at some time points, or for prolactin only at other time points), and injection site evaluations. In addition those standard evaluations, conditional evaluations also are described for special safety situations that may occur; these include evaluations of injection site reactions or evaluations associated with initiations or changes in concomitant medications to manage extrapyramidal symptoms (EPS).

EXPLORATORY EVALUATIONS

Exploratory evaluations are described in the full protocol, they are excluded from this synopsis for brevity.

STATISTICAL METHODS

Sample Size Determination

The sample size for the Double-blind Phase of the study is 549 randomized subjects, based on determinations to provide a minimum of 80% power for the primary endpoint. The sample size determination includes the assumptions that the expected survival rate (percentage of subjects remaining relapse-free at 12 months) in the PP3M group is 85%, and that the 1-sided significance level should be 2.5%. Given these assumptions, 549 subjects randomized in a 2:1 ratio (PP6M:PP3M) are required to demonstrate with 80% power that PP6M is no worse than PP3M by a noninferiority margin of 10% for the percentage of subjects remaining relapse-free at 12 months. This assumes that the efficacy observed in the PP3M group will be similar to the efficacy observed in the previous PP3M registrational Phase 3 studies (R092670PSY3011 and R092670PSY3012).

Pharmacokinetic and Pharmacodynamic Analyses

Descriptive statistics will be calculated for the plasma concentrations of paliperidone and paliperidone palmitate and for the derived PK parameters, as applicable. Statistics will include sample size, mean, standard deviation, coefficient of variation, geometric mean, median, minimum, and maximum. Population PK analysis of plasma concentration-time data of paliperidone will be performed using nonlinear mixed-effects modeling for PP6M, possibly using models previously developed from PP3M studies.

Efficacy Analyses

Primary Efficacy

The primary endpoint is time to relapse in the Double-blind Phase, as described above. Subjects who meet at least 1 of the criteria for relapse (as also described above) during the Double-blind Phase at the time of study completion for the primary analysis will be considered to have had a relapse event. Subjects who do not have a relapse event in the Double-blind Phase will be considered as censored. The statistics to test the primary hypothesis are based on the percentage of subjects who remain relapse-free at Month 12 in the PP6M and PP3M groups per Kaplan-Meier estimate for the Double-blind Phase. The analysis will consider whether the lower limit of the 95% confidence interval of the difference in relapse-free rates between PP6M and PP3M exceeds the noninferiority margin of -10%. Further details are provided in the full protocol.

Secondary Efficacy

Clinically assessed secondary efficacy analyses include maintaining symptom control, functioning personally and socially, and achieving remission in each group (PP6M or PP3M, each sorted by dose level); further details about these analyses are provided in the full protocol. Subject-reported secondary efficacy analyses include analyses of the SPSR and the TSQM-9; further details about these analyses may be detailed in a separate document.

Safety Analyses

Descriptive statistics, summaries, tabulations, listings, etc will be provided for each outcome as appropriate. Analyses will follow precedents per previous studies of PP3M and per established guidelines from Health Authorities.

Exploratory Analyses

Exploratory analyses are described in the full protocol, but are excluded from this synopsis for brevity.

END OF STUDY

A subject will be considered as having completed the study if he or she has had a relapse during the Double-blind Phase and has completed all End-of-Study Visit assessments, or has remained relapse-free during the Double-blind Phase and has completed all End-of-Study Visit assessments. The study is considered completed with the last visit for the last subject participating in the study.

TIME AND EVENTS SCHEDULES

A. Screening, Transition, and Maintenance Phases

A.i. Subjects With Prestudy PP1M or PP3M Stability

Phase	Screening	Maintenance Phase: PP1M or PP3M					EOP [s]
Visit Number (of Study)	**1**	**2**	**3**	**4**	**5**	**6**	**7a [s]**
Day (of Phase), if Maintenance Phase is PP3M	**-28 to -2**	**1**	**3**	**15**	**30**	**60**	**90**
Day (of Phase), if Maintenance Phase is PP1M	**-28 to -2**	**1**	**3**	**8**	**15**	**22**	**30**
Visit Window, ±Days		**n/a**	**-1 to +2**	**±3**	**±3**	**±3**	**±3**
Screening/administrative							
Main ICF [a]	X						
Optional ICF for caregiver	X						
Inclusion/exclusion criteria [b]	X	X					
Medical history and demographics	X						
Pregnancy test [c]	X	X					X
Prestudy therapy	X [d]						
Concomitant therapy	- - - - - - - - - - - Continuous - - - - - - - - - - -						
Concomitant substance testing [e,f] and questions	X	X					X
Dosing							
PP3M (after prestudy PP3M stability)		X [g]					
PP3M (after prestudy PP1M stability, before PP3M prerandomization target)		X [g]					
PP1M (after prestudy PP1M stability, after PP3M prerandomization target)		X [g]					
Safety assessments							
Physical examinations [h]	X						X
Vital signs [i]	X						X
12-lead ECGs [j]	X X	X					X
Assessments of injection site [k]		X	X	X			X [k]
EPS assessments (AIMS, BARS, SAS) [l]	X	X		X			X
Suicidality (C-SSRS Baseline/Screening) [f,m]	X						
Suicidality (C-SSRS Since Last Visit) [f,m]		X			X	X	X
Adverse events	- - - - - - - - - - - Continuous - - - - - - - - - - -						
Efficacy assessments							
Full PANSS [f] + CGI-S [f]	X	X				X	X
Abbreviated PANSS [n] + CGI-S				X	X		
PSP	X	X					X
Collection of biofluids							
Blood for hematology and serum chemistry	X [o]						X [o]
Urinalysis	X						X
Blood for pharmacokinetics [f,p]		X [q]	X	X	X	X	X
Additional exploratory assessments							
HRU questionnaire, [r] IEQ, [r] SQLS	X						X

A.ii. Subjects Without Prestudy PP1M or PP3M Stability

Phase	Screening	Transition Phase					Maintenance Phase: PP1M or PP3M					EOP [s]
Visit Number (of Study)	1	2a	2b	2c	2d	2e[z]	2f	3	4	5	6	7a [s]
Day (of Phase), if Maintenance Phase is PP3M	-28 to -2	1	8	36	64	92	1 [u]	3	15	30	60	90
Day (of Phase), if Maintenance Phase is PP1M	-28 to -2	1	8	36	64	92	1 [u]	3	8	15	22	30
Visit Window, ±Days		n/a	±3	±7	±7	± 7	±3	-1 to +2	±3	±3	±3	±3
Screening/administrative												
Main ICF [a]	X											
Optional ICF for caregiver	X											
Inclusion/exclusion criteria [b]	X						X					
Medical history and demographics	X											
Pregnancy test [c]	X						X					X
Prestudy therapy	X [d]											
Concomitant therapy	- Continuous -											
Concomitant substance testing [e,f] and questions	X						X					X
Oral tolerability test	X or n/a											
Dosing: Transition Phase [v]												
PP1M (after prestudy oral antipsychotic)		X	X	X	X	X	n/a					
PP1M (after prestudy injectable risperidone)		n/a	X	X	X	X	n/a					
PP1M (after 2 prestudy PP1M injections)		n/a	n/a	X	X	X	n/a					
PP1M (after 3 prestudy PP1M injections)		n/a	n/a	n/a	X	X	n/a					
PP1M (after ≥4 prestudy PP1M injections)		n/a	n/a	n/a	n/a	X	n/a					
Dosing: Maintenance Phase												
PP3M (before PP3M prerandomization target)		n/a					X [g]					
PP1M (after PP3M prerandomization target)		n/a					X [g]					
Safety assessments												
Physical examinations [h]	X											X
Vital signs [i]	X											X
12-lead ECGs [j]	X X	X, once before first dose					X					X
Assessments of injection site [k]		X, after every dose					X	X	X			X [k]
EPS assessments (AIMS, BARS, SAS) [l]	X	X, once before first dose					X		X			X
Suicidality (C-SSRS Baseline/Screening) [f,m]	X											
Suicidality (C-SSRS Since Last Visit) [f,m]							X			X	X	X
Adverse events	- Continuous -											
Efficacy assessments												
Full PANSS [f] + CGI-S [f]	X	X, once before first dose					X				X	X
Abbreviated PANSS [n] + CGI-S									X	X		
PSP	X	X, once before first dose					X					X
Subject-reported: TSQM-9 and SPSR [t]	X											X
Collection of biofluids												
Blood for hematology and serum chemistry	X [o]											X [o]
Urinalysis	X											X
Blood for pharmacokinetics [f,p]							X [q]	X	X	X	X	X
Additional exploratory assessments												
HRU questionnaire, [r] IEQ, [r] SQLS, and IMR scale [t]	X											X

B. Double-blind Phase (12 Months)

Phase	Double-blind Phase (12 Months): PP3M or PP6M														
Visit Number (of Study)	**7b** [s]	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20 to 32**	**EOP/33a-**
Day (of Phase)	**1**	**3**	**22**	**29**	**36**	**60**	**92**	**120**	**148**	**155**	**162**	**169**	**176**	**183 to 358**	**365**
Visit Window, ±Days	**±3**	**-1 to +3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±3**	**±3**	**±3**	**±3**	**±3**	**Same as Previous 6-Month Cycle**	**±7 Error! Reference source not found.**
Screening/administrative															
Pregnancy test [c]	X													Same as previous 6-month cycle	X
Concomitant therapy	- Continuous -														
Concomitant substance testing [e,f] and questions	X						X							Same as previous 6-month cycle	X
Dosing															
PP3M & PP3M, or PP6M & placebo	X [w]						X [x]							Same as previous 6-month cycle	
Safety assessments															
Physical examinations [h] and vital signs [i]	X						X							Same as previous 6-month cycle	X
12-lead ECGs [j]	X			X										Same as previous 6-month cycle	X
Assessments of injection site [k]	X	X	X				X	X						Same as previous 6-month cycle	X [k]
EPS assessments (AIMS, BARS, SAS) [l]	X		X	X	X	X								Same as previous 6-month cycle	X
Suicidality (C-SSRS Since Last Visit) [f,m]	X			X		X	X	X		X				Same as previous 6-month cycle	X
Adverse events	- Continuous -														
Efficacy assessments															
Full PANSS [f] + CGI-S [f] + PSP	X						X							Same as previous 6-month cycle	X
Abbreviated PANSS [n] + CGI-S				X		X		X	X	X	X	X	X	Same as previous 6-month cycle	
Subject-reported: TSQM-9, SPSR [t]	X						X							Same as previous 6-month cycle	X
Collection of biofluids															
Blood for hematology and serum chemistry	X [o]		X [y]	X [y]	X [y]									Same as previous 6-month cycle	X [o]
Urinalysis	X													Same as previous 6-month cycle	X
Blood for pharmacokinetics [f,p]	X [q]	X	X	X	X	X	X [q]	X	X	X	X	X	X	Same as previous 6-month cycle	X
Additional exploratory assessments															
HRU questionnaire, [r] IEQ, [r] SQLS, and IMR scale [t]	X						X							Same as previous 6-month cycle	X

C. Follow-up Phase (for Subjects Who Discontinue, Withdraw, or Relapse During the Double-blind Phase)

Phase	**Follow-up Phase**
Visit Number (of Study)	**Varies Per Subject**
Month (of Phase)	**Quarterly (Every 3 Months) After the Subject's Last Double-blind Injection**
Visit Window, ±Weeks	**±1**
Concomitant therapy	X
Adverse events	X
Full PANSS + CGI-S + PSP	X

Note: The Follow-up Phase is applicable only to subjects who have received at least 1 dose of double-blind study drug but then have relapsed or have met other relevant conditions for withdrawal or discontinuation, as described in Section 10.2 (Discontinuation of Study Drug / Withdrawal From the Study). For relevant subjects, participation in the Follow-up Phase is encouraged but not required. The first visit of the Follow-up Phase should be scheduled to match the nearest equivalent quarterly assessment in the Double-blind Phase. Visits thereafter should be quarterly (every 3 months) until 12 months after the subject's first double-blind injection, For example, a subject who withdraws from the Double-blind Phase on Day 29 / Month 1 (and completes an EOP / Early Withdrawal Visit on that day) should, if willing, have the first visit of the Follow-up Phase on the equivalent of Day 92 / Month 3, and then 3 quarterly visits thereafter, for a total of 4 Follow-up Phase visits. If a possible relapse is detected per PANSS criteria, as described in Section 2.1.2.2 (Relapse Criteria), then the investigator should ask the subject to visit the clinical site 3 to 7 days later for a PANSS reassessment, if possible.

D. Keys and Footnotes (for All Time and Events Schedules)

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; EOP = End-of-Phase (Visit), which may be conducted as an End-of-Study Visit or an Early Withdrawal Visit when relevant (see Section 10 [Subject Completion / Discontinuation of Study Drug / Withdrawal From the Study); EPS = extrapyramidal symptoms; HRU = Healthcare Resource Utilization; ICF = Informed Consent Form; IEQ = Involvement Evaluation Questionnaire; IMR = Illness Management and Recovery; n/a = not applicable; PANSS = Positive and Negative Syndrome Scale; PP1M = paliperidone palmitate 1-month (product); PP3M = paliperidone palmitate 3-month (product); PP6M = paliperidone palmitate 6-month (product); PSP = Personal and Social Performance (scale); SAS = Simpson Angus Scale; SPSR = Satisfaction With Participation in Social Roles (scale); SQLS = Schizophrenia Quality of Life Scale; TSQM-9 = abbreviated 9-item Treatment Satisfaction Questionnaire for Medication.

Footnotes:

a. The main ICF must be signed before the first study-related activity; the day that the main ICF is signed is considered to be the first day of the Screening Phase.

b. The minimum criteria for the availability of documentation supporting the eligibility criteria are described in Section 17.4 (Source Documentation). Check clinical status again before the first dose of study drug.

c. The pregnancy test is applicable only to women of childbearing potential. It will be a highly sensitive serum test at screening (via central laboratory) and a urine test at all other time points (via local testing), and must be confirmed negative before study drug is administered at the marked visits.

d. If subjects had been taking oral antipsychotics in addition to their PP1M or PP3M, then the oral antipsychotics should be tapered and discontinued during the Screening Phase, with the last oral dose swallowed on or before Day -1. If the prestudy therapy was PP1M or PP3M, then the next injection must be due within 28 days of the first screening (or first rescreening) visit.

e. These tests for concomitant substances are an alcohol breath test and a urine drug screen for illicit substances, including marijuana (even where legal). Alcohol and illicit substances are strongly discouraged but are not exclusionary and are not cause for withdrawal from the study. For any subject with a positive result for alcohol or illicit substances, the study-site personnel should administer the relevant test again at subsequent visits (even if not marked) until a negative result is obtained. After a negative result is obtained, the subject can resume testing at the standard frequency as indicated in these schedules.

f. In addition to the indicated visits, suspected relapses during the Double-blind Phase should prompt all of the following assessments at all associated clinic visits, even if not designated on these schedules: a pharmacokinetics (PK) sample, a full PANSS assessment, a CGI-S assessment, a C-SSRS assessment, and testing for concomitant substances (both an alcohol breath test and a urine drug screen for illicit substances). If a possible relapse is detected per PANSS criteria, as described in Section 2.1.2.2 (Relapse Criteria), then the investigator should ask the subject to visit the clinical site 3 to 7 days later for a PANSS reassessment (if no such visit is already scheduled). The EOP visit is to occur as soon as possible after relapse confirmation (preferably the same day).

g. For subjects who enter the study with previous PP1M or PP3M stability, the dose in the Maintenance Phase should be administered with timing appropriate to the subject's last prestudy dose (ie, 30±7 days after the last prestudy PP1M dose, or 90±14 days after the last prestudy PP3M dose). For subjects who enter the study without previous PP1M or PP3M stability, the dose in the Maintenance Phase should similarly be administered with timing appropriate to the subject's last dose in the preceding Transition Phase (ie, 28±3 days after previous PP1M dose). For all subjects, the dose in the Maintenance Phase may be in the deltoid or gluteal muscle, but may not be in the left gluteal muscle (because of the anticipated left gluteal injection at the beginning of the Double-blind Phase, as shown in Table 5).

h. Physical examinations include weight, waist circumference, and abnormalities at all marked visits, plus height at screening only. (Height is used in calculations of body mass index.)

i. Vital sign assessments will include blood pressure (first supine, then standing), pulse/heart rate, respiratory rate, and temperature. Vital signs should be measured before any blood draws. See additional instructions in Section 9.4.4 (Vital Signs).

j. For ECGs, see Section 9.4.3 (Electrocardiograms). Note:
   - Before the first dose: 2 ECGs need to be assessed during the Screening Phase, at least 24 hours apart. The first ECG may be from prior medical record within the past year, and the second ECG must be completed by the study site on or before Day -2 of the study (and assessed by the central reader before the first dosing day of the study). Therefore, double Xs are shown in the Screening Phase column. Another ECG is completed by the study site on Day 1 of the relevant phase, prior to the first dose of study drug. All 3 of these ECG results should be compared with the exclusion criteria.
   - After the first dose: if any clinically significant ECG abnormality is observed during the study, then the study-site personnel should add ECG assessments for that subject at subsequent visits (even if not marked) until the abnormality is resolved.
   - At any visit: if blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, then the procedures should be performed in the following order: ECGs, vital signs, blood draw.

k. Both the subject and the investigator assess the injection site at each marked time point, unless noted otherwise below.
   - The subject completes a Visual Analog Scale (VAS) to assess pain within 30 minutes after each injection as the VAS-Acute and at the time points marked days or weeks later as the VAS-Residual. The subject does not complete a VAS at the EOP Visit.
   - The investigator or subinvestigator (but not other study-site personnel) assesses the injection site for tenderness, erythema/redness, and induration/swelling, and should not review the subject's VAS rating of the injection site pain. The investigator/subinvestigator should complete these assessments within 30 minutes after the injection and at all marked visits thereafter; for any characteristic still rated mild, moderate, or severe at the last marked visit, the investigator/subinvestigator should add injection site assessments at subsequent visits (even if not marked) until all of the characteristics are rated absent. At the EOP Visit, the investigator assesses the site of the most recent injection. See Section 9.4.8.2 (Injection Site Evaluations and Follow-up by Investigators) for additional details.

l. For antiparkinsonism medications, initiations or changes should be preceded by an AIMS, BARS, and SAS (even if not designated in these schedules). If beta-adrenergic blockers or benzodiazepines are given for akathisia, then initiations or changes should be preceded by a BARS (even if not designated per these schedules).

m. At the patients first study visit, the C-SSRS Baseline/Screening Form will be used; for all other visits, the C-SSRS Since Last Visit Form will be used.

n. An abbreviated PANSS consists of the positive-symptom items P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), P6 (suspiciousness/persecution), and P7 (hostility), and the general-psychopathology item G8 (uncooperativeness). If the abbreviated PANSS indicates worsening since the last full PANSS assessment or if the subject meets one or more symptom criterion for relapse (as described in Section 2.1.2.2 [Relapse Criteria]), then the full PANSS should be administered.

o. Subjects should be in fasted state (overnight or for at least 8 hours) for these clinical laboratory blood samples.

p. In addition to PK sampling time points indicated in these schedules, sites should collect PK samples (even if unscheduled) at time points associated with serious or severe adverse events, and may collect other unscheduled PK samples at the investigator's discretion for other adverse events (even if the event is not serious or severe).

q. These PK samples are collected before the dose is administered that day.

r. The HRU questionnaire and the IEQ are both administered as the baseline assessment versions during the Screening Phase and as the postbaseline assessment versions at all subsequent visits.
   - The HRU questionnaire is administered by study-site personnel; see details in Section 9.6.1 (Healthcare Resource Utilization Questionnaire).
   - The IEQ is completed by an unpaid caregiver if available; see details in Section 9.6.2 (Involvement Evaluation Questionnaire).

s. At the end of the Maintenance Phase, subjects who are ineligible to proceed to the Double-blind Phase will complete the EOP Visit as an Early Withdrawal Visit. For subjects who are eligible to proceed, the EOP Visit in the Maintenance Phase (Visit 7a) is the same as the first visit of the Double-blind Phase (Visit 7b).

t. The TSQM-9, SPSR, and IMR scale results will only be analyzed for subjects who entered the study on an oral antipsychotic. For consistency of practice in the Screening Phase, these scales are also administered to subjects who entered the study on injectable risperidone, even if the data will not be analyzed. For consistency of practice in the Double-blind Phase, these scales are administered to all subjects, even if the data will not be analyzed. For subjects that require translation of the SPSR into their local language, the collection of the SPSR is optional until the final, approved translation is available.

u. The duration between the last visit of the Transition Phase (applicable only to subjects with reason to change or stabilize their previous antipsychotic) to the first visit of the Maintenance Phase is 28 days.

v. Subjects previously treated with injectable risperidone or previously initiated but not on a stable regimen with PP1M are not required to attend the visits marked "n/a" in the Transition Phase. For these subjects, the first visit in the Transition Phase should be scheduled for the day when the subject would have received the next injectable risperidone dose (14±3 days) or next PP1M dose (30±7 days). See Table 3 and Table 4 for more information about dosing and dose-related eligibility in the Transition Phase.

w. This dose is active drug (PP3M or PP6M) in both treatment groups. Subjects are randomly assigned to their treatment group before dosing at Visit 7b. See Table 5 for more information.

x. This dose is active drug in the PP3M treatment group and placebo (to maintain the blind) in the PP6M treatment group. See Table 5 for more information.

y. These laboratory samples are for prolactin only and do not require fasting.

z. After the PP3M prerandomization target is met, subjects who entered the study at Visits 2a, 2b, 2c, or 2d, will skip Visit 2e and proceed to Visit 2f if the subject is eligible to enter the Maintenance Phase (see Section 4.3, Criteria for Entry Into the Maintenance Phase). If not eligible to enter the Maintenance Phase, the subject will be withdrawn from the study. Visit 2e remains available for subjects with ≥4 prestudy PP1M injections but do not have dose stability.

ABBREVIATIONS AND TERMS

AIMS	Abnormal Involuntary Movement Scale
BARS	Barnes Akathisia Rating Scale
BMI	body mass index
CGI-S	Clinical Global Impression - Severity
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
DB	double blind
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
CCI	[redacted]
FDA	Food and Drug Administration
G[x]	a general-psychopathology item of the PANSS scale, where x is the number of the item
GCP	Good Clinical Practice
HRU	Healthcare Resource Utilization
ICF	Informed Consent Form
ICH	International Conference on Harmonisation / International Council for Harmonisation
IEC	Independent Ethics Committee
IEQ	Involvement Evaluation Questionnaire
IMR	Illness Management and Recovery
IRB	Institutional Review Board
IWRS	Interactive Web Response System
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
PD	pharmacodynamic(s)
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)
Q3	every 3 months
QTc	QT interval, corrected
QTcB	QT interval, corrected according to Bazett's formula
QTcF	QT interval, corrected according to Fridericia's formula
QTcLD	QT interval, corrected according to the linear-derived formula
SAP	statistical analysis plan

SAS	Simpson Angus Scale
SCI-PANSS	Structured Clinical Interview - PANSS
SPSR	Satisfaction With Participation in Social Roles (Short Form 8a)
SQLS	Schizophrenia Quality of Life Scale
SUSAR	suspected unexpected serious adverse reaction
TSQM-9	abbreviated 9-item Treatment Satisfaction Questionnaire for Medication
US	United States
VAS	Visual Analog Scale

Investigational Medicinal Products (IMPs):

- Test product: PP6M
- Comparator product: PP3M
- Placebo: 20% Intralipid® (200 mg/mL) injectable emulsion.

Noninvestigational Medicinal Products (NIMPs):

- Rescue medications: Anti-EPS medications/ Benzodiazepines (Section 8.2: Concomitant Therapy)
- Pretreatment medications: Oral antipsychotics including risperidone, paliperidone ER; injectable risperidone, PP1M and PP3M

1. INTRODUCTION

Paliperidone is a monoaminergic antagonist that exhibits the characteristic dopamine Type 2 and serotonin Type 2A antagonism of the newer, or second-generation, atypical antipsychotic medications. Paliperidone is the active metabolite of risperidone and is available as a daily-dose oral formulation. Paliperidone palmitate is an ester of paliperidone, and is available for intramuscular injection in the paliperidone palmitate 1-month (PP1M) product as the F013 formulation and the paliperidone palmitate 3-month (PP3M) product as the F015 formulation. To further improve adherence and convenience, a paliperidone palmitate 6-month (PP6M) product is now under development. CCI [redacted] (ie, PP3M may be administered into either the deltoid or the gluteal muscle, but the larger volume associated with a PP6M dose requires injection into the larger gluteal muscle).

Doses can be expressed in milligrams of paliperidone palmitate or in milligrams equivalent (mg eq.) to paliperidone. Conversions between products and between units are described in Table 1.

Table 1: Conversions Between Doses of the 1-, 3-, and 6-Month Formulations of Paliperidone Palmitate; Study R092670PSY3015

	PP1M Dose		PP3M Dose		PP6M Dose	
	mg	**mg eq.**	**mg**	**mg eq.**	**mg**	**mg eq.**
Lowest-dose groups [a]	78 mg	50 mg eq.	Not used in this study		- - - - Not available - - - -	
Lower-dose groups	117 mg	75 mg eq.	Not used in this study		- - - - Not available - - - -	
Moderate-dose groups	156 mg	100 mg eq.	546 mg	350 mg eq.	1092 mg	700 mg eq.
Higher-dose groups	234 mg	150 mg eq.	819 mg	525 mg eq.	1560 mg	1000 mg eq.

Key: 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).

[a] Some countries may also have an ultralow dose of PP1M (below the lowest dose stated here), but the ultralow dose is not used in this study.

1.1. Background

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.

All of the material in this "Background" section about the approved paliperidone and paliperidone palmitate products (oral paliperidone, PP1M, and PP3M) is summarized from the Investigator's Brochure, unless otherwise indicated. Statements about the investigational PP6M product may not yet be included in the Investigator's Brochure and/or may evolve with time. For the most comprehensive nonclinical and clinical information regarding paliperidone and paliperidone palmitate, always refer to the latest version of the Investigator's Brochure.

Nonclinical Studies

Pharmacologic Profile

Paliperidone is a racemic mixture. Binding affinities are similar between risperidone and paliperidone for serotonin Type 2A receptors, dopamine Type 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 dopamine Type 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 is now conducting a 6-month local tolerability study in minipigs for CCI [redacted] to be tested in the current clinical study. CCI [redacted] 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). The results of the minipig study now available in an addendum to the Investigator's Brochure.

Clinical Studies

Exposure

Beyond extensive studies of oral paliperidone and PP1M, the Sponsor completed 3 registrational clinical studies of PP3M, CCI [redacted]. 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.[7] The combined exposure to PP3M was 567.6 subject-years.[7] No studies of CCI [redacted] have been conducted in humans using the mass and volume of the dose (and the resultant dosing interval) that characterize PP6M.

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 pharmacokinetic (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, CCI [redacted]

Efficacy

In addition to extensive studies of oral paliperidone and PP1M, the efficacy of PP3M in the maintenance treatment in adults with schizophrenia was established in the 2 registrational 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 the plans for this current study with PP6M, with the longer duration of efficacy to be provided by higher doses CCI [redacted]

Safety

In addition to extensive studies of oral paliperidone and PP1M, the safety profile of PP3M was established in the 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.

Adverse events of special interest with PP3M were investigated as follows: EPS-related adverse events; diabetes mellitus and hyperglycemia-related adverse events; potentially prolactin-related adverse events; suicidality; aggression and agitation; somnolence and sedation; seizures and convulsions; neuroleptic malignant syndrome; cardiac arrhythmias; orthostatic hypotension; and adverse events suggestive of (or related to) proarrhythmic potential, ischemia, rhabdomyolysis, overdose, weight gain, tachycardia, injection site reactions, QT prolongation, and acute kidney injury.[8] Investigations for adverse events of special interest will be similar for PP6M and will be further elaborated in the Statistical Analysis Plan (SAP).

Overall, the previous safety and tolerability outcomes with PP3M support the plans for this current study with PP6M, with acceptable safety and tolerability expected to be possible CCI [redacted]

1.2. Overall Rationale for the Study

Adherence to any medication regimen can be difficult for any patient, and can be especially problematic for patients with schizophrenia. With currently available oral antipsychotics for schizophrenia, full nonadherence occurs in approximately 40% to 50% of patients,[23] and partial adherence occurs in approximately 90% of patients.[36] One analysis found that treatment gaps of as little as 1 to 10 days could double the odds of hospitalization (p=0.004).[36] In contrast to oral formulations, the reliable drug delivery associated with long-acting injectable (LAI) antipsychotics has yielded a reduced risk of relapse and hospitalization and an improved quality of life.[16] Because LAI antipsychotics are administered by a healthcare provider, LAIs offer transparency with respect to medication adherence, alerting healthcare professionals to the occurrence of nonadherence, and ensuring that patients with chronic psychotic illness receive a known quantity of medication at appropriate dosing intervals.

Despite the advantages of LAI formulations over short-acting oral formulations, the development of antipsychotics has not achieved the same durations as some other medications. Many LAI antipsychotics are available with treatment intervals of 2 to 4 weeks,[32] and one LAI antipsychotic (PP3M) is available with a treatment interval of 3 months, but no LAI antipsychotics are available with longer treatment intervals. This unmet medical need stands in contrast to other

injectable or implantable medications for long-term use, such as 6-month and 1-year treatments for prostate cancer, a 1-year treatment for osteoporosis, and a 3-year treatment as hormonal contraception.[32]

The 6-month dosing interval with PP6M offers convenience to stably treated schizophrenia populations (for those who prefer a longer dosing interval) and offers benefits to underserved schizophrenia populations (for those with limited access to healthcare, with geographic or economic problems in coordinating transportation to clinic visits for injections, or with treatment access problems associated with homelessness). The current study is therefore designed to evaluate the efficacy, safety, tolerability, and PK profile of PP6M versus PP3M.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

2.1.1. Objectives

Primary Objective

- The primary efficacy objective is to demonstrate that injection cycles consisting of a single administration of PP6M (700 or 1000 mg eq.) are not less effective than 2 sequentially administered injections of PP3M (350 or 525 mg eq.) for the prevention of relapse in subjects with schizophrenia previously stabilized on corresponding doses of PP1M (100 or 150 mg eq.) or PP3M (350 or 525 mg eq.).

Secondary Objectives

- To evaluate the safety and tolerability of PP6M (700 or 1000 mg eq.) in subjects with schizophrenia who have switched from corresponding doses of PP1M (100 or 150 mg eq.) or PP3M (350 or 525 mg eq.).
- To assess the pharmacokinetic (PK) profile of PP6M (700 or 1000 mg eq.) administered in the gluteal muscle in subjects with schizophrenia who have switched from corresponding doses of PP1M (100 or 150 mg eq.) or PP3M (350 or 525 mg eq.).
- To evaluate the clinically assessed efficacy of PP6M (700 or 1000 mg eq.) versus PP3M (350 or 525 mg eq.) in maintaining symptom control, functioning personally and socially, and achieving or sustaining remission in subjects with schizophrenia who were previously stabilized on corresponding doses of PP1M (100 or 150 mg eq.) or PP3M (350 or 525 mg eq.).
- To evaluate the subject-reported efficacy outcomes of PP6M (700 or 1000 mg eq.) or PP3M (350 or 525 mg eq.) compared with treatment with previous oral antipsychotics in terms of satisfaction with medication and with participation in social roles.

Exploratory Objectives

- To evaluate healthcare resource utilization during treatment with PP6M or PP3M versus previous treatment.
- To assess changes over time in use of nicotine-containing products.

- To evaluate the perspectives of subjects during treatment with PP6M or PP3M versus previous treatment with oral antipsychotics in terms of their ability to manage their illness and achieve their personal goals.
- To evaluate the caregiver's burden during the recipient's treatment with PP6M or PP3M versus previous treatment.
- To evaluate health-related quality of life during treatment with PP6M or PP3M versus previous treatment.

2.1.2. Endpoints

2.1.2.1. Primary Endpoint

The primary endpoint is time to relapse during the Double-blind Phase. This noninferiority primary endpoint will be based on the difference in Kaplan-Meier 12-month estimate of survival (ie, percentage of subjects remaining relapse-free) between PP6M and PP3M.

2.1.2.2. Relapse Criteria

Relapse is defined as 1 or more of the following:

- Psychiatric hospitalization (involuntary or voluntary admission to a psychiatric hospital for decompensation of the subject's schizophrenic symptoms), or
- For Positive and Negative Syndrome Scale for Schizophrenia (PANSS) total score:

The subject has an increase of 25% in total PANSS score from randomization for 2 consecutive assessments separated by 3 to 7 days if the score at randomization was >40, or

The subject has a 10-point increase in the total PANSS score from randomization for 2 consecutive assessments separated by 3 to 7 days if the score at randomization was ≤40, or

- The 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, or
- The subject has suicidal or homicidal ideation and aggressive behavior that is clinically significant (in frequency and severity) in the investigator's judgment, or
- For PANSS items P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), P6 (suspiciousness/persecution), P7 (hostility), and G8 (uncooperativeness):

The subject has a score of ≥5 after randomization for 2 consecutive assessments separated by 3 to 7 days on any of the above items if the maximum score for the above PANSS items was ≤3 at randomization, or

The subject has a score of ≥6 after randomization for 2 consecutive assessments separated by 3 to 7 days on any of the above items if the maximum score for the above PANSS items was 4 at randomization.

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

The above criteria for relapse in this study are the same as the criteria in the Sponsor's pivotal studies of PP3M.[8,9]

Refer to Section 9 (Study Evaluations) for evaluations related to endpoints. See Attachment 2 for the correct calculation of percentage change in full PANSS total scores relevant to relapse criteria.

2.1.2.3. Secondary Endpoints

The secondary efficacy endpoints include the changes from baseline during the 12 months of the Double-blind Phase in the following scales: the PANSS total score and subscale scores, the Clinical Global Impression - Severity (CGI-S), and the Personal and Social Performance (PSP) scale. Additionally, the proportion of subjects during the Double-blind Phase who meet criteria for symptomatic remission will be summarized; the definition of remission is provided in Section 11.3.2 (Secondary Efficacy Analyses).

The secondary PK endpoint is plasma paliperidone exposure.

The secondary endpoints for satisfaction with medication and with participation in social roles are abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) and Satisfaction with Participation in Social Roles (SPSR), respectively.

The secondary endpoints that measure safety and tolerability include physical examinations, vital signs, adverse events, electrocardiograms (ECGs), the Columbia Suicide Severity Rating Scale (C-SSRS Baseline/Screening and C-SSRS Since Last Visit), the Abnormal Involuntary Movement Scale (AIMS), the Barnes Akathisia Rating Scale (BARS), the Simpson Angus Scale (SAS), clinical laboratory assessments (in full [including prolactin] at some time points, or for prolactin only at other time points), and injection site evaluations.

2.2. Hypothesis

The primary hypothesis is that the efficacy of PP6M is noninferior to PP3M for preventing relapse in subjects with schizophrenia who were previously stabilized on corresponding doses of PP1M or PP3M. See Section 11.3.1 (Primary Hypothesis and Efficacy Analyses).

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a randomized, double-blind, active-controlled, multicenter, interventional, parallel-group study. All eligible subjects who progress without relapse will participate in a Screening Phase (of up to 28 days), a Maintenance Phase that includes 1 injection cycle with either PP1M or PP3M (yielding a phase duration of 1 or 3 months, accordingly), and a Double-blind Phase (of 12 months). The Double-blind Phase is designed to include at least 2 injection cycles of PP6M (investigational drug with alternating placebo) or 4 injection cycles of PP3M (active control). In addition to standard participation as described above, further conditional/additional participation is possible as follows:

- Before the Maintenance Phase, some subjects will participate in a Transition Phase, with 1 to 5 injections of PP1M, if they entered the study on an oral antipsychotic, on injectable risperidone, or on PP1M previously initiated but not yet stabilized).
- The planned closure will be 12 months after the last subject has been randomized in the Double-blind Phase.
- If a subject has already received at least 1 dose of double-blind study drug but then has relapsed or has met other relevant conditions for withdrawal or discontinuation, then the subject should enter a Follow-up Phase. The Follow-up Phase ends 12 months after the subject's first double-blind injection. The Follow-up Phase collects supplementary poststudy data from willing affected subjects, in an effort to document minimum safety information (ie, adverse events) and minimum efficacy information (ie, relapse status) for at least 6 months after a possible PP6M injection. The Follow-up Phase is designed to be as low-burden and noninvasive as possible, in order to encourage participation by the affected subjects.

The duration of exposure to study drug (ie, the number of injections) and the duration of study participation are variable based on a subject's flow through treatment types, on participation in conditional phases or parts as described in the 3 bullet points above, and on whether a subject experiences a relapse during the study:

- For subjects without relapse,
  - The longest expected duration is for a subject who enters the study on an oral antipsychotic and who enrolls early enough to be assigned to PP3M during the Maintenance Phase and then to participate in 12 months in the Double-blind Phase. Such a subject could have ~ 19 months of participation with exposure to paliperidone palmitate (4 months during the Transition Phase, 3 months during the Maintenance Phase, 12 months of the Double-blind Phase.
  - The shortest expected duration for a subject who enters the study with stability on PP1M will be ~13 months of participation with exposure to paliperidone palmitate (1 month during the Maintenance Phase and 12 months during the Double-blind Phase).
- For subjects with relapse, the duration of exposure and participation would be shorter and would depend on the timing of the relapse. For example, a subject might receive a first study injection providing 1 month of treatment in the Maintenance Phase and a second study injection at the beginning of the Double-blind Phase; if a relapse occurred a few weeks thereafter, then the subject would receive no further study drug injections, but would have an End-of-Study Visit associated with the confirmation of the relapse, and would contribute poststudy Follow-up Phase data if willing for the remainder of the yearly cycle.

Due to the long-acting nature of the study drugs, exposure to residual yet potentially subtherapeutic levels of paliperidone is expected to continue past the last study assessment, as addressed in the eligibility criteria, prohibitions, and restrictions that are relevant to the poststudy period (see Section 4 [Subject Population]).

The approximate participation targets are 903 subjects entering the Screening Phase, approximately 840 subjects entering the Transition/Maintenance Phase, and 549 subjects entering the Double-blind Phase. Of subjects entering the Double-blind Phase, the

prerandomization targets are approximately one-half entering from a PP3M group, and one-half entering from a PP1M group. The Sponsor will inform sites when enrollment targets have been met and when no further subjects should be enrolled; the subjects who are already enrolled at that point may continue in the study until the Sponsor gives instructions to the sites about how to begin closing the study. The Sponsor also will inform sites when phase-specific targets or limits have been met, as follows: when the PP3M prerandomization target has been met in the Maintenance Phase (see Section 6.1.3 [Maintenance Phase]), and when the pathway to enrollment that includes the Transition Phase is closed (see Section 6.1.2 [Transition Phase]).

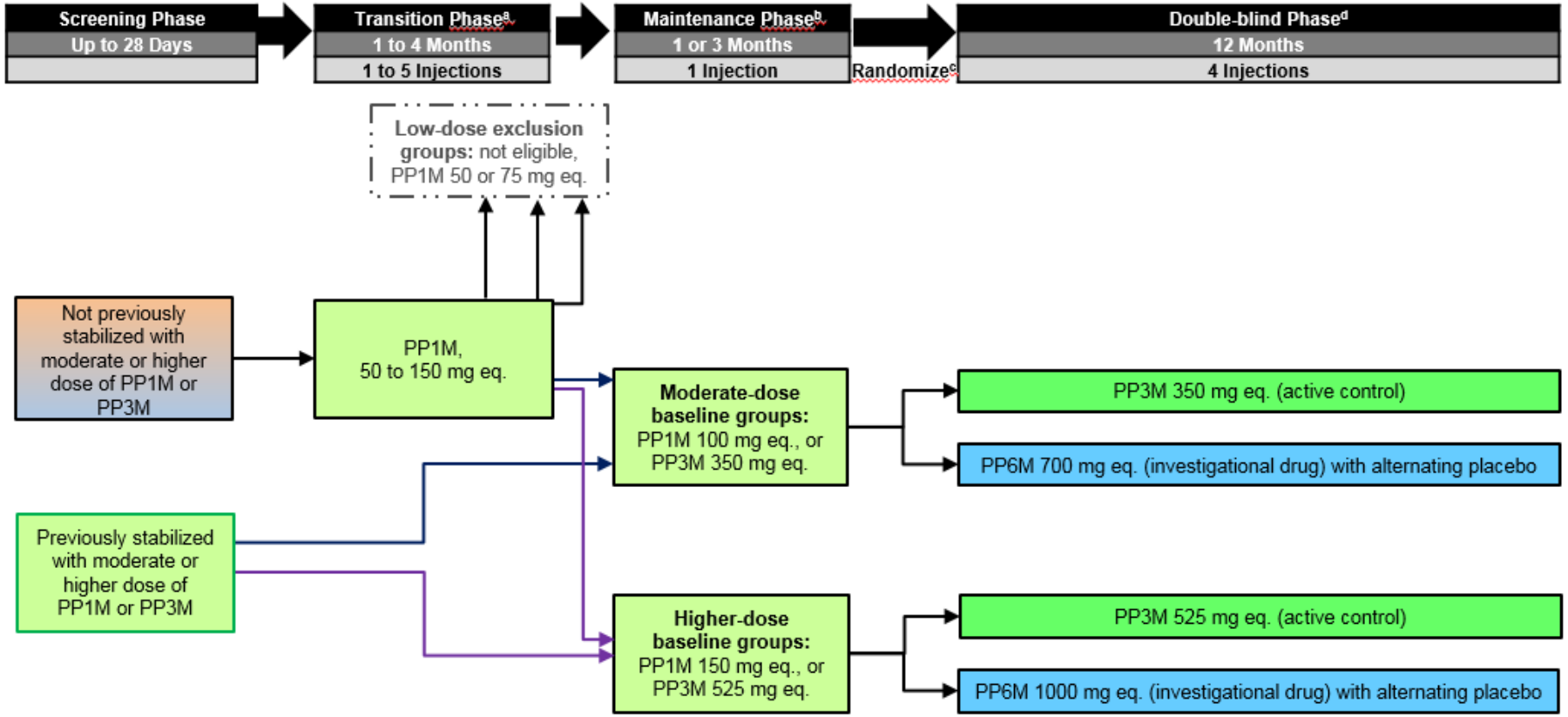
At the start of the Double-blind Phase,

- Subjects in the moderate-dose baseline groups (who had achieved stability before or during the study with a PP1M dose of 100 mg eq. or a PP3M dose of 350 mg eq.) will be randomized in a 2:1 ratio (with dose level as a stratification factor) to receive either the investigational PP6M at a 700 mg eq. dose or the active control PP3M at a 350 mg eq. dose.
- Subjects in the higher-dose baseline groups (who had achieved stability before or during the study with a PP1M dose of 150 mg eq. or a PP3M dose of 525 mg eq.) will be randomized in a 2:1 ratio (with dose level as a stratification factor) to receive either the investigational PP6M as a 1000 mg eq. dose or the active control PP3M as a 525 mg eq. dose.

Safety, efficacy, and pharmacokinetics are monitored throughout the study, as specified in the Time and Events Schedules.

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

Figure 1: Schematic Overview; Study R092670PSY3015



Key: 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).

[a] During the Transition Phase, the dose levels and the number of injections will depend first on a subject's previous treatment and then on his or her individual efficacy and tolerability results, as described in Section 6.1.2 (Transition Phase). See Figure 2 for more details.

[b] Entry to the Maintenance Phase requires eligibility as specified in Section 4.3 (Criteria for Entry Into the Maintenance Phase). Each subject's Maintenance Phase dose will be matched by straightforward progression (PP1M to PP1M, or PP3M to PP3M) or will be matched by established conversion (PP1M to PP3M) from the same dose that they had been receiving during the Screening Phase or at the end of the Transition Phase, as applicable. See Figure 3 and Figure 4 for more details.

[c] Randomization will occur on the day of the first double-blind injection (ie, 1 month after the Maintenance Phase injection of PP1M, or 3 months after the Maintenance Phase injection of PP3M). Only subjects who are eligible as specified in Section 4.4 (Criteria for Entry Into the Double-blind Phase) will be randomized.

[d] The Double-blind Phase includes 4 injections for all treatment groups. The active control groups receive 1 injection of PP3M every 3 months. The investigational drug groups receive 1 injection every 3 months in the following sequence: PP6M → placebo → PP6M → placebo. The planned closure will be 12 months after the last subject to be randomized and remain in the study completes 12 months of the Double-blind Phase, which will be marked by completion of Visit 33a The Sponsor will inform the sites when the study is closing and no further dosing should be conducted in the Double-blind Phase.

Note: This figure does not show the Follow-up Phase, which is applicable only to subjects who have received at least 1 dose of double-blind study drug but then have relapsed or have met other relevant conditions for withdrawal or discontinuation, as described in Section 10.2 (Discontinuation of Study Drug / Withdrawal From the Study). The Follow-up Phase ends 12 months after the subject's first double-blind injection,

3.2. Study Design Rationale

Blinding and Control

An active control (PP3M) will be used to determine the sensitivity of the clinical endpoints in this study. Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Double-blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

Additional special blinding conditions are as follows:

- The Sponsor and all study-site personnel will be blinded to the results of PK measurements (as described in Section 9.3.1 [Pharmacokinetic Evaluations]) and prolactin measurements (as described in Section 9.4.2 (Clinical Laboratory Tests).
- The Sponsor and all study-site personnel except for the study drug administrator will be blinded to the administration of the study drug during the Double-blind Phase, as described in Section 5 (Treatment Allocation and Blinding).
- An investigator/subinvestigator who evaluates an injection site should not review the subject's Visual Analog Scale (VAS) ratings of pain associated with the injection site, as described in Section 9.4.8.2 (Injection Site Evaluations and Follow-up by Investigators).
- Cardiologists at the central electrocardiogram (ECG) facility will be blinded to the treatment group assignments of subjects, as described in Section 9.4.3 (Electrocardiograms).
- The Sponsor will be blinded to the interim PK analysis, as described in Section 11.4 (Pharmacokinetic and Pharmacodynamic Analyses).

Study Phases

The phases in this study are similar to phases in the Sponsor's pivotal studies of PP3M (R092670PSY3011 and R092670PSY3012), with incorporation of lessons learned from those studies and feedback from Health Authorities. The early phases of this PP6M study (Screening, Transition, and Maintenance) are similar to Study R092670PSY3012,[9] but with added flexibility (and therefore added complexity) to allow either PP1M→PP6M or PP1M→PP3M→PP6M treatment pathways. The Double-blind Phase of this PP6M study is similar to Study R092670PSY3011,[9] but with more intensive safety assessments around potential peak plasma paliperidone concentrations and more intensive efficacy assessments around potential trough plasma paliperidone concentrations. For a subset of subjects with relapses, study withdrawals, or treatment discontinuations during the Double-blind Phase, a subsequent Follow-up Phase is applicable. The Follow-up Phase in this PP6M study is similar to the Follow-up Visit in Study R092670PSY3011,[9] but with additional visits and assessments to attempt to collect minimum safety data (ie, adverse events) and minimum efficacy data (ie, relapse status) until 12 months after the first double-blind injection, In this way, the Follow-up Phase can provide information about the primary efficacy endpoint for 12 months after a subject's first possible

PP6M injection (see Section 11.3.1.1.3 [Sensitivity Analyses for Primary Efficacy]) and can provide minimum information about efficacy and safety for at least 6 months after a subject's last possible PP6M injection (see Section 10.4 [Process for Planned Study Closure]).

Dose Levels of Paliperidone Palmitate for Eligibility

To be eligible for randomization, subjects must have stability with either PP1M as 100 or 150 mg eq. or PP3M as 350 or 525 mg eq., as described in the inclusion criteria. Both products are available in lower dose levels; the eligible dose levels represent the second-highest and highest available doses of each product. These dose levels are the ones that have been most commonly prescribed in postmarketing experience,[11] and are the ones that were most commonly selected by clinical investigators to achieve stabilization for subjects in the Sponsor's pivotal studies of PP3M (Studies R092670PSY3011 and R092670PSY3012).[8,9] Both pivotal PP3M studies included open-label, flexible-dose, lead-in, 17-week periods with PP1M; the doses of PP1M from those open-label periods then were converted to doses of PP3M for the subsequent double-blind periods. In those studies, the final open-label doses of PP1M were 150 mg eq. for ~40% to ~50% of subjects, 100 mg eq. for ~40% to ~50% of subjects, 75 mg eq. for ≤9% of subjects, and 50 mg eq. for ≤3% of subjects. The large percentages for PP1M as 100 or 150 mg eq. in the open-label periods resulted in similarly large percentages for PP3M as 350 or 525 mg eq. in the double-blind periods. Given the frequent use of these moderate-dose and higher-dose levels in clinical studies and in postmarketing experience, the Sponsor selected these dose levels for eligibility in the current study.

Dose Levels of Paliperidone Palmitate for Investigation

The conversion of doses of PP1M or PP3M in the Maintenance Phase to doses of PP6M in the Double-blind Phase was based on population PK simulations. CCI [redacted]

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).[7] 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.[10] 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.

Site of Administration

Although PP1M and PP3M are approved for administration into either the deltoid or the gluteal muscle, the larger volume associated with a PP6M dose requires injection into the larger gluteal muscle. The PP6M product will be provided in a syringe prefilled with 700 mg eq. (3.5 mL) or 1000 mg eq. (5.0 mL). These volumes are expected to be well tolerated as gluteal injections, for the following reasons:

- The maximum volume is aligned with the guidance in "Intramuscular injections: a review of best practice for mental health nurses," which states that "relatively large doses up to 5 mL can be given."[10]
- The Sponsor's previous Study R092670PSY1005 indicated no clinically meaningful difference in tolerability of the largest-volume dose of PP3M (2.625 mL) versus the smaller doses, by randomly assigned PP3M dose level. Most pain ratings were below 10 mm on a 100-mm scale.
- Paliperidone palmitate is provided as an aqueous suspension, unlike early oil-based LAI antipsychotic formulations that were that were often associated with pain after injection.[6,28]

Benefit-risk Assessment

To consider all endpoints that may have an appreciable effect on the benefit-risk balance, the benefits and risks of PP6M will be assessed using a structured approach to benefit-risk assessment following the principles described both in the Benefit-risk Action Team Framework,

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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 19 June 2017.

[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 19 June 2017.

a general platform for benefit-risk assessment,[25,26] and in the relevant guideline from the International Conference on Harmonisation / International Council for Harmonisation (ICH).[d]

Timing of PK Samples

The PK profile of PP3M has been well characterized. After a single intramuscular injection of PP3M over the dose range of 175 to 525 mg eq., the plasma concentrations of paliperidone gradually rose to a maximum at approximately 30 to 33 days.[7] Similarly, the Sponsor's modeling for PP6M has indicated that the maximum plasma paliperidone concentration at steady state should occur approximately 1 month after injection of PP6M. Therefore, PK sampling (and the associated safety evaluations) are scheduled in this study at weekly time points (ie, more intensive) near the expected peak. Thereafter, the PK sampling is conducted at monthly time points (ie, less intensive) throughout the elimination phase. Finally, the PK sampling (and the associated efficacy evaluations) resumes weekly time points (ie, more intensive) when approaching the end of the 6-month dosing interval.

Overall Study Evaluations

The efficacy, safety, pharmacokinetic, pharmacodynamic, benefit-risk, and exploratory evaluations for PP6M in this study are similar to evaluations for PP3M in the Sponsor's pivotal studies (R092670PSY3011 and R092670PSY3012), with incorporation of lessons learned from those studies. The study evaluations have also incorporated feedback from Health Authorities.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed within the period from 28 to 2 days before the first administration of the study drug.

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.

If a subject does not meet all inclusion criteria (is a screen failure) with respect to dose level, dose duration, or dose timing of prestudy treatment with paliperidone palmitate or injectable risperidone, but at some point in the future is expected to meet these inclusion criteria, then the subject may be rescreened on 1 occasion. Subjects who are rescreened will be assigned a new subject number, will undergo the informed consent process, and then will restart the Screening Phase. Conditions that are permissible for rescreening include the following:

[d] ICH. ICH Harmonized Tripartite Guideline M4E(R2): Revision of M4E guideline on enhancing the format and structure of benefit-risk information in ICH. www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4E_R2_Efficacy/M4E_R2__Step_4.pdf. Dated 15 June 2016. Accessed 19 June 2017.

- Duration/stability of prestudy dosing. For example, if a potential subject has not been treated with the same dose for the minimum amount of time, then the potential subject may return for rescreening after the minimum duration as specified in the inclusion criteria.
- Strength/level of prestudy dosing. For example, if a potential subject is being treated with a dose that is too low for eligibility, but insufficient efficacy with a lower dose means that a higher dose is already planned, then the subject may return for rescreening after being treated with an eligible dose level for the minimum duration as specified in the inclusion criteria.
- Timing of the last prestudy dose. For example, if the last prestudy dose was not within the appropriate window, then the potential subject may return for rescreening at an appropriate time.

If a subject meets any exclusion criteria (is a screen failure) with respect to safety parameters, then rescreening is not allowed. However, retesting may be permitted for results (eg, laboratory or ECG values) that may be transient or inaccurate in the opinion of the investigator. This exceptional and limited retesting of abnormal screening values that lead to exclusion is allowed only once using an unscheduled visit during the Screening Phase, to reassess eligibility.

Rescreening is permitted with the medical monitor's approval for subjects who were withdrawn during the Transition Phase or Maintenance Phase due to an incomplete injection or an unintended dosing or administration of a study drug.

4.1. Inclusion Criteria

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

1. May be either male or female.

2. Must be 18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place) to 70 years of age, inclusive, at the time of informed consent.

3. Must meet the diagnostic criteria for schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) for at least 6 months before screening.

4. Must be receiving treatment with paliperidone palmitate (as either the PP1M or PP3M formulation), or injectable risperidone, or any oral antipsychotic.
   a. If the treatment is paliperidone palmitate, then:
      1) The dose strength must be PP1M as 100 or 150 mg eq. or PP3M as 350 or 525 mg eq.
      2) The dose timing must fit the study schedule. The next injection must be due within 28 days of the first screening (or first rescreening) visit.
   b. If the treatment is injectable risperidone, then the dose strength must be 50 mg, the dosing cycle must be every 2 weeks, the efficacy and tolerability must have been established as adequate with the same strength and frequency for at least 3 injection cycles before screening, and the subject must have a preference for a longer-acting injectable medication.
   c. If the treatment is an oral antipsychotic, then the subject must have a valid reason to discontinue the previous treatment, such as problems with efficacy, safety, or tolerability, or preference for a long-acting injectable medication.

5. Must be able, in the opinion of the investigator, to discontinue any antipsychotic medication other than PP1M or PP3M during the Screening Phase.

6. Must have a full PANSS score of <70 points at screening.

7. Must have a body mass index (BMI) between 17 and 40 kg/m2 (inclusive) and must have a body weight of at least 47 kg at screening.

8. Must be willing to receive gluteal injections of medication during the Double-blind Phase.

9. Must, if a woman of childbearing potential, have a negative highly sensitive serum (β-human chorionic gonadotropin) at screening.

10. Criterion modified per Amendment 1

    10.1 Must use contraception consistent with local regulations for subjects participating in clinical studies. Before receiving study drug, 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 (s*exual 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 drug; 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.
- Agreeing to remain on a highly effective method throughout the study and for at least 12 months after the last dose of study drug. 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 consent to starting a highly effective method of contraception after a negative pregnancy test. If the subject declines consent for start of a highly effective method of contraception, the subject must be withdrawn from the study.

11. Criterion modified per Amendment 3
    11.1 Must, if a man, agree that during the study and for a minimum of 12 months after receiving the last dose of study drug, his female partner(s) will use a highly effective method of contraception as described above, and:
    - 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).
    - He must, if being sexually active with a woman who is pregnant, use a condom.
    - He must agree not to donate sperm.

12. Must 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).

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

14. Must be fluent in the language of the investigator, study staff, and raters.

15. Criterion deleted per Amendment 2.

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

4.2. Exclusion Criteria

1. Must not be receiving any form of involuntary treatment, such as involuntary psychiatric hospitalization, parole-mandated treatment, or court-mandated treatment.

2. Must not have attempted suicide within 12 months before screening and must not be at imminent risk of suicide or violent behavior, as clinically assessed by the investigator at the time of screening.

3. Must not have a DSM-5 diagnosis of moderate or severe substance use disorder (except for nicotine and caffeine) within 6 months of screening; however, acute or intermittent substance use prior to screening is not exclusionary, depending upon the clinical judgment of the investigator.

4. Must not have a history of neuroleptic malignant syndrome or tardive dyskinesia.

5. Must not have a history of intolerability or severe reactions to moderate or higher doses of antipsychotic medications and must not have any other factors that would, in the judgment of the investigator, indicate that treatment with moderate or higher doses of paliperidone palmitate would be intolerable or unsafe.

6. Criterion modified per Amendment 3

   6.1 Must not have been treated with long acting injectable formulations of neuroleptic drugs based on active ingredients other than risperidone or paliperidone (eg, haloperidol decanoate, fluphenazine decanoate, etc) during the 6 months before screening.

7. Criterion modified per Amendment 1

   7.1 Must not have a clinically significant and unstable medical illness in history or at screening, including (but not limited to) cardiac arrhythmias or other cardiac disease, hematologic disease, coagulation disorders (including any abnormal bleeding or blood dyscrasias), significant pulmonary disease including bronchospastic respiratory disease, diabetes mellitus (poorly controlled or requiring insulin), hepatic insufficiency, thyroid disease (poorly controlled based on recent thyroid stimulating hormone [TSH] level), neurologic or other psychiatric disease (except schizophrenia), infection, cancer, or any other illness that the investigator considers should exclude the subject or that could interfere with the interpretation of the efficacy or safety measurements.

8. Must not have a primary, active DSM-5 diagnosis other than schizophrenia (eg, dissociative disorder, bipolar disorder, major depressive disorder, schizoaffective disorder, schizophreniform disorder, autistic disorder, primary substance-induced psychotic disorder) and must not have dementia-related psychosis.

9. Must not have clinically significant abnormal values during screening for hematology, serum chemistry (including aspartate aminotransferase or alanine aminotransferase greater than 2 times the upper limit of normal), or urinalysis, as deemed appropriate by the investigator.

10. Must not have clinically relevant abnormality in the physical examination, vital signs, or 12-lead electrocardiogram (ECG) during screening, as deemed appropriate by the investigator.

11. Must not have known allergies, hypersensitivity, or intolerance to paliperidone palmitate, paliperidone, risperidone, Intralipid (the placebo), or any excipients (refer to the Investigator's Brochure for details) of the formulations, which include soybean oil, egg yolk, phospholipids, and glycerol.

12. Criterion modified per Amendment 1

    12.1 Must not have a history of treatment resistance, defined as failure to respond to 2 adequate trials with adequate doses of different antipsychotic medications (where an adequate trial is defined as a minimum of 4 weeks at a therapeutic dosage), based on the available medical records. Final determination of eligibility is based on investigator judgment.

13. Must not have been treated in the last 2 months with clozapine for treatment-resistant or treatment-refractory illness.

14. Must not have a history of unresponsiveness to (lack of efficacy with) any risperidone or paliperidone products.

15. Must not have a history of intolerance to doses ≥9 mg/day of oral paliperidone or ≥6 mg/day of oral risperidone, where the intolerance was treatment-limiting (ie, leading to discontinuation or reduction of dose).

16. Must not have a history or presence of circumstances that may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including:

    a. Heart rate <50 bpm, based on 12-lead ECG and/or vital signs, on repeated occasions (2 or more times) during the screening and before the first dosing day of the study.
    b. Prolonged QTc interval corrected according to Fridericia's formula (QTcF) >450 msec, based on 12-lead ECG, on repeated occasions (2 or more times) during screening or from prior medical record within the past year).
    c. Cardiac conditions as follows: bradycardia, sick sinus syndrome, complete atrioventricular block, congestive heart failure, or polymorphic ventricular tachycardia.
    d. Electrolyte conditions as follows: clinically relevant hypocalcemia, hypokalemia, or hypomagnesemia.
    e. Concomitant use of drugs that prolong the QTc 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); and some antipsychotics (eg, chlorpromazine or ziprasidone).
    f. Congenital prolongation of the QT interval (Romano-Ward syndrome or Jervell and Lange-Nielsen syndrome).

17. Must not concomitantly use any 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, or St. John's Wort, within 14 days prior to the first screening visit.

18. Must not have any primary movement disorders (such as Parkinson's disease, Huntington's disease, or others) that could, in the investigator's judgment, affect the safety or tolerability for the subject or affect the results of the study.

19. If an oral tolerability test is required (ie, if the subject has no documented tolerability to any oral or injectable risperidone or paliperidone formulations), then the subject must not have a history of any severe pre-existing gastrointestinal narrowing (pathologic or iatrogenic) or inability to swallow oral paliperidone ER/PR tablets whole with the aid of water.

20. Must not have received an investigational drug or have used an invasive investigational medical device within 3 months or within a period less than 5 times the drug's half-life, whichever is longer, before the planned first dose of study drug. This criterion does not apply if the prestudy investigational drug was PP1M or PP3M.

21. Must not, if a woman, be pregnant, breastfeeding, or planning to become pregnant while enrolled in this study or within 12 months after the last dose of study drug.

22. Must not, if a man, have plans to father a child while enrolled in this study or within 12 months after the last dose of study drug.

23. Must not have plans for a surgery or procedures that would interfere with the conduct of the study.

24. Must not be an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.

25. Must not have 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.

26. Must not have moderate to severe renal impairment (ie, those with creatinine clearance as estimated by Cockcroft-Gault of <60 mL/min).

27. Subjects must not have the following:

    - Electroconvulsive therapy (ECT) within 60 days before screening
    - Nonselective/irreversible monoamine oxidase inhibitors (MAOI) antidepressants within 30 days before screening
    - Other antidepressants unless at a stable dosage for 30 days before screening (If the dosage has been stable for less than 30 days and the subject does not require the antidepressant, it can be washed out by the baseline visit; if the dosage has been stable for less than 30 days and the subject requires antidepressant treatment, the subject should not be included in this study)

28. Must not be concomitantly treated with mood stabilizers including lithium, or valproate, or other antiepileptics/anticonvulsants within 14 days of the first screening visit.

29. Must not have been treated with a dopamine agonist (eg, ropinirole or pramipexole) within 90 days of the first screening visit.

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 drug 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 9.1 (Study Procedures), describes options for retesting. Section 17.4 (Source Documentation) describes the required documentation to support meeting the enrollment criteria.

4.3. Criteria for Entry Into the Maintenance Phase

1. On Day 1 of the Maintenance Phase, subjects must have a full PANSS total score of <70 points.

2. Criterion modified per Amendment 2

   2.1. For subjects proceeding from the Transition Phase to the Maintenance Phase, the PP1M dose prior to entering the Maintenance Phase must have been 100 or 150 mg eq. and, in the investigator’s judgment, the subject should continue on the same dose level (ie, either the equivalent PP3M dose [before the PP3M prerandomization target is met] or the same PP1M dose [after the PP3M prerandomization target is met]).

3. For subjects proceeding from the Transition Phase to the Maintenance Phase, they must not have during the Transition Phase:

    a. required psychiatric hospitalization (involuntary or voluntary admission to a psychiatric hospital for decompensation of the subject's schizophrenic symptoms), or

    b. inflicted deliberate self-injury or exhibited violent behavior resulting in suicide, clinically significant injury to him/her self or another person, or significant property damage, or

    c. had suicidal or homicidal ideation and aggressive behavior that is clinically significant (in frequency and severity) in the investigator's judgment

4. For subjects proceeding from the Screening Phase directly to the Maintenance Phase, the PP1M dose or PP3M dose must not be planned for adjustment in the foreseeable future and must have been unchanged in the recent past (as described in "a" and "b" below). The specific dose stability criteria are as follows:

    a. For PP1M, at least 3 months of injections with the last 2 doses being the same strength before the Screening Phase.

    b. For PP3M, at least 1 injection cycle before the Screening Phase.

Subjects who do not meet the criteria above will be withdrawn from the study, will undergo End-of-Phase Visit / Early Withdrawal Visit procedures, and will be treated thereafter according to clinical judgment for acceptable standard of care. If withdrawal is due to an incomplete injection or an unintended dosing or administration of a study drug, rescreening is permissible with the medical monitor's approval.

4.4. Criteria for Entry Into the Double-blind Phase

Eligibility to enter the Double-blind Phase requires all of the following:

1. For the last 2 assessments before randomization (ie, at Visit 6 and Visit 7a/b), subjects must have a PANSS total score of <70 points.

2. For the last 2 assessments before randomization (ie, at Visit 6 and Visit 7a/b), subjects must have scores of ≤4 points for PANSS items P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), P6 (suspiciousness/ persecution), P7 (hostility), G8 (uncooperativeness), and G14 (poor impulse control).

3. Subjects must not, per investigator judgment, have significant EPS despite adequate treatment with anti-EPS medications, based on standard clinical evaluation and information from the Abnormal Involuntary Movement Scale (AIMS) for dyskinesia, the Barnes Akathisia Rating Scale (BARS) for akathisia, and the Simpson Angus Scale (SAS) for parkinsonism.

4. Subjects must not have received any oral antipsychotic supplementation during the Maintenance Phase.

5. Subjects must not have during the Maintenance Phase:

    a. required psychiatric hospitalization (involuntary or voluntary admission to a psychiatric hospital for decompensation of the subject's schizophrenic symptoms), or

    b. inflicted deliberate self-injury or exhibited violent behavior resulting in suicide, clinically significant injury to him/her self or another person, or significant property damage, or

    c. had suicidal or homicidal ideation and aggressive behavior that is clinically significant (in frequency and severity) in the investigator's judgment

Subjects who do not meet the criteria above for entry into the Double-blind Phase will be withdrawn from the study, will undergo End-of-Phase Visit / Early Withdrawal Visit procedures, and will be treated thereafter according to clinical judgment for acceptable standard of care. These subjects do not need to enter the Follow-up Phase, since they do not receive any double-blind treatment. If withdrawal is due to an incomplete injection or an unintended dosing or administration of a study drug, rescreening is permissible with the medical monitor's approval.

4.5. 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. Must follow Section 8.3 (Prohibited Concomitant Medications), regarding prohibited and restricted therapy during the study.

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

3. Must, 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 drug. (Women who have a positive pregnancy test during the study will be withdrawn from the study.)

4. Must, 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 drug.

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 for at least 6 months after completion of the study.

2. Should not participate in an investigational drug study 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 8.3 [Prohibited Concomitant Medications]).

4. Criterion modified per Amendment 3.

   4.1. 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. Deleted per Amendment 3.

6. Deleted per Amendment 2.

5. TREATMENT ALLOCATION AND BLINDING

See also the "Blinding and Control" subheading under Section 3.2 (Study Design Rationale).

Treatment Allocation: Procedures for Randomization and Stratification

At entry into the Double-blind Phase, subjects who had received a moderate dose in the Maintenance Phase will be randomly assigned to 1 of 2 treatment groups (active control or investigational drug as moderate doses) and subjects who had received a higher dose in the Maintenance Phase will be randomly assigned to 1 of 2 treatment groups (active control or investigational drug as higher doses), based on a computer-generated randomization schedule prepared before the study by or under the supervision of the Sponsor. The randomization (2:1 ratio, PP6M:PP3M) will be balanced by using randomly permuted blocks and will be stratified by study site and by moderate or high dose in the Maintenance Phase. Based on this randomization code, the study drug will be packaged and labeled for each subject. Medication kit numbers will be preprinted on the study drug labels and assigned as subjects qualify for the Double-blind Phase and are randomly assigned to treatment.

Central randomization will be implemented in this study. The Interactive Web Response System (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject. Details regarding use of the IWRS will be provided in the IWRS Manual.

Unblinded Study Drug Administrator

Special precautions will be used to reduce potential bias during data collection and evaluation of clinical endpoints. Differences in syringe sizes for PP3M versus PP6M pose a potential for the

study drug administrator to become unblinded to the subject's treatment assignment. The subject and study staff, other than the study drug administrator, should not be allowed to view the syringe or needle or to observe the injection. (The subject must be instructed to look away during the injection and related steps before and after.) To minimize the potential for unblinding, the study drug administrator will be allowed to perform only the following study-related procedures: preparing injections, administering injections, contacting IWRS, receiving subject medication kit numbers, and keeping drug administration and accountability information. The study drug administrator will not be allowed to perform any other study-related procedures (including efficacy, safety, or other study evaluations) or to communicate subject-related information to study-site personnel, including the investigator. If the subject informs the study drug administrator of any adverse events that occurred since the last injection, the subject should be instructed to provide the same information to other study staff. The investigator must explain to the subjects that the only subject-facing role for the study drug administrator is to administer the injections.

In exceptional circumstances, where an assigned study drug administrator is not available to administer study drug, another adequately trained investigational staff member may administer study drug during the Maintenance Phase only. As with the study drug administrator, any other person responsible for study drug administration will not be allowed to perform any other study-related procedures (including efficacy, safety, or other study evaluations) or to communicate subject-related information to study-site personnel, including the investigator.

Blinding: Investigational Staff

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual subject.

Data that may potentially unblind the treatment assignment (ie, study drug serum concentrations or prolactin levels) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

The investigator/subinvestigator who assesses the injection site for tenderness, erythema/redness, and induration/swelling should not review the subject's VAS rating of the injection site pain. (This is not applicable to other study-site personnel.)

Intentional Unblinding

Under normal circumstances, the blind should not be broken until all subjects have completed the study and the database is finalized. Otherwise, the blind should be broken only if specific emergency treatment or emergent course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator or designee may in an emergency determine the identity of the treatment by contacting the IWRS. It is recommended that the investigator contact the Sponsor or its designee if possible to discuss the particular situation, before breaking

the blind. Telephone contact with the Sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the Sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented in the appropriate section of the electronic Case Report Form (eCRF) and in the source document. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner. Subjects who have had their treatment assignment unblinded should be withdrawn from the study.

6. DOSAGE AND ADMINISTRATION

6.1. Dosage

6.1.1. Screening Phase

During the Screening Phase, subjects must have already been receiving PP1M at 100 or 150 mg eq., PP3M at 350 or 525 mg eq., injectable risperidone at 50 mg, or an oral antipsychotic at any dosage with a reason to change, as described in Section 4.1 (Inclusion Criteria).

If subjects have no documented tolerability to any oral or injectable risperidone or paliperidone formulations, then an oral tolerability test should be conducted. To demonstrate oral tolerability, paliperidone ER/PR 6 mg tablets or risperidone 3 mg/day (dose may be divided) will be given during the Screening Phase for 4 to 6 consecutive days with the last dose swallowed on or before Day -1. The recommended dose is paliperidone ER/PR of 6 mg/day or risperidone 3 mg/day (dose may be divided), but higher doses of paliperidone or risperidone may be used if clinically indicated, based on investigator judgment. Oral tolerability testing may be concurrent with any required washout of other medications. Tapering of oral tolerability medication during this period is not required. Subjects should be instructed not to chew, divide, dissolve, or crush the paliperidone ER/PR tablets, since an effect on the release profile is possible. The oral tolerability test will allow the investigator to assess possible problems with tolerability (including allergic or hypersensitivity reactions) that may be related to paliperidone. Examples of problems that would lead to exclusion of the subject would include intolerable sedation, clinically symptomatic orthostatic hypotension, torticollis or other severe EPS, or evidence of an allergic reaction.

For subjects with previously established tolerability to at least 1 oral or injectable risperidone or paliperidone formulation, the appropriate documentation may include medical or pharmacy records, a letter from a previous provider, or a written statement by the investigator of a credible report from the subject or subject's identified support person. These records must be filed in the source documents.

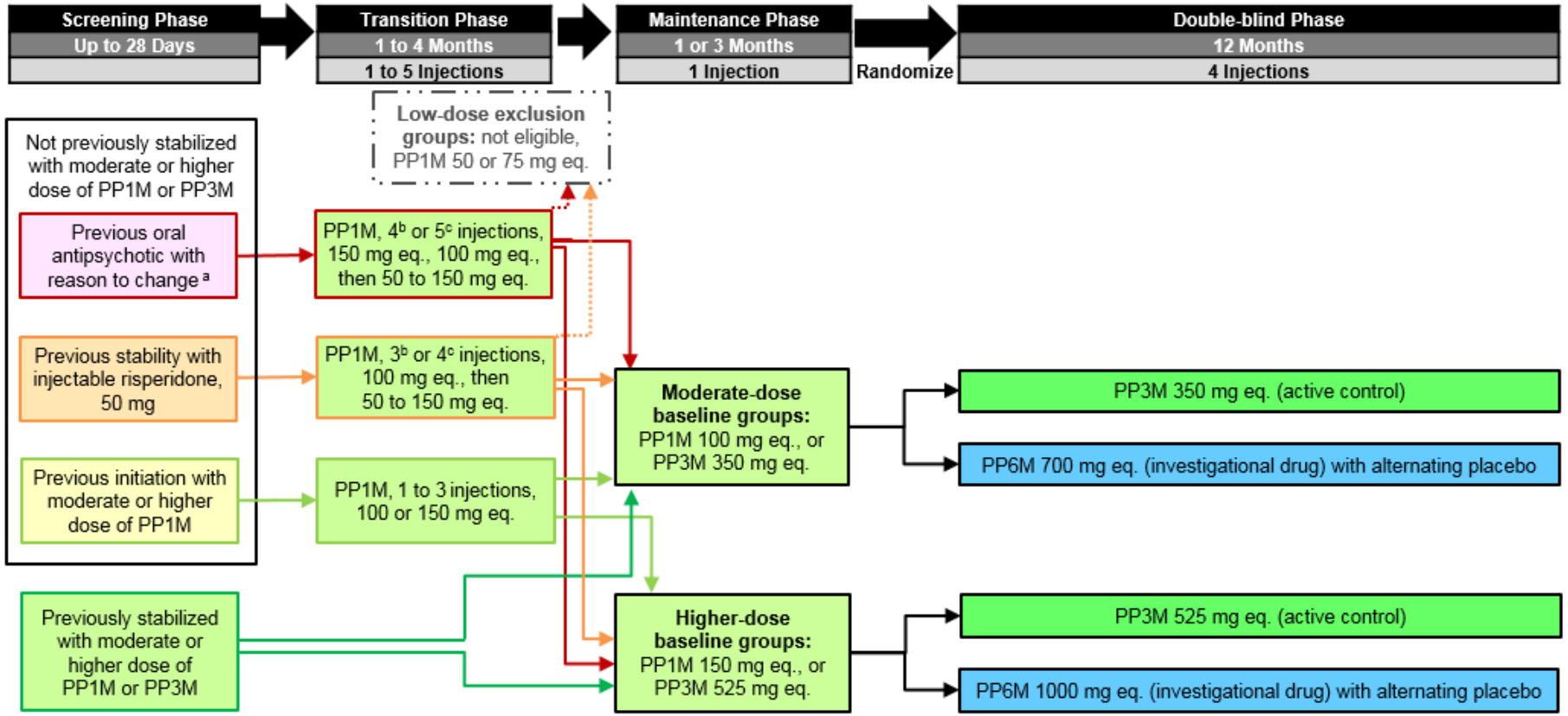
6.1.2. Transition Phase

The Transition Phase is applicable only to subjects who entered the Screening Phase without previous PP1M or PP3M stability. These subjects may have been previously treated with oral antipsychotics, injectable risperidone, or a moderate or higher dose of PP1M with previous initiation but without previous stabilization (where stabilization is defined is at least 3 months of injections with the last 2 doses being the same strength), as shown in Figure 2 and as described below. In order to appropriately balance study groups at the Double-blind Phase baseline and to

complete the study in a timely manner, the pathway to study enrollment that includes the Transition Phase will be open for only a limited time. The Sponsor will inform the sites when this pathway and this phase have closed to enrollment.

See also Section 6.2.1 (Administration During the Open-label Phases).

Figure 2: Schematic Overview, Showing Additional Details for the Screening Phase and Transition Phase; Study R092670PSY3015



Key: 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).

[a] If subjects in this group have no documented tolerability to any oral or injectable risperidone or paliperidone formulations, then an oral tolerability test should be conducted during the Screening Phase.

[b] After meeting the PP3M prerandomization target.

[c] Before meeting the PP3M prerandomization target.

Note: See Figure 1 for other relevant explanatory notes.

Transition Phase: Subjects Previously Treated With Oral Antipsychotics

In the Transition Phase, subjects previously treated with oral antipsychotics will receive PP1M as 150 mg eq. on Day 1 and 100 mg eq. on Day 8. Thereafter, the PP1M doses on Days 36, 64, and 92 will be flexible (as 50, 75, 100, or 150 mg eq.), based on clinical judgment and shared decision-making. Days 1, 8, 36, 64, and 92 correspond to Visits 2a, 2b, 2c, 2d, and 2e, respectively (see Table 3 and Table 4). Administration should be in the deltoid muscle on Days 1 and 8 and may be either in the deltoid or gluteal muscles on Days 36, 64, and 92, as shown in Table 3 and Table 4.

After the PP3M prerandomization target is met, these subjects will skip Visit 2e and proceed to Visit 2f if the subject is eligible to enter the Maintenance Phase (see Section 4.3, Criteria for Entry Into the Maintenance Phase). If not eligible to enter the Maintenance Phase, the subject will be withdrawn from the study.

If a subject was previously treated with oral paliperidone ER/PR tablets and had acceptable efficacy and tolerability, then the Day 36 dose of PP1M may be based on the conversion provided in Table 2. If the previous dosage of oral paliperidone had insufficient efficacy, then the investigator may consider a higher dosage of PP1M. If the previous dosage of oral paliperidone caused problems with intolerability, then the investigator may consider a lower dosage of PP1M.

Table 2: Doses of Paliperidone ER/PR Tablets and PP1M Needed to Attain Similar Steady-state Paliperidone Exposure

Previous Paliperidone ER/PR Tablet, Once Daily	PP1M Injection, Once Every 4 Weeks
12 mg	150 mg eq.
9 mg	100 mg eq.
6 mg	75 mg eq.
3 mg	50 mg eq.

Key: ER/PR = extended-release/prolonged-release; mg eq. = (paliperidone palmitate) milligrams equivalent (to paliperidone); PP1M = paliperidone palmitate 1-month (product).
Source: Adapted from the United States Prescribing Information for PP1M.[e] the lowest dose of PP1M is omitted because it is not relevant to this study.

Transition Phase: Subjects Previously Stabilized on Injectable Risperidone (Biweekly – Risperdal CONSTA™ formulation, also named as RISPERDAL CONSTA 50 mg powder and solvent for prolonged-release suspension for injection formulation in certain countries)

In the Transition Phase, subjects previously stabilized on injectable risperidone 50 mg are not required to attend the Day 1 visit. On the Day 8 visit, when the subject's next planned injectable risperidone dose would have been administered (ie, 14±3 days after the last prestudy dose), PP1M 100 mg eq. is administered instead. (This conversion scheme is established in the

[ee] INVEGA SUSTENNA® [United States Prescribing Information]. Titusville, NJ: Janssen Research & Development. www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=022264. Accessed 19 June 2017.

prescribing information of some countries.[f]) Thereafter, the PP1M doses on Days 36, 64, and 92 will be flexible (50, 75, 100, or 150 mg eq.), based on clinical judgment and shared decision-making. Administration should be in the deltoid muscle on Day 8 and may be either in the deltoid or gluteal muscles on Days 36, 64, and 92, as shown in Table 3 and Table 4.

After the PP3M prerandomization target is met, these subjects will skip Visit 2e and proceed to Visit 2f, if eligible to enter the Maintenance Phase (see Section 4.3, Criteria for Entry Into the Maintenance Phase). If not eligible to enter the Maintenance Phase, the subject will be withdrawn from the study.

Transition Phase: Subjects Previously Initiated (But Not on a Stable Regimen) With Moderate or Higher Doses of PP1M (Invega Sustenna ™ or Xeplion ™ formulation)

In the Transition Phase, subjects who entered the study on PP1M as 100 or 150 mg eq., but who do not yet meet criteria for stabilization with those doses, are treated with additional doses of PP1M during the Transition Phase, as shown in Table 3 and Table 4.

After the PP3M prerandomization target is met, subjects previously initiated on PP1M (but not on a stable regimen) who enter the study at Visit 2c or 2d will skip Visit 2e and proceed to Visit 2f, if eligible to enter the Maintenance Phase (see Section 4.3, Criteria for Entry Into the Maintenance Phase). Subjects with ≥4 prestudy PP1M injections with the last 2 doses being the same strength will enter the study at Visit 2f. Subjects with ≥4 prestudy PP1M injections with the last 2 doses being different (ie, do not have dose stability) will enter the study at Visit 2e. If not eligible to enter the Maintenance Phase, the subject will be withdrawn from the study.

Owing to potential differences in release characteristics, only subjects who are taking Invega Sustenna ™ or Xeplion ™ PP1M formulations will be permitted to enter this phase of the study. Subjects who are taking non-branded formulations of once monthly paliperidone LAI or other once monthly LAIs will not be permitted to enter this phase.

[f] XEPLION® [European Union Product Information]. Beerse, Belgium: Janssen-Cilag International. www.ema.europa.eu/ema/index.jsp%3Fcurl%3Dpages/medicines/human/medicines/002105/human_med_001424.jsp. Accessed 19 June 2017.

Table 3: Dosage and Administration Schedule for PP1M During the Transition Phase (Before Meeting the PP3M Prerandomization Target); Study R092670PSY3015

Phase	Screening	Transition; PP1M				
Visit Number (of Study)	**1**	**2a**	**2b**	**2c**	**2d**	**2e**
Day (of Phase) [a]	**-28 to -2**	**1**	**8**	**36 or EW**	**64 or EW**	**92 or EW** [b]
Visit Window, ±Days		**n/a**	**±3**	**±7**	**±7**	**±7**
PP1M after prestudy oral antipsychotic						
Treatment/dose	Last prestudy dose of oral antipsychotic	150 mg eq.	100 mg eq.	50,[c] 75, 100, or 150 mg eq.	50,[d] 75,[d] 100, or 150 mg eq.	50,[d] 75,[d] 100, or 150 mg eq.
Injection site	not applicable	D	D	D or G	D or G	D or G
Day (of participation) [a]	-28 to -2	1st	8th	36th	64th	92nd
PP1M after prestudy injectable risperidone						
Treatment/dose	Last prestudy dose of injectable risperidone, 50 mg	Skip	100 mg eq.	50, 75, 100, or 150 mg eq.	50,[d] 75,[d] 100, or 150 mg eq.	50,[d] 75,[d] 100, or 150 mg eq.
Injection site	D or G	Skip	D	D or G	D or G	D or G
Day (of participation) [a]	-14 to -2	Skip	1st [e]	29th	57th	85th
PP1M after 2 prestudy PP1M injections						
Treatment/dose	Last prestudy dose of PP1M, 100 or 150 mg eq.	Skip	Skip	100 or 150 mg eq.	100 to 150 mg eq.	100 to 150 mg eq.
Injection site	D or G	Skip	Skip	D or G	D or G	D or G
Day (of participation) [a]	-28 to -2	Skip	Skip	1st [f]	29th	57th
PP1M after 3 prestudy PP1M injections						
Treatment/dose	Last prestudy dose of PP1M, 100 or 150 mg eq.	Skip	Skip	Skip	100 or 150 mg eq.	100 or 150 mg eq.
Injection site	D or G	Skip	Skip	Skip	D or G	D or G
Day (of participation) [a]	-28 to -2	Skip	Skip	Skip	1st [f]	29th
PP1M after ≥4 prestudy PP1M injections [g]						
Treatment/dose	Last prestudy dose of PP1M, 100 or 150 mg eq.	Skip	Skip	Skip	Skip	100 or 150 mg eq.
Injection site	D or G	Skip	Skip	Skip	Skip	D or G
Day (of participation) [a]	-28 to -2	Skip	Skip	Skip	Skip	1st [f]

(See Keys below Table 4)

Table 4: Dosage and Administration Schedule for PP1M During the Transition Phase (After Meeting the PP3M Prerandomization Target); Study R092670PSY3015

Phase	Screening	Transition; PP1M				
Visit Number (of Study)	**1**	**2a**	**2b**	**2c**	**2d**	**2e**
Day (of Phase) [a]	**-28 to -2**	**1**	**8**	**36 or EW**	**64 or EW**	**92 or EW** [b]
Visit Window, ±Days		**n/a**	**±3**	**±7**	**±7**	**±7**
PP1M after prestudy oral antipsychotic						
Treatment/dose	Last prestudy dose of oral antipsychotic	150 mg eq.	100 mg eq.	50,[c] 75, 100, or 150 mg eq.	50,[d] 75,[d] 100, or 150 mg eq.	
Injection site	not applicable	D	D	D or G	D or G	
Day (of participation) [a]	-28 to -2	1st	8th	36th	64th	Skip
PP1M after prestudy injectable risperidone						
Treatment/dose	Last prestudy dose of injectable risperidone, 50 mg	Skip	100 mg eq.	50, 75, 100, or 150 mg eq.	50,[d] 75,[d] 100, or 150 mg eq.	
Injection site	D or G	Skip	D	D or G	D or G	
Day (of participation) [a]	-14 to -2	Skip	1st [e]	29th	57th	Skip
PP1M after 2 prestudy PP1M injections						
Treatment/dose	Last prestudy dose of PP1M, 100 or 150 mg eq.	Skip	Skip	100 or 150 mg eq.	100 to 150 mg eq.	
Injection site	D or G	Skip	Skip	D or G	D or G	
Day (of participation) [a]	-28 to -2	Skip	Skip	1st [f]	29th	Skip
PP1M after 3 prestudy PP1M injections						
Treatment/dose	Last prestudy dose of PP1M, 100 or 150 mg eq.	Skip	Skip	Skip	100 or 150 mg eq.	
Injection site	D or G	Skip	Skip	Skip	D or G	
Day (of participation) [a]	-28 to -2	Skip	Skip	Skip	1st [f]	Skip
PP1M after ≥4 prestudy PP1M injections [g]						
Treatment/dose	Last prestudy dose of PP1M, 100 or 150 mg eq.	Skip	Skip	Skip	Skip	Skip or 100 or 150 mg eq.
Injection site	D or G	Skip	Skip	Skip	Skip	D or G
Day (of participation) [a]	-28 to -2	Skip	Skip	Skip	Skip	1st [f]

Keys for Table 3 and Table 4: D = deltoid muscle; EW = Early Withdrawal; G = gluteal muscle; mg eq. = (paliperidone palmitate) milligrams equivalent (to paliperidone); PP1M = paliperidone palmitate 1-month (formulation).

[a] Because some subjects skip visits during the Transition Phase, the day of the phase will not match the day of a subject's participation in all cases, as shown in this table.

[b] Dose flexibility is permitted at this visit in order to accommodate individual needs for efficacy and tolerability, but if the dose at Day 92 is not the same as the dose at Day 64, then the subject will later be ineligible to proceed to the next phase, as described in Section 4.3 (Criteria for Entry Into the Maintenance Phase). If the dose at Day 92 is not the same as the dose at Day 64, then study-site personnel should anticipate the future ineligibility of the subject and should conduct the Day 92 visit as an Early Withdrawal Visit. See Section 10.2 (Discontinuation of Study Drug / Withdrawal From the Study).

[c] The 50 mg eq. dose is permitted at this visit in order to accommodate individual needs for efficacy and tolerability, but use of the 50 mg eq. dose at this visit shows that a subject is unlikely to later achieve the 100 or 150 mg eq. dose required for eligibility to proceed to the next phase, as described in Section 4.3 (Criteria for Entry Into the Maintenance Phase). If the 50 mg eq. dose is administered, then study-site personnel should anticipate the future ineligibility of the subject and should conduct the visit as an Early Withdrawal Visit. See Section 10.2 (Discontinuation of Study Drug / Withdrawal From the Study).

[d] The 50 and 75 mg eq. doses are permitted at these visits in order to accommodate individual needs for efficacy and tolerability, but use of these doses at these visits shows that subjects will later be ineligible to proceed to the next phase, as described in Section 4.3 (Criteria for Entry Into the Maintenance Phase). If these doses are administered, then study-site personnel should anticipate the future ineligibility of the subject and should conduct the visit as an Early Withdrawal Visit. See Section 10.2 (Discontinuation of Study Drug / Withdrawal From the Study).

[e] This visit should be scheduled to match the subject's next planned injectable risperidone dose (ie, 14±3 days after the last prestudy dose).

[f] This visit should be scheduled to match the subject's next planned PP1M dose (ie, 30±7 days after the last prestudy dose).

[g] Subjects with ≥4 prestudy PP1M injections may be eligible to skip the Transition Phase and proceed from the Screening Phase directly to the Maintenance Phase, if they have already achieved dose stability as described in Section 4.3 (Criteria for Entry Into the Maintenance Phase). If they have not, then the dose in this Transition Phase can be used to establish dose stability.

6.1.3. Maintenance Phase

For all subjects, the Maintenance Phase includes only 1 dose of PP1M as 100 or 150 mg eq. or PP3M as 350 or 525 mg eq. Each subject's Maintenance Phase dose will be matched by straightforward progression (PP1M to PP1M, or PP3M to PP3M) or will be matched by established conversion (PP1M to PP3M) to the same dose that they had been receiving during the Screening Phase or at the end of the Transition Phase. Progression versus conversion will depend on prestudy treatment types and on the need to balance the PP1M and PP3M groups in the Maintenance Phase, as described below.

To properly characterize outcomes when switching to PP6M from either PP1M or PP3M, adequate numbers of subjects treated with either PP1M or PP3M must be available during the Maintenance Phase for randomization to the Double-blind Phase. However, low enrollment of subjects previously treated with PP3M is expected. To address this issue, some subjects (after appropriate treatment with PP1M) will be switched to PP3M during the Maintenance Phase. This will occur early in the course of the study, until the target of approximately one-half of the total Maintenance Phase sample is treated with PP3M. In this document, the target is referred to as the "PP3M prerandomization target." The process is described in more detail below and is shown in Figure 3 and Figure 4.

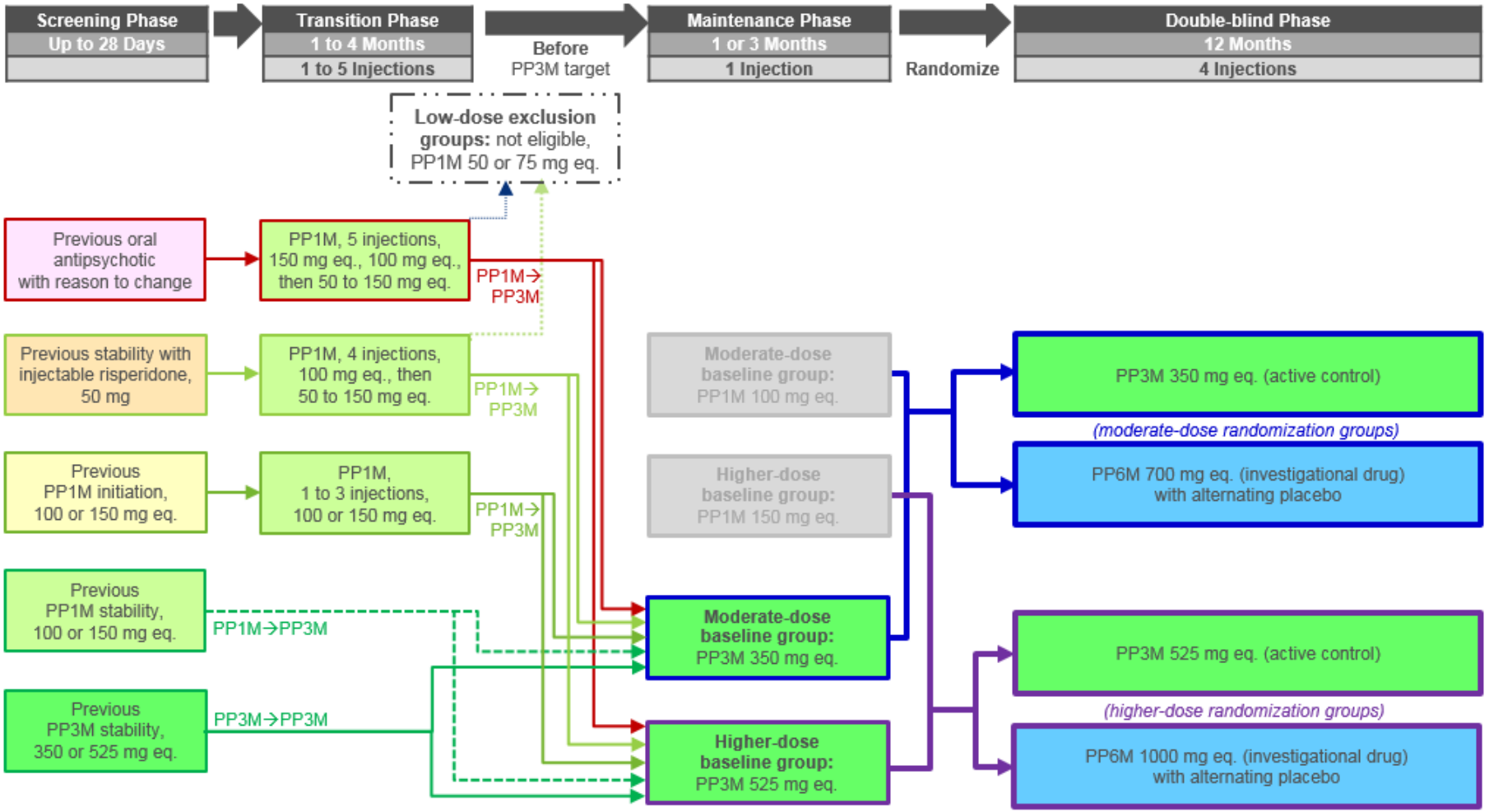
- **Throughout the study,** subjects who were receiving PP3M as 350 or 525 mg eq. before the study will receive the same formulation and strength in the Maintenance Phase.
- **Early in the study (before the PP3M prerandomization target is met),** subjects with PP1M stability achieved before the study or during the Transition Phase will be converted to PP3M in the Maintenance Phase in accordance with the approved prescribing information. That is, subjects who were receiving PP1M as 100 or 150 mg eq. will receive PP3M as 350 or 525 mg eq. See Figure 3. The Sponsor will inform sites when they should stop using this pathway.
- **Later in the study (after the PP3M prerandomization target is met),** subjects with PP1M stability achieved before the study or during the Transition Phase will progress with PP1M in the Maintenance Phase. That is, subjects who were receiving PP1M as 100 or 150 mg eq. will again receive PP1M as 100 or 150 mg eq. See Figure 4 The Sponsor will inform sites when they should start using this pathway.

For subjects who enter the study with previous PP1M or PP3M stability, the dose in the Maintenance Phase should be administered with timing appropriate to the subject's last prestudy dose (ie, 30±7 days after the last prestudy PP1M dose, or 90±14 days after the last prestudy PP3M dose). In order to appropriately balance the number of PP1M and PP3M subjects in the Maintenance Phase and to complete the study in a timely manner, the pathway to study enrollment that includes subjects who enter the study with previous PP3M stability will be open for only a limited time. The Sponsor will inform the sites when this pathway has closed to enrollment.

For subjects who enter the study without previous PP1M or PP3M stability, the dose in the Maintenance Phase should similarly be administered with timing appropriate to the subject's last dose in the preceding Transition Phase (ie, 28±3 days after previous PP1M dose).

See also Section 6.2.1 (Administration During the Open-label Phases).

Figure 3: Schematic Overview, Showing Additional Details for the Maintenance Phase (Before Meeting the PP3M Prerandomization Target); Study R092670PSY3015

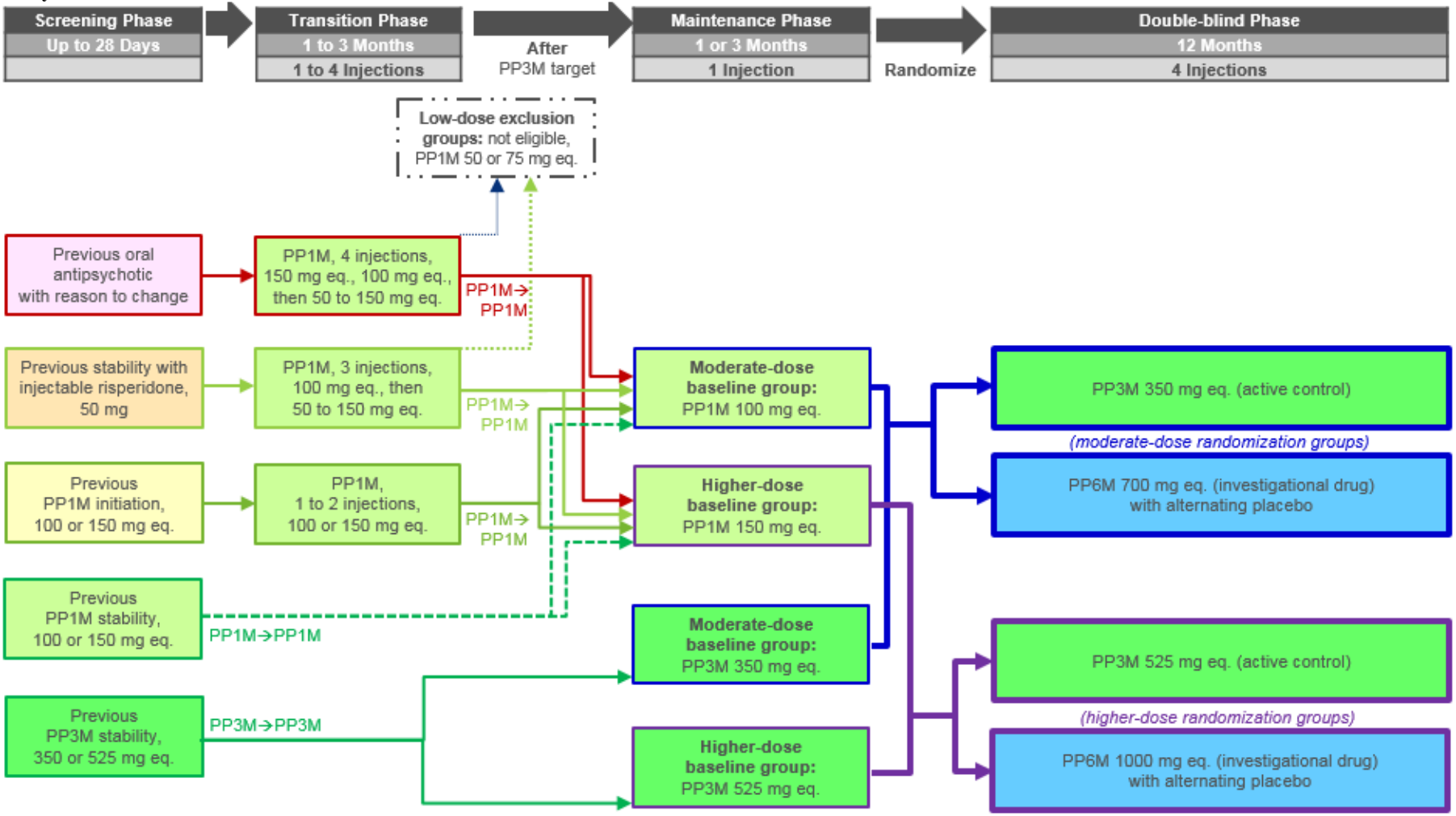


Key: mg eq. = (paliperidone palmitate) milligrams equivalent (to paliperidone); PP1M = paliperidone palmitate 1-month (product); PP3M = paliperidone palmitate 3-month (product); PP6M = paliperidone palmitate 6-month (product).

Note: See Figure 1 and Figure 2 for other relevant explanatory notes.

Note: The grayed-out treatment pathway in the Maintenance Phase is not applicable before the meeting the PP3M prerandomization target, but is shown here for consistency with other figures, especially Figure 4. Of subjects entering the Double-blind Phase, the prerandomization targets are approximately one-half entering from a PP3M group, and one-half entering from a PP1M group.

Figure 4: Schematic Overview, Showing Additional Details for the Maintenance Phase (After Meeting the PP3M Prerandomization Target); Study R092670PSY3015



Key: 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).

Note: See Figure 1 and Figure 2 for other relevant explanatory notes.

Note: Of subjects entering the Double-blind Phase, the prerandomization targets are approximately one-half entering from a PP3M group, and one-half entering from a PP1M group.

6.1.4. Double-blind Phase

The PP1M and PP3M dose levels that were administered in the Maintenance Phase will be converted to PP3M or PP6M dose levels for the Double-blind Phase as follows:

- For the active control group,

The open-label PP1M doses (100 or 150 mg eq.) will be converted to double-blind PP3M doses (350 or 525 mg eq.) in accordance with the approved prescribing information for PP3M.

The open-label PP3M doses (350 or 525 mg eq.) will continue at the same double-blind dose level.

- For the investigational drug group,

The open-label 100 mg eq. PP1M and 350 mg eq. PP3M doses will be converted to double-blind 700 mg eq. PP6M doses.

The open-label 150 mg eq. PP1M and 525 mg eq. PP3M doses will be converted to double-blind 1000 mg eq. PP6M doses.

To maintain the blind, the subjects who are assigned to treatment with PP6M will receive injections of placebo at the 3-month time points between their 6-month doses of investigational drug. The placebo is 20% Intralipid® (200 mg/mL) injectable emulsion. Therefore, the 12 month Double-blind Phase should include a total of 4 doses at 3-month intervals, no matter which treatment group.

Conversions between doses are summarized in Table 1. The actual dates and times of each study drug administration will be recorded in the eCRF.

6.1.5. Treatment After the Study or in the Follow-up Phase

See Section 10.3 (Antipsychotic Therapy After the Study or in the Follow-up Phase). Such treatments are nonstudy treatments and therefore are not described here.

6.2. Administration

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.

6.2.1. Administration During the Open-label Phases

During the Transition Phase and Maintenance Phase, injections will be in the deltoid or gluteal muscles in accordance with the prescribing information for PP1M or PP3M, and will use injection kits equivalent to commercially available kits. For the Transition Phase, see also Table 3 and Table 4 for more information about sites (deltoid or gluteal). For the Maintenance Phase, the injection may be in the deltoid or gluteal muscle (note: Day 1 injection should not be

administered at the same site as the last injection), but may not be in the left gluteal muscle (because of the anticipated left gluteal injection at the beginning of the Double-blind Phase, as shown in Table 5).

6.2.2. Administration During the Double-blind Phase

During the Double-blind Phase, injections will be in the gluteal muscles only, will use study-specific injection kits, and will rotate across sides of the body as described in Table 5.

Table 5: Administration of Study Agent During the Double-blind Phase; Study R092670PSY3015

Time Point in Double-blind Phase	Day 1	Day 92	Day 183	Day 274
Double-blind Injection	First	Second	Third	Fourth
Active Control Groups				
Agent	PP3M	PP3M	PP3M	PP3M
Body side	Left	Right	Right	Left
Investigational Groups				
Agent	PP6M	Placebo	PP6M	Placebo
Body side	Left	Right	Right	Left

Key: PP3M = paliperidone palmitate 3 month (product); PP6M = paliperidone palmitate 6 month (product).
Note: All administrations are gluteal during the Double-blind Phase.

See Attachment 1 for more details about administration during the Double-blind Phase.

7. TREATMENT COMPLIANCE

The study drug 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, and deltoid or gluteal muscle) in the eCRF.

8. PRESTUDY AND CONCOMITANT THERAPY

8.1. Prestudy Medical Therapy and Psychotherapy

Except as described in Section 4.2 (Exclusion Criteria), Section 4.5 (Prohibitions and Restrictions), Section 8.2 (Concomitant Therapy), and Section 8.3 (Prohibited Concomitant Medications), medications that are ongoing and stable at screening may be allowed to continue thereafter into the study. Ongoing psychotherapy and other psychosocial interventions are allowed to continue. For psychiatric medications of special interest at study entry:

- Antipsychotics: Other than PP1M or PP3M, no concomitant antipsychotic medications being used at screening are allowed to continue. Oral antipsychotics, including those being taken concomitantly with PP1M or PP3M, should be tapered and discontinued during the Screening Phase, with the last oral dose swallowed on or before Day -1. The appropriate tapering and washout schedule is at the discretion of the treating physician. Note that subjects who enter the study on oral antipsychotic(s) alone (without PP1M or PP3M being used concomitantly) must have a valid reason to discontinue the oral antipsychotic(s), such

as problems with efficacy, safety, or tolerability, or preference for a LAI medication, as described in Section 4.1 (Inclusion Criteria).

- 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

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; nonpharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) administered and/or used within 90 days of the first study drug dose, at entry, and throughout the study must be recorded in the eCRF. For subjects with prior PP3M stability, the date of the last prestudy dose would be 90±14 days prior to the first study drug dose, so its last date of administration must be recorded, even if >90 days from the first study drug dose. The study drug is not recorded as concomitant therapy in the eCRF. Recorded information will include a description of the type of drug, start and end dates of treatment, dosing regimen, and indication. Modification of an effective pre-existing therapy should not be made for the explicit purpose of entering a subject into the study.

Except as listed in Section 4.2 (Exclusion Criteria) and Section 8.3 (Prohibited Concomitant Medications), concomitant medications may be initiated during the study for medical or psychiatric reasons. New psychotherapies and psychosocial treatments may be started.

- Anti-EPS medications: For antiparkinsonism medications, initiations or changes should be preceded by an AIMS, BARS, and SAS (even if not designated per Time and Events Schedules). If beta-adrenergic blockers or benzodiazepines are given for akathisia, then initiations or changes should be preceded by a BARS (even if not designated per Time and Events Schedules). See Section 9.4.6 (Extrapyramidal Symptoms). 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. If lorazepam is unavailable, then another equivalent short-acting benzodiazepine may be used; examples of allowed types and dosages are shown in Table 6, and others are similarly allowed per clinical judgment. Long-acting benzodiazepines (specifically, chlordiazepoxide, flurazepam, diazepam, and clorazepate) are prohibited. Investigators are encouraged to use the lowest dose of benzodiazepine that is clinically necessary. Benzodiazepines must not be used in the 8 hours preceding any scheduled efficacy assessment or rating scale. If clinically needed, an injectable (intramuscular or intravenous) dose of lorazepam may be given through the first 4 weeks of study participation.

  If benzodiazepines were used regularly during the Screening Phase, then the benzodiazepine treatment should be tapered in accordance with the maximum dosages stated in Table 6. Use of benzodiazepine dosages higher than the stated in the table must be approved by the medical monitor prior to dose increase.

Table 6: Maximum Allowable Benzodiazepine Daily Dosages; Study R092670PSY3015

Benzodiazepine	Approximate Equivalent Oral Dose, mg	Maximum Daily Dosage (mg/day)		
		Screening Phase and First 4 Weeks of Study Participation	Second 4 Weeks of Study Participation	After 8 Weeks of Study Participation, Through End-of-Study Visit
Preferred				
Lorazepam	6	6	3	2
Other				
Clonazepam	3	3	1.5	1
Temazepam	90	90	45	30

If benzodiazepines are being initiated or changed for the treatment of akathisia, then a BARS should be conducted first (even if unscheduled), as described in Section 9.4.6.2 (Barnes Akathisia Rating Scale).

- 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. The frequency should not exceed once daily and the duration should not exceed 7 consecutive days without reassessment. Sleep aid medications should not be used in the 8 hours preceding any scheduled efficacy assessment or rating scale.

8.3. Prohibited Concomitant Medications

- The concomitant medications described below may not be used during the study. Concomitant oral and injectable antipsychotics are prohibited as follows:

After the Screening Phase, oral or injectable risperidone formulations and supplementary oral or injectable paliperidone formulations are prohibited.

During the Maintenance Phase, if any oral antipsychotic is required, then the subject is not eligible to continue to randomization.

During the Double-blind Phase, if any oral antipsychotic is required, then the subject should be evaluated according to parameters in Section 2.1.2.2 (Relapse Criteria).

During any phase (including the Screening Phase, during determination of eligibility), injectable formulations of neuroleptic drugs based on active ingredients other than risperidone or paliperidone (eg, haloperidol decanoate, fluphenazine decanoate, etc) are prohibited.

Concomitant antipsychotics are prohibited even if they are used for nonpsychotic indications (eg, nausea, sleep, depression, etc).

Although concomitant antipsychotics are prohibited during the study as described above, these medications may be initiated at the discretion of the investigator if considered necessary for the safety or wellbeing of the subject. If a concomitant antipsychotic is initiated, then:

- Section 2.1.2.2 (Relapse Criteria) is relevant if the subject is completing the study related to the need for an antipsychotic, or
- Section 10.2 (Discontinuation of Study Drug / Withdrawal From the Study) is relevant if the subject is withdrawing from the study related to the need for an antipsychotic.

- 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); and some antipsychotics (eg, chlorpromazine or ziprasidone) and tricyclic anti-depressants are prohibited. (All concomitant antipsychotics are prohibited for reasons related to assessment of efficacy as described in the bullet points above, but antipsychotics that prolong the QT interval are specifically restated here due to relevance to safety.)
- 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.
- Long-acting benzodiazepines (specifically, chlordiazepoxide, flurazepam, diazepam, and clorazepate) are prohibited.
- Mood stabilizers and anticonvulsants including, but not limited to: lithium, valproate, lamotrigine, carbamazepine, phenytoin, and gabapentin.
- Antidepressants not taken at a stable dosage for 30 days before screening, and all nonselective/irreversible MAOIs. Throughout the study, an antidepressant (other than a nonselective MAOI) may be initiated in rare circumstances only after consultation with the Medical Monitor.
- Any prescription, herbal, or over-the-counter agents with psychotropic actions, including any substances with stimulant and cognitive-enhancing properties.
- Dopamine agonists, including, but not limited to: ropinirole, pramipexole, pergolide, cabergoline, lisuride and amantadine.
- Nonantipsychotic dopamine antagonists, including, but not limited to, antiemetic medications with dopamine-blocking activity.

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 Schedules summarize the frequency and timing of measurements applicable to this study. If multiple assessments are scheduled for the same visit, then ECG and vital signs should be collected prior to blood sample collections (eg, PK, and/or laboratory tests) and blood sample collections should be collected prior to study drug injection. Evaluations of the injection site occur after study drug injection, as described in Section 9.4.8. Actual dates and times of assessments will be recorded in the source documentation.

Beyond timing specified in the Time and Events Schedules, additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

For any 6 months of participation in the study, the total blood volume to be collected from each subject is expected to be less than 400 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Screening Phase

Screening procedures are outlined in the Time and Events Schedules and in associated text descriptions. For exclusion criteria relating to safety parameters, rescreening is not allowed, but retesting may be permitted, as described in Section 4 (Subject Population). For inclusion criteria related to prestudy medication parameters, rescreening is permitted once, as described in Section 4 (Subject Population).

Transition Phase

The Transition Phase is applicable only to subjects who entered the Screening Phase without previous PP1M or PP3M stability. These subjects may have been previously treated with oral antipsychotics, injectable risperidone, or a moderate or higher dose of PP1M with previous initiation but without previous stabilization (where stabilization is defined is at least 3 months of injections with the last 2 doses being the same strength). During this phase, subjects will be initiated and/or stabilized on PP1M, as shown in the relevant Time and Events Schedule and in associated text descriptions. At the end of this phase, subjects with adequate efficacy and tolerability on PP1M as 100 or 150 mg eq. may be eligible to continue to the Maintenance Phase (see Section 4.3 [Criteria for Entry Into the Maintenance Phase]); subjects receiving PP1M as 50 or 75 mg eq. will exit the study. If possible, the subject's identified support person should accompany the subject to the first visit in this phase.

Maintenance Phase

The procedures for the Maintenance Phase are outlined in the Time and Events Schedules and in associated text descriptions. At the end of this phase, subjects who do not meet the criteria for randomization (see Section 4.4 [Criteria for Entry Into the Double-blind Phase]) must withdraw from the study and have End-of-Phase Visit / Early Withdrawal Visit assessments performed, as outlined in the Time and Events Schedules. For subjects who did not take part in the Transition Phase, the subject's identified support person should accompany the subject to the first visit in this phase, if possible.

Double-blind Phase

The procedures for the Double-blind Phase are outlined in the Time and Events Schedules and in associated text descriptions. During this phase, investigators should ask subjects to return to the clinical site for unscheduled visits as required for any assessment of symptom worsening or possible adverse events. If a possible relapse is detected per PANSS criteria at a scheduled or unscheduled visit, as described in Section 2.1.2.2 (Relapse Criteria), then the investigator should

ask the subject to visit the clinical site 3 to 7 days later for a PANSS reassessment (if no such visit is already scheduled). Suspected relapses should prompt all of the following assessments at all associated clinic visits, even if not designated on the Time and Events Schedules:

- A PK sample, per Section 9.3.1 (Pharmacokinetic Evaluations),
- A full PANSS assessment, per Section 9.2.2 (Positive and Negative Syndrome Scale),
- A CGI-S assessment, per Section 9.2.3 (Clinical Global Impression - Severity),
- A Columbia Suicide Severity Rating Scale (C-SSRS) assessment, per Section 9.4.7 (Columbia Suicide Severity Rating Scale), and
- Testing for concomitant substances (both an alcohol breath test and a urine drug screen for illicit substances), per Section 9.4.2 (Clinical Laboratory Tests).

The EOP visit is to occur as soon as possible after relapse confirmation (preferably the same day).

Follow-up Phase

The procedures for the Follow-up Phase are outlined in the Time and Events Schedules and in associated text descriptions. 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 and efficacy data. Accordingly during the Follow-up Phase, suspected relapses do not prompt the additional breadth of assessments (as described for the Double-blind Phase above), but should prompt the additional frequency of assessments if relevant (ie, if PANSS scores indicate potential relapse, then PANSS assessments should repeated 3 to 7 days later to confirm a relapse event).

9.2. Efficacy Evaluations

9.2.1. Qualified Raters

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

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

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

In addition, the qualified rater must have had:

- Recent experience in performing PANSS ratings in psychiatry clinical studies,[g] and
- At least 3 years of experience in evaluating patients with schizophrenia in an inpatient or outpatient setting, and
- Qualification training in performing PANSS assessments (per certification by the Sponsor) and CGI-S assessments (per training by the Sponsor), and
- Overall completion of the Sponsor's rater training.

9.2.2. Positive and Negative Syndrome Scale

Full PANSS

The neuropsychiatric symptoms of schizophrenia will be assessed using the 30-item PANSS scale,[20] 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 Schedules, and at any clinic visit associated with a suspected relapse; see Section 2.1.2.2 (Relapse Criteria). The full PANSS should be administered using the Structured Clinical Interview (SCI-PANSS) format, or using an equivalent structured interview format to be provided by the Sponsor.

Abbreviated PANSS

At some time points (indicated in the Time and Events Schedule), an abbreviated form of the PANSS will be used to assess for change in symptoms. An abbreviated PANSS consists of the positive-symptom items P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), P6 (suspiciousness/persecution), and P7 (hostility), and the general-psychopathology item G8 (uncooperativeness). If the abbreviated PANSS indicates worsening since the last full PANSS assessment or if the subject meets one or more symptom criterion for relapse, then the full PANSS should be administered (as the SCI-PANSS). For abbreviated PANSS assessments, raters should use the relevant questions from the SCI-PANSS or equivalent format.

9.2.3. Clinical Global Impression - Severity

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).[13] 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.[8,9] This modified

[g] If a rater meets all criteria except the experience requirement, and is a subinvestigator at a study site where an investigator does meet the experience requirement, then the experience requirement can be waived for the subinvestigator, in order to facilitate training of raters.

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 Schedules, and at any clinic visit associated with a suspected relapse.

9.2.4. Personal and Social Performance Scale

The PSP scale assesses the degree of dysfunction a subject exhibits 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.[29] Individual domain items of the PSP will be collected and recorded in the eCRF.

9.2.5. Satisfaction With Participation in Social Roles

The Patient-Reported Outcomes Measurement Information System (PROMIS) group developed and evaluated the Satisfaction With Participation in Social Roles Short Form 8a (SPSR) with funding from the US National Institutes of Health (NIH) and other academic and research grants.[14] A study in a diverse clinical population demonstrated the SPSR's responsiveness to change.[14] The SPSR asks subjects to consider the past 7 days and to rate 8 items on 5-point Likert scales, with higher scores representing higher satisfaction. An example of the SPSR is provided in the Manual of Assessments.

Note: For subjects that require translation of the SPSR into their local language, the collection of the SPSR is optional until the final, approved translation is available.

9.2.6. Abbreviated Treatment Satisfaction Questionnaire for Medication

The 9-item abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) was found to be a reliable and valid measure to assess treatment satisfaction in naturalistic study designs.[5] Items are scored on 5- or 7-point Likert scales, with higher scores representing higher satisfaction. Subjects are asked to consider the time frame of the last 2 to 3 weeks, or since the last time the medication was used. An example of the TSQM-9 is provided in the Manual of Assessments.

9.3. Pharmacokinetic and Pharmacodynamic Evaluations

9.3.1. Pharmacokinetic Evaluations

Venous blood samples of approximately 4 mL will be collected to obtain approximately 2 mL of plasma, for measurement of plasma concentrations of paliperidone (and on selected samples, paliperidone palmitate) at the time points indicated in the Time and Events Schedules. During the study, the nominal sample collection times may be changed by the Sponsor with clear

communication to the investigator, but the total number of samples will not increase without a formal protocol amendment. The exact dates and times of blood sample collection must be recorded on the laboratory requisition form. Information about the collection, handling, and shipment of biological (PK) samples will be provided in a Laboratory Manual. Genetic analyses will not be performed on these PK samples. Subject confidentiality will be maintained.

The aim of the PK evaluations will be to characterize the time course of plasma paliperidone concentrations and PK parameters such as maximum and minimum plasma concentrations and timing. Therefore, 3 PK samples are scheduled weekly around the expected paliperidone peak at approximately 1 month after the PP6M dose, and 6 PK samples are scheduled weekly when approaching the end of the 6-month dosing interval. For paliperidone palmitate, PK evaluations will be performed on samples collected 2 days after the injections indicated in the Time and Events Schedules, to check for any prodrug in the bloodstream from possible partial intravascular injections.

In addition to PK sampling time points indicated in the Time and Events Schedules, sites should collect unscheduled PK samples associated with important efficacy or safety events, as follows:

- **If a relapse event occurs or is suspected,** as defined in Section 2.1.2.2 (Relapse Criteria), then a PK sample should be collected in association with this efficacy outcome.
- **If a serious or severe adverse event occurs**, then a PK sample should be collected in association with this safety outcome.
- **At the investigator's discretion,** an unscheduled PK sample related to an adverse event may be collected even if the event is not serious or severe.

To preserve the treatment blind, the results of any PK samples will not be revealed to the Sponsor or the study-site personnel (until use by the internal independent analyst for the Sponsor-blinded interim PK analysis and then by the Sponsor in the final analyses after database lock).

9.3.2. Analytical Procedures

Plasma samples will be analyzed to determine concentrations of paliperidone at all indicated time points (and paliperidone palmitate at 2 days after injections) using a validated, specific, and sensitive method (eg, liquid chromatography with tandem mass spectrometry), by or under the supervision of the Sponsor. If deemed necessary to explain the study results, drug concentrations may be determined for paliperidone palmitate (at time points in addition to 2 days after injections), for paliperidone enantiomers, or for other antipsychotics (such as risperidone).

9.3.3. Pharmacokinetic Parameters

Based on the individual plasma concentration-time data, using the actual dose taken and the actual sampling times, PK parameters and exposure information of paliperidone will be derived using population PK modeling. Baseline covariates (eg, body weight, age, sex, creatinine clearance, race) may be included in the model, if relevant. The PK analyses will be detailed in

one or more separate methods plans (outside the standard SAP) and one or more separate results reports (outside the standard Clinical Study Report [CSR]).

9.3.4. Pharmacodynamic Evaluations

Samples collected for PK evaluations may also be used for pharmacodynamic (PD) evaluations. For safety outcomes, pharmacokinetic-pharmacodynamic (PK-PD) relationships may be evaluated in terms of any potential clustering of adverse events around the time of the maximum plasma paliperidone concentration after a dose of PP6M. For efficacy outcomes such as relapse, PK-PD relationships may be evaluated, if appropriate. Any PK/PD analyses would be performed after database lock. The PK-PD analyses may be detailed in one or more separate methods plans (outside the standard SAP) and one or more separate results reports (outside the standard CSR).

9.4. 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 Schedules.

9.4.1. 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).

9.4.2. 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 (except for prolactin results, which are blinded to study-site personnel and Sponsor) must be filed with the source documents.

The tests below will be performed by the central laboratory. For full panels, subjects should be in fasted state overnight or for at least 8 hours (and nonfasting exceptions should be noted). For the prolactin-only samples, fasting is not required. Information about the collection, handling, and shipment of biological (laboratory test) samples will be provided in a Laboratory Manual.

- **Hematology Panel**

  - hemoglobin
  - hematocrit
  - platelet count
  - red blood cell count
  - white blood cell count with differential
  - hemoglobin A1c (only during the Screening Phase and the Double-blind Phase)

- **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

  CCI [redacted]

  - prolactin, which will be blinded to the study-site personnel and Sponsor; some samples will be for prolactin only (not the other analytes listed above), as designated in the Time and Events Schedules.
  - thyroid stimulating hormone.

- **Urinalysis**

  Dipstick
  - specific gravity
  - pH
  - glucose
  - protein
  - blood*
  - ketones
  - bilirubin
  - urobilinogen
  - nitrite*
  - leukocyte esterase*

  Sediment (performed if dipstick result is abnormal)
  - red blood cells
  - white blood cells
  - epithelial cells
  - crystals
  - casts
  - bacteria
  - any other findings

  *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, highly sensitive serum pregnancy testing (for (β-human chorionic gonadotropin) will be conducted during the Screening Phase, and urine pregnancy tests will be provided for local testing during the subsequent phases.

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 kits (for illicit substances, including marijuana, even where legal) and alcohol breath tests will be provided for local use at the time points specified in the Time and Events Schedules. For any subject with a positive result for alcohol or illicit substances, the study-site personnel should administer the relevant test again at subsequent visits (even if not marked in the Time and Events Schedules) until a negative result is obtained. After a negative result is obtained, the subject can resume testing at the standard frequency as indicated in the Time and Events Schedules. These tests should also be administered whenever a relapse is suspected. Alcohol and illicit substances are strongly discouraged but are not exclusionary and are not cause for withdrawal from the study.

9.4.3. Electrocardiograms

Specific procedures for the 12-lead ECGs will be provided in a separate manual. Blinded cardiologists at a central ECG laboratory will read all ECGs in this study.

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, then the procedures should be performed in the following order: ECGs, vital signs, blood draw.

During the Screening Phase, the 2 required ECGs should be recorded at least 24 hours apart. The first ECG may be from prior medical record within the past year. The second ECG should be scheduled in a timely manner to ensure the cardiologist-read report is available before Visit 2; therefore, the Time and Events Schedules show the Screening Phase to extend through Day -2 (not Day -1), to allow at least a day for ECG reading and reporting. On Day 1 of the relevant phase for the subject (ie, the first day of the Transition Phase for subjects without prestudy PP1M or PP3M stability, or the first day of the Maintenance Phase for subjects with prestudy PP1M or PP3M stability), a third ECG should be recorded and compared against the exclusion criteria before the first dose of study medication is administered; see Section 4.2 (Exclusion Criteria).

If any clinically significant ECG abnormality is observed during the study, then the study-site personnel should add ECG assessments for that subject at all subsequent visits (even if not marked in the Time and Events Schedules) until the abnormality is resolved.

A printout of all ECG recordings must be filed in the source document. Any clinically relevant changes that occur during the study must be recorded on the Adverse Event section of the eCRF.

9.4.4. 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 twice (first after at least 5 minutes rest in supine position and then after 2 minutes standing, if possible) with a completely automated device. Pulse/heart rate will be measured each time 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. The same arm should be used for both supine and standing measurements.

If a subject is unable to stand up or is unable to remain standing for 2 minutes as a result of symptoms of orthostatic hypotension, 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.

9.4.5. Physical Examinations

Physical examinations at the time points designated on the Time and Events Schedules include weight, waist circumference, and abnormalities. Height should also be measured at screening only, in order to facilitate calculations of BMI (weight/height² as kg/m²).

9.4.6. Extrapyramidal Symptoms

The scales to assess EPS will be the AIMS for dyskinesia, the BARS for akathisia, and the SAS for parkinsonism, at the visits noted in the Time and Events Schedules. Particular attention is given to assessing EPS around the expected timing of the maximum plasma paliperidone concentration after a PP6M dose.

In addition to scheduled AIMS, BARS, and SAS assessments, unscheduled assessments of these scales should be conducted before initiating or changing any antiparkinsonism drugs (all 3 scales) or any beta-adrenergic blockers or benzodiazepines for akathisia (BARS only), as described in Section 8.2 (Concomitant Therapy).

9.4.6.1. Abnormal Involuntary Movement Scale

The AIMS is included in the Early Clinical Development Evaluation Unit Assessment Manual from the US NIMH.[13] 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.

9.4.6.2. 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.[3] 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.

9.4.6.3. Simpson Angus Scale

The SAS is led by signs (rather than by symptoms) to measure drug-induced parkinsonism.[34] 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.[8,9] 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.

9.4.7. Columbia Suicide Severity Rating Scale

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.[31] The C-SSRS is a clinical interview providing a summary of both ideation and 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. The appropriate version of the C-SSRS should be administered at the time points indicated in the Time and Events Schedules, and at any clinic visit associated with a suspected relapse. Examples of the C-SSRS (Baseline/Screening Version and "Since Last Visit" Versions) are provided in the Manual of Assessments.

9.4.8. Evaluations of the Injection Site

9.4.8.1. Injection Site Evaluations by Subjects

The VAS to measure pain has been widely used in diverse adult populations.[15] 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).[15] The instructions, time period for reporting, and verbal descriptor anchors have varied widely in the literature depending on the intended use of the scale.[15] In some settings, test-retest reliability and ability to detect change have been demonstrated.[15]

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.[8,9]) The VAS-Acute will assess pain once within 30 minutes after each injection. The VAS-Residual will assess pain at the time points days or weeks later as indicated in the Time and Events Schedules; 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.

9.4.8.2. 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, at the same time points as the VASs completed by the subject, 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,[8,9] and from a US FDA guidance.[h] The results will be recorded on the eCRF. The investigator/subinvestigator should complete these assessments within 30 minutes after the injection and at all visits marked in the Time and Events Schedules thereafter; 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.

[h] 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 14 April 2017.

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.

9.5. Benefit-risk Evaluations

Evaluations already defined for efficacy and safety will be used for the benefit-risk assessment. Benefit will be evaluated as described in Section 2.1.2.2 (Relapse Criteria), and will include relapse per all causes, relapse per psychiatric hospitalization, or relapse per PANSS total score. Risk will be evaluated as described in Section 9.4 (Safety Evaluations), and will include the following: adverse events overall; adverse events of special interest (eg, from the list in Section 1.1 [Background]); adverse events that are serious or that lead to discontinuation; clinical laboratory tests (for risk of hyperprolactinemia or hyperglycemia); ECGs (for risk of QTcF increase >60 milliseconds); and physical examinations (for risk of weight gain ≥7%). The benefit-risk evaluations may also include other unexpected clinically relevant adverse events that occur during the Double-blind Phase, or that are a consequence of a pre-existing condition that has worsened since the start of the Double-blind Phase.

9.6. Other Exploratory Evaluations

9.6.1. Healthcare Resource Utilization Questionnaire

The Healthcare Resource Utilization (HRU) 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.[24] 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. Examples of the HRU questionnaires (baseline assessment and postbaseline assessment) are provided in the Manual of Assessments.

9.6.2. Involvement Evaluation Questionnaire

The Involvement Evaluation Questionnaire (IEQ) was designed to measure levels of caregiver consequences among family members and friends of subjects with schizophrenia.[35] The version of the IEQ to be used in this study will contain 5 questions about the demographics of the caregiver, and will pose the 31 standard items in the IEQ, and will exclude the "supplementary" questions. The 31 standard questions are answered on 5-point Likert response scales to address consequences among 4 dimensions (tension, supervision, worrying, and urging). Data are available to support its reliability.[35] The IEQ should be completed by a designated caregiver for the subject. The designated caregiver who will be completing the questionnaire is someone who is mutually agreed upon between the subject and the investigator, should not be a paid caregiver but may be a family member, significant other, or friend who provides at least 1 hour of support to the subject per week. The same individual should complete the questionnaire throughout the study and should attend study visits when the IEQ is scheduled to be completed. In order to support the interpretation of the data and further explore the impact of caregiving, supplemental questions about the sociodemographics, time spent caregiving, and health care utilization of the caregiver will be collected from the designated caregiver at the times the IEQ is administered according to the Time and Events Schedules. This IEQ may be completed by mail or telephone or may be performed one month before or after the visit, based on availability of the caregiver. If a subject has no caregiver providing at least 1 hour of support per week, then the IEQ may be omitted. Examples of the IEQ (baseline assessment and postbaseline assessment) are provided in the Manual of Assessments; along with the comments about the IEQ recall periods.

9.6.3. Concomitant Substances Questions

Use of nicotine will be questioned as indicated in the Time and Events Schedules. Examples of the questions are provided in the Manual of Assessments.

9.6.4. Illness Management and Recovery Scale

The Illness Management and Recovery (IMR) scale (client self-report version) for schizophrenia and other severe mental illnesses was developed as part of the US National Implementing Evidence-based Practices Project and is made available by the US Substance Abuse and Mental Health Services Administration.[30] The IMR scale asks subjects to consider the past 3 months and to rate 15 items about personal goals, knowledge of mental illness, involvement with significant others, impaired functioning, symptoms, stress, coping, relapse prevention, hospitalization, medication, and use of drugs and alcohol. The response range for each item is from 1 to 5 points, with higher scores indicating better outcomes. An example of the IMR scale (client self-report version) is provided in the Manual of Assessments. This study uses a version of the IMR that is slightly modified from the original, to make the recall periods more appropriate to the study.

9.6.5. Schizophrenia Quality of Life Scale (Revision 4)

The Schizophrenia Quality of Life Scale (SQLS) was initially developed using items generated from in-depth patient interviews (ie, the perspective of patients was used to develop the SQLS).[27] Thereafter, the SQLS was further developed and revised to improve its psychometric properties. The most recent version (Revision 4) has been translated into dozens of languages through standardization procedures.[22]

The SQLS (Revision 4) has 33 items covering topics such as psychosocial feelings and vitality. Response options are never, rarely, sometimes, often, or always. Scoring algorithms yield a 0 to 100 scale, with higher scores indicating lower quality of life. The factor structure and internal reliability have been verified in patients with schizophrenia in the Netherlands and further replicated in patients with schizophrenia in the United Kingdom and Taiwan.[22,27]

An example of the SQLS (Revision 4) is provided in the Manual of Assessments.

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

An End-of-Phase Visit (as outlined in the Time and Events Schedules) may be conducted as an Early Withdrawal Visit if a subject is unable to complete a phase before reaching randomization, or unable to progress between phases before reaching randomization, or unable to complete the Double-blind Phase. An End-of-Phase Visit (as outlined in the Time and Events Schedules) may be conducted as an End-of-Study Visit if a subject is completing the Double-blind Phase (see Section 10.1 [Completion]).

10.1. Completion

A subject will be considered as having completed the study if he or she has had a relapse during the Double-blind Phase and has completed all End-of-Study Visit assessments, or has remained relapse-free during the Double-blind Phase and has completed all End-of-Study Visit assessments. The definition for completing the Double-blind Phase is the same as for completing the study. The Follow-up Phase, when applicable, is supplementary after study completion.

10.2. Discontinuation of Study Drug / Withdrawal From the Study

Discontinuation of Study Drug

A subject will not be automatically withdrawn from the study if he or she discontinues treatment before the end of the treatment regimen. A subject's study drug must be discontinued if the investigator believes that for safety reasons or tolerability reasons (eg, adverse event) it is in the best interest of the subject to discontinue study drug, or if the subject becomes pregnant.

- If a subject discontinues after receiving at least 1 dose of open-label study drug but before receiving any double-blind study drug, then End-of-Study Visit assessments should be obtained and no Follow-up Phase is applicable.
- If a subject discontinues after receiving at least 1 dose of double-blind study drug, then:

If possible, the scheduled assessments (including PK samples) should be continued through the relevant 6-month cycle of assessments (Visits 7 to 20, or Visits 20 to 33) - If the subject has not completed at least 1 year of the Double-blind Phase, then either:

- The subject may, if preferred, continue with assessments (but without study drug administration) until Visit 33a (the End-of-Study Visit), or
- The subject may, if preferred, complete Visit 20 as an End-of-Study Visit, and then enter the Follow-up Phase until the full year of data have been collected after the first double-blind injection.

In any case, the last assessment of the relevant 6-month cycle (ie, Visit 20 or 33) should be conducted as an End-of-Study Visit.

- If it is not feasible for scheduled assessments to be continued through the relevant 6-month cycle of assessments, then End-of-Study assessments should be obtained as soon as possible. The subject should then, if willing, enter the Follow-up Phase until 12 months of data have been collected after the first double-blind injection.

Withdrawal From the Study

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

- Lost to follow-up.
- Withdrawal of consent.
- The blind is broken by the investigator.
- Treatment with concomitant antipsychotic medication when relapse criteria are not met but, in the investigator's judgment, a concomitant antipsychotic medication is necessary for the subject's wellbeing, and viable alternatives are either not available or have been exhausted.
- The subject fails to meet criteria for entry to Maintenance Phase.
- The subject fails to meet criteria for entry to Double-blind Phase.
- For subjects in the Transition Phase:
  - If the dose at Visit 2e is different than the dose at Visit 2d.
  - If the dose at Visit 2d or 2e is <100 mg eq.
  - If the dose is 50 mg eq. at any time.
- For subjects in the Maintenance Phase:
  - If the dose at Visit 2f is different from the preceding dose or is not a dose equivalent of the preceding dose.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced.

- If a subject withdraws from the study after receiving at least 1 dose of open-label study drug but before receiving any double-blind study drug, then End-of-Study Visit assessments should be obtained if the subject is willing to complete that visit.
- If a subject withdraws from the study after receiving at least 1 dose of double-blind study drug but before the end of the Double-blind Phase, then End-of-Phase Visit / Early Withdrawal Visit assessments should be obtained if the subject is willing to complete that visit, even if the subject is withdrawing consent to complete any other visits. Thereafter:

If the subject is withdrawing consent, then the subject's study participation is complete.

If the subject is withdrawing for a reason unrelated to consent, then the subject should enter the Follow-up Phase.

Loss to Follow-up

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.

10.3. Antipsychotic Therapy After the Study or in the Follow-up Phase

Open-label Treatment: Poststudy

If a subject discontinues or withdraws from the study in the Transition Phase or Maintenance Phase, then he or she may be considered for poststudy treatment with PP1M, PP3M, or another LAI antipsychotic at an interval appropriate to the open-label identity of the last study dose, as described in the approved prescribing information. Oral antipsychotic medications, if appropriate, may be restarted regardless of the timing of the last study injection. However, consideration should be given to the long-acting nature of paliperidone palmitate when the oral antipsychotic medication and dose(s) are selected. At the End-of-Phase Visit / Early Withdrawal visit and thereafter, the poststudy treatment after open-label treatment is at the discretion of the subject's physician; the study no longer follows these subjects.

Double-blind Treatment: Poststudy or Follow-up Phase

After discontinuation, withdrawal, or completion of the study in the Double-blind Phase, investigators/treating physicians may choose to continue treatment with paliperidone palmitate, switch to treatment with a different LAI antipsychotic treatment, or switch to oral antipsychotic treatment. Treatment selection is at the discretion of the subject's physician and is not a study medication. However, given the double-blind conditions and durations of activity expected from PP6M and PP3M, recommendations (not requirements) for poststudy or Follow-up Phase treatment schedules are provided in Figure 5 and Table 7 and Table 8 below.

Figure 5: Post Study Medication Algorithm

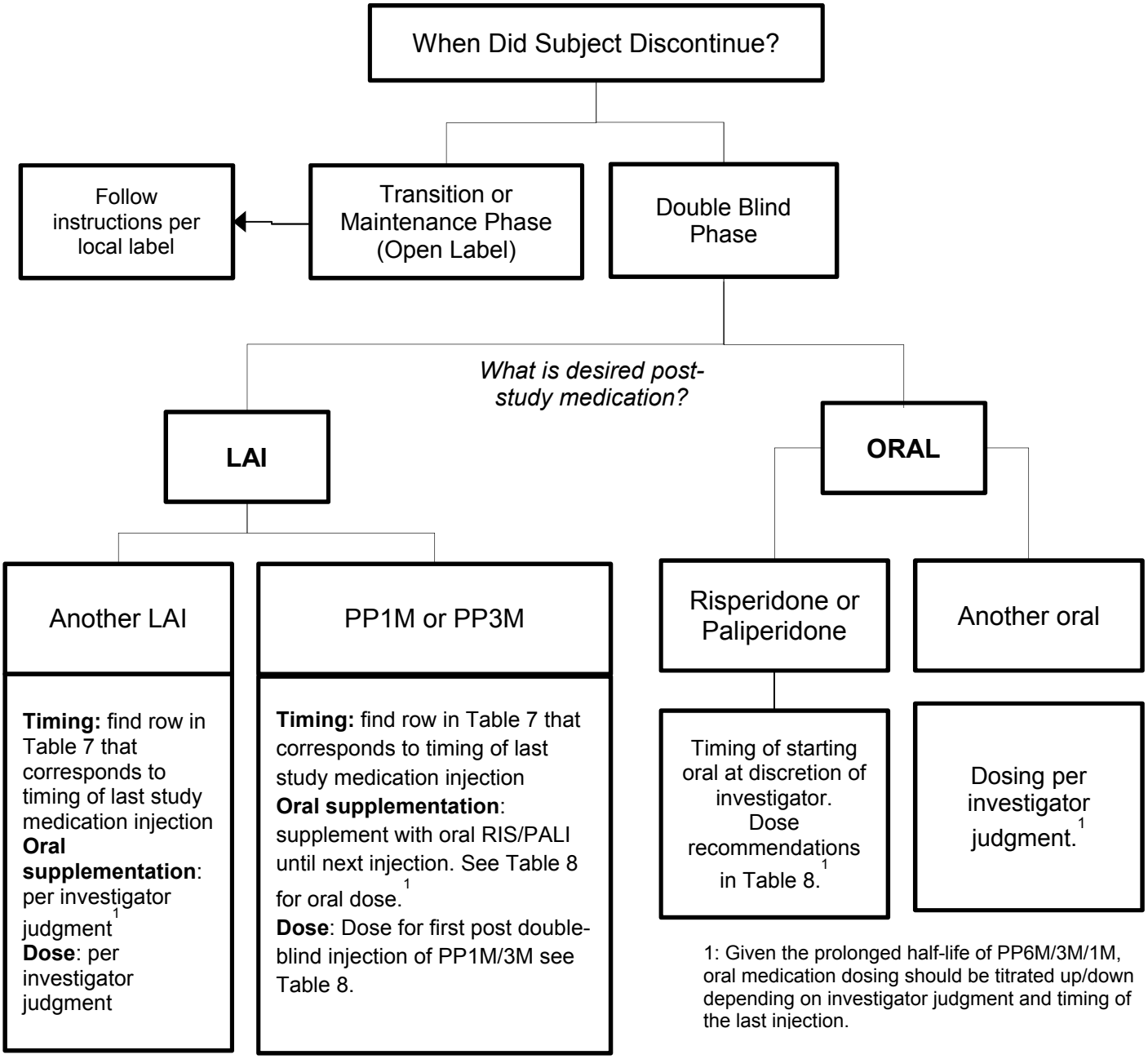


Table 7: Timing of Resumption of PP1M/3M after the Double-blind Study or in Follow-Up Phase

Visit #	Day[1]	Study Medication Injection	Time to wait until next PP1M/PP3M injection (days)[2]	Visit #	Day[1]	Study Medication Injection	Time to wait until next PP1M/PP3M injection (days)[2]
7b	1	PP6M or PP3M	180	21	185		178
8	3		177	22	204		159
9	22		158	23	211		152
10	29		151	24	218		145
11	36		144	25	242		121
12	60		120	26	274	Placebo or PP3M	89
13	92	Placebo or PP3M	88	27	302		61
14	120		60	28	330		33
15	148		32	29	337		26
16	155		25	30	344		19
17	162		18	31	351		12
18	169		11	32	358		5
19	176		4	33	365		0
20	183	PP6M or PP3M	0	Footnotes: 1: Does not include visit window 2: Timing of resumption of oral antipsychotic may be at any time depending on investigator judgment			

Table 8: Switching Conversion Table (Oral and LAI Paliperidone and Oral Risperidone)

	PP1M	PP3M	PP6M	Oral Paliperidone	Oral Risperidone
Moderate Dose Group:	100 mg eq.	350 mg eq.	700 mg eq.	9 mg/day	3-4 mg/day
Higher Dose Group: .	150 mg eq.	525 mg eq.	1000 mg eq.	12 mg/day	5-6 mg/day
	Footnote: 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.				

10.4. Process for Planned Study Closure

The calendar date of the end of Study R092670PSY3015 will be determined when a sufficient number of subjects have been randomized to the Double-blind Phase. To ensure that subjects can be assessed for 6 months after their last potential PP6M injection but cannot have End-of-Study Visits after the calendar date that marks the end of the study, subjects will not receive injections that are potentially PP6M after the last subject randomized receives his or her last potential PP6M injection. The process for determining the calendar date of the end of the study and further explanation of the timing of End-of-Study Visits is described below.

Throughout the study, the Sponsor will monitor the number of subjects in the Transition, Maintenance, and Double-blind Phases. The Sponsor will notify all sites to close screening and

enrollment activities when an adequate number of subjects have been enrolled to achieve the target number (549 randomized) needed for participation in the Double-blind Phase. Subjects already participating in the Transition and Maintenance Phases will continue to progress through the study as described in the Time and Events Schedules, including progress into the Double-blind Phase if eligibility criteria are met as described in Section 4.4 (Criteria for Entry Into the Double-blind Phase). Study R092670PSY3015 will conclude when the last subject to be randomized and remain in the study completes 12 months of the Double-blind Phase, which will be marked by completion of Visit 33a

During the Double-blind Phase, only the odd-numbered (ie, 1st, 3rd) injections are potentially PP6M.

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 SAP.

11.1. Subject Information

The populations for efficacy analyses, the double-blind intent-to-treat analysis population and the per-protocol analysis population, are described in Section 11.3 (Efficacy Analyses). Other analysis populations will be defined in a manner similar to a previous study of PP3M,[8] and may include sets such as the following: the open-label intent-to-treat analysis population, the all randomized analysis population, and the safety analysis population. Full details will be provided in the SAP.

11.2. Sample Size Determination

The sample size for the Double-blind Phase of the study is 549 randomized subjects, based on determinations to provide a minimum of 80% power for the primary endpoint. The sample size determination includes the assumptions that the expected survival rate (percentage of subjects remaining relapse-free at 12 months) in the PP3M group is 85%, and that the 1-sided significance level should be 2.5%. Given these assumptions, 549 subjects randomized in a 2:1 ratio (PP6M:PP3M) are required to demonstrate with 80% power that PP6M is no worse than PP3M by a noninferiority margin of 10% for the percentage of subjects remaining relapse-free at 12 months. This assumes that the efficacy observed in the PP3M group will be similar to the efficacy observed in the previous PP3M registrational Phase 3 studies (R092670PSY3011 and R092670PSY3012). The noninferiority margin of 10% and statistical methods for this analysis were selected based on the Sponsor's previous studies and on advice from experts and health authorities, as follows:

- In the Sponsor's previous placebo-controlled relapse prevention studies with oral paliperidone ER/PR, PP1M, and PP3M,[9,18,21] a Kaplan-Meier estimate indicated that the meta-analytic estimate of treatment benefit of paliperidone over placebo was 42.1% (95% confidence interval: 28.4% to 55.8%).[19]

- A panel of experts in the field of schizophrenia relapse prevention studies was convened to obtain recommendations for the clinical noninferiority margin to be used in this study. Using a modified Delphi approach, the mean value obtained after anonymous voting for the noninferiority margin was 13.4% (median 13.0%; range 10% to 20%).[19] This clinical judgment based on expert opinion thus provided guidance on the largest loss of efficacy that could be considered clinically acceptable; in accordance with the relevant US FDA guidance,[i] the maximum was therefore set at 13.0%.[19]
- Prior scientific advice from the Committee for Medicinal Products for Human Use had recommended a noninferiority margin of 10%.[19]
- For all of the above reasons, an effect of 10% was chosen as the margin.

Further details are available in a separate statistical support document.[19]

The study design assumes discontinuation rates during the Transition and Maintenance Phases of 20% for subjects who entered the study with previous PP1M or PP3M stability and 40% for subjects who entered the study without previous PP1M or PP3M stability. The study design also assumes a dropout rate of 10% during the Double-blind Phase (where the dropout rate also accounts for subjects excluded due to protocol violations). Given these assumptions for discontinuation, the study targets approximately 840 subjects to enter the Transition/Maintenance Phase.

11.3. Efficacy Analyses

11.3.1. Primary Hypothesis and Efficacy Analyses

The primary hypothesis is that the efficacy of PP6M is noninferior to PP3M for preventing relapse in subjects with schizophrenia who were previously stabilized on corresponding doses of PP1M or PP3M.

11.3.1.1. Double-blind Intent-to-Treat Analysis Population

11.3.1.1.1. Primary Estimand

1. The *population* is restricted to those who are stabilized on either PP1M or PP3M during the Maintenance Phase and meet the inclusion/exclusion criteria.
2. The *variable* is time to a relapse event, and will be defined during the Double-blind Phase if the subject experiences a relapse during the Double-blind Phase.
3. The *intercurrent effects* are none, regardless of whether or not major protocol deviations had occurred.
4. The *population-level summary* is the difference in Kaplan-Meier estimate at Month 12 of relapse-free proportions between the 2 treatment groups.

[i] US FDA. Non-inferiority clinical trials to establish effectiveness: guidance for industry. www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm202140.pdf. Issued November 2016. Accessed 15 May 2017.

11.3.1.1.2. Primary Efficacy Analyses

All subjects who receive at least 1 dose of study drug during the Double-blind Phase will be included in the double-blind intent-to-treat population. The primary endpoint is time to relapse in the Double-blind Phase, as described in Section 2.1.2.1 (Primary Endpoint). Subjects who meet at least 1 of the criteria for relapse (see Section 2.1.2.2 [Relapse Criteria]) during the Double-blind Phase at the time of study completion for the primary analysis will be considered to have had a relapse event. Subjects who do not have a relapse event in the Double-blind Phase will be considered as censored. The statistics to test the primary hypothesis are based on the percentage of subjects who remain relapse-free at Month 12 in the PP6M and PP3M groups per Kaplan-Meier estimate for the Double-blind Phase. The analysis will consider whether the lower limit of the 95% confidence interval of the difference in relapse-free rates between PP6M and PP3M exceeds the noninferiority margin of -10%. The standard error estimates will be based on Greenwood's formula. The null and alternative hypotheses use a 1-sided α=0.025 level, and are written as follows:

$$\text{Null Hypothesis: } (\%\ \text{relapse-free})_{PP6M} - (\%\ \text{relapse-free})_{PP3M} \leq -10\%$$

$$\text{Alternative Hypothesis: } (\%\ \text{relapse-free})_{PP6M} - (\%\ \text{relapse-free})_{PP3M} > -10\%$$

11.3.1.1.3. Sensitivity Analyses for Primary Efficacy

Additional sensitivity analyses with the double-blind intent-to-treat population will be performed to evaluate impact of censoring for subjects who withdraw from the Double-blind Phase before Month 12 by using the data collected from the Follow-up Phase. Consistency of effect across various geographic regions will also be evaluated.

11.3.1.2. Per-protocol Analysis Population

11.3.1.2.1. Estimand

The primary efficacy analysis will also be performed on the per-protocol analysis population. The estimand of the per-protocol analysis population is defined by the following components:

1. The *population* is restricted to those who are stabilized on either PP1M or PP3M during the Maintenance Phase and meet the inclusion/exclusion criteria.
2. The *variable* is time to first occurrence of a relapse event, and will be defined if a subject experiences a relapse during the Double-blind Phase.
3. The *intercurrent events* are major protocol violations that may impact efficacy; these include errors in treatment assignment, errors in the delivery of active medication, or use of prohibited medications.
4. The *population-level summary* is the difference in Kaplan-Meier estimate at Month 12 of relapse-free proportions between the 2 treatment groups.

11.3.1.2.2. Analyses

The analysis performed on the per-protocol analysis population will be based on the comparison between 2 treatment groups in subjects without the aforementioned intercurrent events; that is, in

randomized subjects who receive at least 1 dose of study drug during the Double-blind Phase, and do not have major protocol violations that may impact efficacy such as errors in the delivery of active treatment, errors in treatment assignment, or use of prohibited medication. The noninferiority analysis with 10% noninferiority margin as specified in Section 11.3.1.1 (Double-blind Intent-to-Treat Analysis Population) will be repeated on the per-protocol analysis population.

11.3.2. Secondary Efficacy Analyses

Clinically assessed secondary efficacy analyses include maintaining symptom control, functioning personally and socially, and achieving remission in each group (PP6M or PP3M, each sorted by dose level). The secondary efficacy analyses will be conducted using the double-blind intent-to-treat analysis population.

- **Maintaining Symptom Control:** For the Double-blind Phase, analysis of change in PANSS total and factor scores and in the CGI-S scores will be made based on a mixed model for repeated measurement analysis that will include a random effect for subject and fixed effects terms for treatment, visit (as a categorical variable), country, baseline score, and treatment-by-visit interaction. For the Maintenance Phase, descriptive summaries (sorted by PP1M or PP3M dose groups) will also be provided.
- **Functioning Personally and Socially:** Analyses of the PSP scores will be similar to the analyses for maintaining symptom control, as described in the bullet above.
- **Achieving 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).[2] For multiple observations, durable symptomatic remission is defined as meeting those remission criteria for a 6-month period.[2] For each treatment group, the number and percentage of subjects achieving durable symptomatic remission at the end of the Double-blind Phase will be presented. The point estimate and 2-sided 95% confidence interval will be provided for the relative risk using a Mantel-Haenszel test controlling for country. The count and percentage of remission status at each Double-blind Phase outcome time point will be presented by treatment group for subjects who were in remission at Double-blind Phase baseline. Point estimates and 2-sided 95% confidence interval will also be provided for subjects meeting the remission criteria at each time point (including at the end of the study). Time to remission and maintenance of remission for longer than the 6-month period may also be assessed.

Subject-reported secondary efficacy analyses (ie, of the SPSR and the TSQM-9 outcomes) may be detailed in a separate report (outside the standard SAP and CSR).

11.4. Pharmacokinetic and Pharmacodynamic Analyses

Descriptive statistics will be calculated for the plasma concentrations of paliperidone and paliperidone palmitate and for the derived PK parameters, as applicable. Statistics will include sample size, mean, standard deviation, coefficient of variation, geometric mean, median, minimum, and maximum. Population PK analysis of plasma concentration-time data of

paliperidone will be performed using nonlinear mixed-effects modeling for PP6M, possibly using models previously developed from PP3M studies.

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

The study will include a Sponsor-blinded interim PK analysis of available paliperidone concentration data at the time when at least 6 months of double-blind treatment has been completed by no more than 140 (26%) of 549 randomized subjects. The objective of this interim analysis is to verify that the observed PK properties of PP6M are conforming to the expected PK behavior of PP6M. The following analyses will be conducted:

1. Assess whether the observed concentrations of paliperidone after injection of PP6M are consistent with previous population PK predictions;
2. Assess whether PK sampling times need to be adjusted to fully characterize the PK behavior of PP6M. (These potential changes would be communicated to study sites via a protocol amendment.)

An internal independent analyst (not associated with the study team) or an external vendor will be granted access to the treatment assignment information of the subjects included in the analysis. The external vendor or study-independent analyst will work in a secured environment to ensure no accidental unblinding of the Sponsor. To further ensure no accidental unblinding of the Sponsor, the data transfer to the internal independent analyst or external vendor will be done in a blinded way by using dummy subject identifiers.

No unblinding information will be shared with the Sponsor throughout this process prior to locking of the database. No efficacy or safety data measures will be included in this analysis. However, the Sponsor-blinded PK analysis will include a selection of demographic information needed for evaluation of PK (eg, potential PK covariates such as body weight, age, sex, creatinine clearance, and race) and will include information about study drug administration (volume, dose, muscle site, and history of similar parameters from the Maintenance Phase). The procedural steps to enable the Sponsor-blinded PK analysis will follow the Sponsor's internal operating procedures.

In addition, a snapshot date for PK samples to be analyzed will be defined, if required, to allow a further Sponsor-blinded PK analysis prior to database lock. Samples collected before this date will be analyzed for paliperidone concentrations and will be included in the population PK analysis. Samples collected after the snapshot date will be analyzed at a later date, and will be included in a population PK re-analysis when they become available after database lock.

After database lock, PK-PD analyses may be performed. For safety outcomes, PK-PD relationships may be evaluated in terms of any potential clustering of adverse events around the timing of the maximum plasma paliperidone concentration after a dose of PP6M. For efficacy outcomes such as relapse, PK-PD relationships may be evaluated, if appropriate.

The population PK analysis and the PK-PD analyses will be detailed in one or more separate methods plans and one or more separate results reports.

11.5. Safety Analyses

11.5.1. 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). Treatment-emergent adverse events are adverse events with onset during the treatment 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 by treatment group. In addition, comparisons between treatment groups will be provided if appropriate.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an adverse event, or who experience a severe or a serious adverse event. Analyses of the adverse events of special interest, as described in Section 1.1 (Background), will be described in the SAP. Adverse events will be analyzed separately for the open-label phases (Transition Phase and Maintenance Phase) and for the Double-blind Phase.

11.5.2. Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the SAP) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. A listing of subjects with any laboratory results outside the reference ranges will be provided. A listing of subjects with any markedly abnormal laboratory results will also be provided.

11.5.3. Electrocardiograms

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 (with the prerandomization ECG used as baseline).

The ECG variables that will be analyzed include heart rate, PR interval, QRS interval, QT interval, and corrected QT (QTc) interval using the following correction methods: QT interval corrected according to the linear-derived formula (QTcLD) as the primary method, as well as according to Bazett's formula (QTcB) and according to Fridericia's formula (QTcF) as supplemental methods.[4,17,33]

In the Double-blind Phase, descriptive statistics of QTc intervals and changes from baseline will be summarized at each scheduled time point. The criteria for abnormal QTc interval values will

be based on the classification from the relevant ICH guideline[j] (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.

11.5.4. 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.

A frequency table of the occurrence of orthostatic hypotension will be presented. Orthostatic hypotension is defined as a decrease in systolic (>20 mm Hg) or diastolic (>10 mm Hg) blood pressure after standing for at least 2 minutes that is associated with an increase in pulse/heart rate of >15 bpm compared with supine measurements.[12]

11.5.5. 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. Frequency tabulations of the abnormalities will be made.

11.5.6. Extrapyramidal Symptom Scales

The results of the EPS scales (AIMS, BARS, and SAS) will be summarized descriptively at each time point. See also Section 11.5.1 (Adverse Events) for analyses of EPS-related adverse events.

11.5.7. Columbia Suicide Severity Rating Scale

C-SSRS Baseline/Screening Form will be used at screening. C-SSRS Since Last Visit Form will be used at other visits, as per Time and Events Schedules. Suicide-related thoughts and behaviors based on the C-SSRS scale will be summarized by treatment group in incidence and shift tables.

11.5.8. Evaluations of the Injection Sites

The results of the evaluations by the subjects and by the investigators will be summarized descriptively at each time point.

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[j] 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 14 March 2017.

11.5.9. Anticipated Event Review Committee

An Anticipated Event Review Committee will be established to monitor safety data on an ongoing basis. The Anticipated Event Review Committee will consist of at least one medical expert in the relevant therapeutic area and at least one statistician. After each review meeting, the Anticipated Event Review Committee will make recommendations regarding reporting of anticipated events, as described in Section 12.3.1 (All Adverse Events) and Attachment 3.

11.6. Benefit-risk Analyses

Efficacy and safety outcomes for the benefit-risk analysis will be considered in the Double-blind Phase; ie, excluding results that may arise from treatment with PP1M or PP3M during the Transition or Maintenance Phases. All general rules and conventions from the statistical methods section will be applied to the benefit-risk analyses, unless otherwise noted in the SAP. CCI [redacted] the benefit-risk analyses will be based on the efficacy and safety outcomes previously used for the PP3M formulation.[7]

Treatment comparisons of PP6M versus PP3M will be evaluated using the excess number of events between groups, where the benefits are harmful events to be prevented and the risks are harmful events that may be reported. The benefit-risk analyses will be based on a post-hoc interpretation of the excess numbers of events using clinical judgment to consider the clinical impact of each outcome. The excess number of events is defined as the product of the risk difference between PP6M and PP3M and the size of a hypothetical population (eg, 1,000 patients). This can be interpreted as the additional number of patients in this hypothetical population who would experience a particular event when treated with PP6M minus that in the same population receiving PP3M. For benefit-risk assessment, point estimates will be shown with 95% confidence intervals; however, statistical tests on risk differences will not be specified. Tabular and graphical displays of data may be created. Important benefits and risks are listed in Section 9.5 (Benefit-risk Evaluations).

11.7. Other Exploratory Analyses

If applicable, exploratory analyses may be described in one or more separate methods plans (outside the standard SAP) and one or more separate results reports (outside the standard CSR).

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 noninvestigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or noninvestigational) product, whether or not related to that medicinal (investigational or noninvestigational) product. (Definition per 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 paliperidone palmitate, 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 Drug

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

12.1.2. Attribution Definitions

Not Related

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

Doubtful

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

Possible

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

Probable

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

Very Likely

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

12.1.3. Severity Criteria

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

- **Mild:** Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.
- **Moderate:** Sufficient discomfort is present to cause interference with normal activity.
- **Severe:** Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

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

12.2. Special Reporting Situations

Safety events on a Sponsor study drug that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a Sponsor study drug.
- Suspected abuse/misuse of a Sponsor study drug.
- Accidental or occupational exposure to a Sponsor study drug.
- Any failure of expected pharmacologic action (ie, lack of effect) of a Sponsor study drug.
- Unexpected therapeutic or clinical benefit from use of a Sponsor study drug.
- Medication error involving a Sponsor product (with or without subject/patient exposure to the Sponsor study drug, eg, name confusion).
- Exposure to a Sponsor study drug from breastfeeding.
- Exposure to a Sponsor study drug 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 nonserious, 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 drug, 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. As permitted per local regulations, anticipated events will be recorded and reported as described in Attachment 3.

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the 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). For anticipated events reported as individual serious adverse events the Sponsor will make a determination of relatedness in addition to and independent of the investigator's assessment. The Sponsor's Anticipated Event Review Committee will periodically evaluate the accumulating data and, when there is sufficient evidence and the Sponsor has determined there is a reasonable possibility that the drug caused a serious anticipated event, they will submit a safety report in narrative format to the investigators (and the head of the investigational institute where required). 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. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

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 drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

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

- Study-designated hospitalizations.
- 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 drug, is considered a serious adverse event.

See also Section 9.3.1 (Evaluations) regarding collection of PK samples associated with serious adverse events.

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 drug.

Because the effect of the study drug 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 DRUG INFORMATION

14.1. Physical Description of Study Drugs

Study drugs will be supplied in prefilled syringes, as follows:

- PP1M:

50 mg eq. (78 mg) in 0.5 mL

75 mg eq. (117 mg) in 0.75 mL

100 mg eq. (156 mg) in 1.0 mL

150 mg eq. (234 mg) in 1.5 mL

- PP3M:

350 mg eq. (546 mg) in 1.75 mL

525 mg eq. (819 mg) in 2.625 mL

- PP6M:

CCI [redacted]

[redacted]

- Placebo: The placebo consists of 20% Intralipid (200 mg/mL) injectable emulsion. It has the same milky-white appearance as the active compound, and was used as placebo in the Sponsor's previous studies of PP3M.

CCI [redacted]

[redacted]

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

14.2. Packaging

The study drug will be packaged in individual subject kits. Each kit will consist of a safety needle, instructions for use, and a blister-packed, 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 drug is dispensed to a subject.

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

14.4. Preparation, Handling, and Storage

All study drug and matching placebo must be stored at controlled temperatures as instructed by the clinical label.

14.5. Drug Accountability

The unblinded study drug administrator (see Section 5 [Treatment Allocation and Blinding]) is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The study drug administered to the subject must be documented on the drug accountability form. All study drug will be stored and disposed of according to the Sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

Study drug 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 drug 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 drug will be documented on the drug return form. When the study site is an authorized

destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Potentially hazardous materials (such as used ampules, needles, syringes, and vials containing hazardous liquids) should be disposed immediately in a safe manner. Therefore, these will not be retained for drug accountability purposes.

Study drug 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 drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug 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

Locally approved prescribing information and patient information for the marketed study drugs (oral paliperidone, PP1M, and PP3M) that precede the investigational study drug (PP6M) in this study. Investigators should provide subjects with the appropriate patient information files that are relevant to their treatment paths through the study.

Manuals:

  - For assessments (ie, questionnaires and scales)
  - For ECGs
  - For biological samples (including for laboratory tests, PK samples)
  - For IWRS
  - For electronic data capture completion guidelines

Study-site investigational product binder

- Supplies:

Blood collection tubes, storage tubes, preprinted labels (or tubes labeled with preprinted labels), and related supplies for the collection and shipment of biological samples (including for laboratory tests, PK samples). These supplies will be provided by the central laboratories (where different central laboratories may be used for different sample types, such as one for PK samples, etc).

Urine and routine blood collection kits

Urine pregnancy test kits

Urine drug screen test kit

Alcohol breath test

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.

Primary study-specific ethical concerns and study-specific mitigations are as follows:

- Changing medications:

For subjects with prestudy PP1M or PP3M stability, a concern may be associated with changing from an antipsychotic that had been providing acceptable levels of efficacy and tolerability before the study to a new investigational antipsychotic within the study. This risk is limited in the current study by changing only the formulation or dose, not the active substance, of the antipsychotic.

For subjects with prestudy injectable risperidone stability, the above risk is limited in the current study by providing an equivalently converted antipsychotic dose and by the minimal nature of the change in antipsychotic type (substituting the combination of parent molecule [risperidone] and metabolite [paliperidone] for the metabolite [paliperidone] alone).

For subjects with reason to change their prestudy oral antipsychotic, the above concern does not apply; they will be enrolled only per valid reason to change their previous antipsychotic (including problems with efficacy, safety, or tolerability, or per preference for a LAI medication).

For all subjects, the study also allows subjects to continue taking other nonantipsychotic medications that they had been using at entry to the study, to initiate or make changes to nonantipsychotic medications during study (within some limitations), and to receive supplementation with oral antipsychotics during the study (within some limitations).

- Long-acting formulation: A concern may be associated with the long-acting nature of the study drug. 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.
- High doses: A concern may be associated with the high doses of the investigational study drug. The Sponsor has performed PK simulations to select these doses, and has 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 should yield tolerability that is similar to existing paliperidone and risperidone formulations. Beyond those aggregate analyses, the Sponsor also considered individual cases of subjects who had high exposures to PP3M during previous studies, and found that high concentrations of paliperidone were well tolerated. Still, the current study includes extra safety assessments around the time of expected peak plasma paliperidone levels.

- Large volumes: A concern may be associated with the large volumes of the intramuscular injections. The Sponsor has consulted nursing guidelines for the acceptability of these volumes, and has accordingly restricted the administration of PP6M into the gluteal muscle. The study also includes structured assessments of the injection sites and guidelines for handling any associated adverse events.

The volume of blood to be collected in this study is not considered to pose an ethical concern or a special risk. The volume to be collected over any 6-month period of the study is less than the volume collected in a single day (with an allowed 2-month frequency) associated with a charitable blood donation.[1]

More generally, the study also includes many safety assessments and eligibility criteria designed to ensure that the population is appropriate for enrollment and is carefully assessed throughout the study.

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 drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

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

At least once a year, the IEC/IRB will be asked to review and reapprove this study, 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 (not a legal representative, but the subject himself or herself) 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.

A separate ICF will also be signed by the subject's designated unpaid caregiver (such as a family member, significant other, or friend, with knowledge of the subject) who is willing to complete the IEQ assessments and who is willing to support the investigator and subject during other study assessments if requested. The designated caregiver must sign the ICF prior to the first baseline assessment. In case no designated caregiver is available for a subject or in case the designated

caregiver cannot or is not willing to provide informed consent, the subject will nevertheless be eligible for participation upon his or her own informed consent.

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.

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 nonacceptance, 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 drug to the study site:

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

- Signed and dated Clinical Trial Agreement, which includes the financial agreement.
- Any other documentation required by local regulations.

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

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

17.3. Subject Identification, Enrollment, and Screening Logs

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

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth (as allowed by local regulations). In cases where the subject is not randomized into the study, the date seen and date of birth (as allowed by local regulations) 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; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

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

The eCRFs are prepared and provided by the Sponsor for each subject. 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 the eCRF, 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 electronic data capture tool. If corrections to an 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 electronic data capture tool at their own initiative or as a response to an auto-query (generated by the electronic data capture 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 eCRFs 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 eCRFs 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 post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records). 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.

Central monitoring will take place for data identified by the Sponsor as requiring central review.

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. Poststudy followup information, eg, as described in Section 12.3.1 (All Adverse Events), will not be considered to be part of a "last visit" and will not be included in the study database. 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

In addition to the planned closure at 12 months after the last subject has been randomized in the Double-blind Phase, the Sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

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

17.10. On-Site Audits

Representatives of the Sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. 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 paliperidone palmitate 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, 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 paliperidone palmitate 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 CSR 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 important assessment parameters of the study will be used to determine a coordinating investigator. 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 data specific to the study site after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the Sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the Sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the Sponsor will review these issues with the investigator. The Sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have

been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the Sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

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

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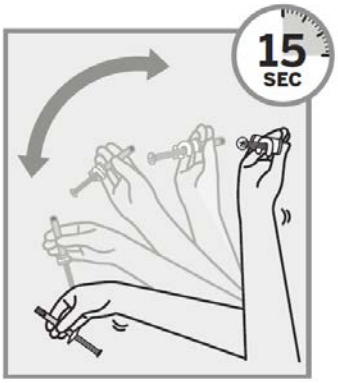
ATTACHMENTS

Attachment 1: Guidelines for the Intramuscular Injection of Paliperidone Palmitate or Placebo During the Double-blind Phase

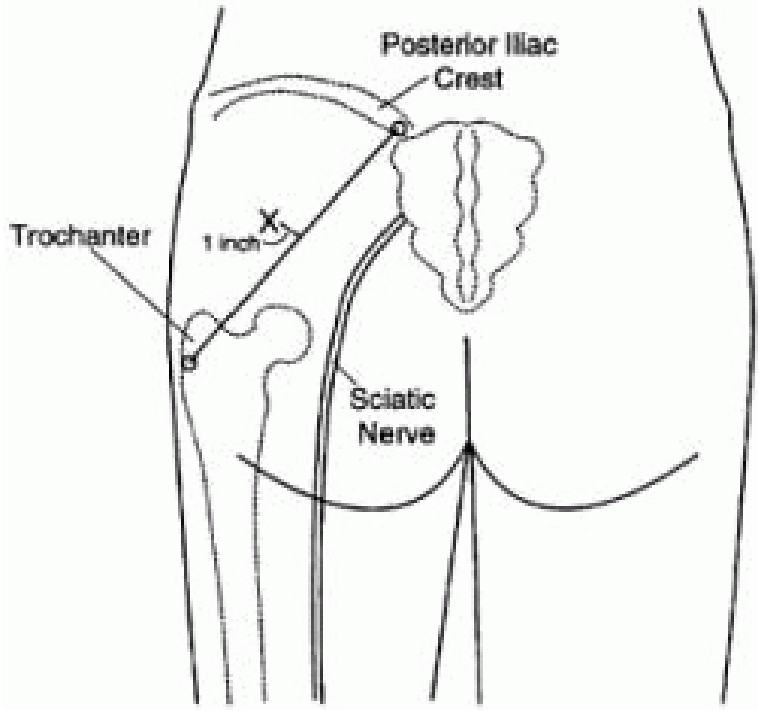
In the Double-blind Phase, these guidelines should be used. In the Transition Phase and the Maintenance Phase, the guidelines in the prescribing information for PP1M and PP3M should be used.

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.

During the Double-blind Phase, injections will rotate across sides of the body (left or right), as shown in Table 5, 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: Relapse Criteria for PANSS Total Score

A prespecified minimum change in PANSS total score is one of the possible qualifying criteria for relapse. The table below correlates a subject's score at randomization to the minimum posttreatment score during the Double-blind Phase that would meet the relapse criterion. If a subject's score during the Double-blind Phase is greater than or equal to the value in the second column, then the subject should be considered for relapse. The relapse should then be re-evaluated for confirmation at a visit 3 to 7 days later (previously unscheduled, if necessary).

Criteria for Relapse According to PANSS Total Score

Score at Randomization	Relapse Criterion Score
≤40 Points	Increase of 10 points
30[a]	40
31	41
32	42
33	43
34	44
35	45
36	46
37	47
38	48
39	49
40	50
>40 Points	Increase of 25%
41	44
42	45
43	47
44	48
45	49
46	50
47	52
48	53
49	54
50	55
51	57
52	58
53	59
54	60
55	62
56	63
57	64
58	65
59	67
60	68
61	69
62	70
63	72
64	73
65	74
66	75
67	77
68	78
69	79
≥70 Points	Not eligible to enter study or to continue to Double-blind Phase

Key: PANSS = Positive and Negative Syndrome Scale.
[a] A score of 30 is the lowest possible value on the PANSS.

Criteria for Relapse According to PANSS Total Score

Note: The percent change is calculated after subtracting 30 from the Randomization score, as this represents the lowest score on the PANSS:

$$\%\ increase = \frac{Current\ score - Score\ at\ randomziation}{Score\ at\ randomization - 30} \times 100$$

Attachment 3: Anticipated Events for Study R092670PSY3015

Anticipated Event

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

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

- Schizophrenia
- Psychotic disorder
- Hallucination, auditory
- Hallucination, visual
- Hallucination
- Paranoia
- Delusion
- Apathy
- Substance use

Reporting of Anticipated Events

All adverse events will be recorded in the eCRF regardless of whether considered to be anticipated events and will be reported to the Sponsor as described in Section 12.3.1 (All Adverse Events). Any anticipated event that meets serious adverse event criteria will be reported to the Sponsor as described in Section 12.3.2 (Serious Adverse Events). These anticipated events are exempt from expedited reporting as individual single cases to Health Authorities. However, if based on an aggregate review, it is determined that an anticipated event is possibly related to study drug, the Sponsor will report these events in an expedited manner.

Anticipated Event Review Committee

An Anticipated Event Review Committee will be established to perform reviews of prespecified anticipated events at an aggregate level. The Anticipated Event Review Committee is a safety committee within the Sponsor's organization that is independent of the Sponsor's study team. The Anticipated Event Review Committee will meet to aid in the recommendation to the Sponsor's study team as to whether there is a reasonable possibility that an anticipated event is related to the study drug.

Statistical Analysis

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate Anticipated Events Safety Monitoring Plan.

INVESTIGATOR AGREEMENT

R092670 (paliperidone palmitate)
Clinical Protocol R092670PSY3015 Amendment 3

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 intervention, 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): Arun Singh, DO

Institution: PPD Janssen Research & Development

PPD

[redacted]

(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.

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Approved, Date: 11 February 2019

Janssen Research & Development *

Clinical Protocol

COVID-19 Appendix

A Double-blind, Randomized, Active-controlled, Parallel-group Study of Paliperidone Palmitate 6-Month Formulation

Protocol R092670PSY3015; Phase 3
Amendment 3/USA-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: 2017-001941-28

Status: Approved
Date: 20 April 2020
Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-RIM-32995, 1.0

Local: EDMS-ERI-130495167, 5.0

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

PROTOCOL AMENDMENTS

DOCUMENT HISTORY	
Document	**Date**
Amendment 3/USA-1	20 April 2020
Amendment 3	11 February 2019
Amendment 2	28 September 2018
Amendment 1	21 March 2018
Original Protocol	28 August 2017

Amendment 3/USA-1, 20 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 judgement of the investigator to protect the health and well-being of participants and site staff.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible 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, evaluation of relapse criteria, and questionnaires. Please note, the visit windows included in the Time and Events Schedule are still applicable.
  - *Administration of study drug:* All subjects in the R092670PSY3015 study have received all injections of study drug; therefore, there will be no interruptions in administration of study drug.
  - *Study assessments:*
    - Relapse assessment: Please evaluate as many elements of the relapse criteria as possible. The Positive and Negative Syndrome Scale for Schizophrenia (PANSS) total score is the most important element for assessment of relapse. After the PANSS has been administered, the investigator or delegate must perform a review to determine if the relapse criteria have potentially been met (per Section 2.1.2.2 and Attachment 2). If so, a confirmation visit will need to be conducted as outlined in Section 2.1.2.2 and Attachment 2. The confirmation visit may be performed remotely.
    - Evaluation of secondary and exploratory endpoints (Personal and Social Performance scale, Clinical Global Impression - Severity, Columbia Suicide Severity Rating Scale, Healthcare Resource Utilization Questionnaire, Involvement Evaluation Questionnaire, Schizophrenia Quality of Life Scale, Illness Management and Recovery, 9-item Treatment Satisfaction Questionnaire for Medication, Satisfaction With Participation in Social Roles): 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.
    - 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 is 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 visit, if applicable.
  - Please notify the treating physician of the subject's participation in Study R092670PSY3015, and details of the study treatments in a blinded fashion.
- **Monitoring:** In addition to subject study visits, monitoring visits and data cleaning activities need to be completed prior to final database lock. On-site monitoring visits may not be possible due to local regulations, restrictions and guidance. In these cases, the Site Manager (and Independent Drug Monitor) will arrange to conduct site monitoring visits and activities remotely. Site closeout visits will be postponed until Site Managers and Independent Drug Monitors are able to return to the site to complete final closeout activities.

INVESTIGATOR AGREEMENT

R092670 (paliperidone palmitate) Clinical Protocol R092670PSY3015 Amendment 3/USA-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): Panna Sanga, MD

Institution: PPD Janssen Research & Development

Signature: PPD Date: 20th APR 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. 6
Approved, Date: 20 April 2020