Janssen Research & Development *

Statistical Analysis Plan

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

Protocol R092670PSY3015; Phase 3

R092670 (paliperidone palmitate)
Revised on 26 May 2020

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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TABLE OF CONTENTS

AMENDMENT HISTORY

26 May 2020	Change since Version 3.0	
Section	Change	Rationale
5.2.2.3	Added one supplementary analysis S5	Evaluate the potential impact of COVID-19 related remote visits to the primary efficacy analysis

8 May 2020	Change since Version 2.0	
Section	Change	Rationale
2.1	Added PSP in tables 1a and few notes in Tables 1a to 1f	According to Time and Events Table
2.1	Modified text about how to deal with the data for five subjects from Turkey who received a Month 12 injection	Five subjects from Turkey who received a Month 12 injection
2.3.4.	Added criteria of identifying Major Protocol Violation	Per an agreement with the FDA dated on 2Mar2020
2.4.	Replace subgroup BMI at Baseline (MA) by BMI Baseline (DB)	After screen visit, the body weight was only corrected at the start of DB phase
2.5.1	Added definition of Date of DB Month 12 for five Turkey subjects who received a Month 12 injection	Five subjects from Turkey who received a Month 12 injection
5.2.2.3	Added supplementary Analysis S4	Per an agreement with the FDA, to exclude 3 Mexico subjects who were affected by the delay of drug supply
5.3.6.1	Made the changes so it's consistent with the analysis in Study PSY3011	Due to protocol amendment 3
5.4.1.2	Added scoring algorithm for SPSR	Requested by programming
5.4.2.2	Added scoring algorithm for TSQM-9	Requested by programming
6.2.1	Removed analysis related to insulin	Insulin data are not collected in the study
8	Added scoring algorithm for SQLS-R4	Requested by programming
Reference	Added a reference related to TSQM-9	The reference is needed in Section 5.4.2.2
6.1.1, 6.1.2, 6.1.3, and Attachment 1	Changed AEDECOD for Special Interest AEs	Due to the new MedDRA version

5 April 2019	Change since Version 1.0	
Section	Change	Rationale
1.2, 1.4, 2.1, 2.3.4, 2.6.2, 6.1	Limit Double-blind phase to 12 months	Per Protocol Amendment 3
2.1	Summarize number of post-study contacts	Per a Missing data Prevention Plan imposed in April/May 2019
2.1 Table 1c, and 6.4	In the analysis, the average predose ECG value will be summarized separately for those who were on pre-study status categories (oral antipsychotic, on injectable risperidone, PP1M initiation, PP1M stability, and PP3M stability).	Clarify analysis of ECG data
2.3.1	Way to handle re-screened subjects	Per Protocol Amendment 2
2.4	Add three sub-groups	
2.5.1	Definition of reference days, and dates for each phase.	Necessary for programming
2.5.1, and throughout the SAP	Define date of DB Month 12	Due to Protocol Amendment 3
4.1	Remove “alcohol” from analysis	Per Protocol Amendment 2
4.4.1	Define duration of exposure	Needed in analysis
5.2, 5.3 and their	Based on protocol amendment 3,	Per Protocol Amendment 3

sub-sections	limiting DB phase to 12 Month	
5.2 and its sub-sections	Restructure these sections to include upfront the definition of the primary estimand, followed by the corresponding analyses. Clarify the definitions for the primary and supplementary estimands. The changes made do not affect the detailed analyses specified in the previous version of the SAP finalized on 16Mar2018.	Per new ICH E9(R1) guidance. The guidance could be found online: http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html#9-2
5.4.1.2 and 5.4.2.2	Remove ANCOVA models for SPSR and TSQM-9	The data will only be summarized for subjects who entered the study on an oral antipsychotic. No ANCOVA models are needed.
8	Data about Use of Nicotine will only be listed	Too many types/units for the data of use of nicotine
8	Add scoring algorithm for calculating the total SQLS-R4	Necessary for programming

ABBREVIATIONS

ADA	American Diabetes Association
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ANCOVA	analysis of covariance
BARS	Barnes Akathisia Rating Scale
BMI	body mass index
C-SSRS	Columbia-Suicide Severity Rating Scale
CGI-S	Clinical Global Impression-Severity
CI	confidence interval
CRF	case report form
CSR	Clinical Study Report
DB	double-blind
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	electrocardiogram
EOP	end-of-phase
EOS	end-of-study
EPS	extrapyramidal symptoms
ER	extended release
EU	European Union
FDA	Food and Drug Administration
FU	follow-up
HOMA	homeostasis model assessment
HRUQ	Health Resource Utilization Questionnaire
ICH	International Conference on Harmonization
IEQ	Involvement Evaluation Questionnaire
IMR	Illness Management and Recovery
ITT	intent-to-treat
IWRS	Interactive Web Response System
KM	Kaplan-Meier
LOCF	last observation carried forward
LS	least-squares
MA	Maintenance
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
MPV	major protocol violation
OL	Open-label
PANSS	Positive and Negative Syndrome Scale for Schizophrenia
PP	per protocol
PP1M	paliperidone palmitate 1-month formulation
PP3M	paliperidone palmitate 3-month formulation
PP6M	paliperidone palmitate 6-month formulation
PSP	Personal and Social Performance Scale
PSRE	potentially suicide-related event
ROW	Rest of World
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Simpson and Angus Rating Scale
SD	standard deviation
SE	standard error
SPSR	Satisfaction With Participation in Social Roles (scale)
SQLS-R4	Schizophrenia Quality of Life Scale, Revision 4
TRANS	Transition
TSQM-9	abbreviated 9-item Treatment Satisfaction Questionnaire for Medication
VAS	Visual Analog Scale

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis populations, derived variables and statistical methods for the analysis of efficacy and safety data from study R092670PSY3015.

1.1. Trial 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 evaluate 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 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.

1.2. Trial 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.

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 total 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.

1.3. Statistical Hypotheses for Trial Objectives

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

1.4. Sample Size Justification

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 JRD's previous placebo-controlled relapse prevention studies with oral paliperidone ER/PR, PP1M, and PP3M,[1],[2],[3] 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%).[4]
- 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%).[4] 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,[5] the maximum was therefore set at 13.0%.[4]

- Prior scientific advice from the Committee for Medicinal Products for Human Use had recommended a noninferiority margin of 10%.[4]
- 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. [4]

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 or Maintenance Phase.

1.5. Randomization and Blinding

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.

The randomization code and treatment code are assigned using an Interactive Web Response System (IWRS). The investigator will not be provided with randomization codes. To maintain the blind, due to differences in the syringe sizes used between PP6M and PP3M, the study drug administrator is not allowed to perform any other study-related procedures. The study staff, other than the study drug administrator, are not allowed to view the syringe or needle or observe the injection.

Subjects in the PP6M treatment group will receive matched placebo injections every 3 months when not receiving active medication to maintain the blind.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

Because subjects do not always adhere to the protocol visit schedule, the following rules are applied to assign visit windows to protocol-defined visits for data analysis. These windows are distinct from the visit windows specified in the Time and Event (T&E) Schedule in the protocol to inform the conduct of the study. Listed in Tables 1 are the visit windows (time points), and the corresponding day ranges and the target days for each protocol-defined visit. The relative days are with respect to the start date of Transition (Trans.), Maintenance (MA), and Double-blind phases, depending on which phase a visit belongs to. No data from the Follow-up phase will be considered with visit windows.

If a subject has 2 or more actual visits in 1 visit window [other than Screening windows, Baseline (OL, MA, or DB) window, and Average Pre-dose window for ECG], the visit closest to the target day will be used as the protocol-defined visit for that visit window. If 2 actual visits are equidistant from the target day within a visit window, the later visit will be used.

If a visit window has no scheduled visits but does have unscheduled visits, then the unscheduled visit closest to the scheduled visit will be used for that protocol visit.

PANSS scores measured at the confirmation visit (solely for the purpose of confirming relapse) will not be included in statistical analyses. As specified in the protocol, once relapse is confirmed in the Double-blind phase, subject will have the EOP/Early withdrawal visit performed. PANSS scores measured close to (and including) the date of confirmation visit will be recorded in the EOP/Early withdrawal visit. Hence there won't be information loss by discarding PANSS score measured at the confirmation visit.

Final post-baseline (OL) assessment during the Open-label Phase will be used as the value for Baseline (DB) visit.

Based on the Amendment 3 of the protocol that was issued on 13 February 2019, the Double-blind (DB) phase is limited to 12 months. However, there were five subjects from Turkey who have received a Month 12 injection and have data after Month 12 of the DB phase because the protocol amendment 3 was not approved in the country when these subjects reached Month 12. The date of DB Month 12 is defined in Section 2.5.1. of the SAP. As shown in Tables 1a to 1f, the efficacy and safety data collected after Month 12 of Double-blind phase (visit 33b) will not be included in over-time summaries, nor be considered as the End point of the DB phase. However, all data from the Double-blind phase, regardless of whether the data are collected before or after the DB Month 12 date, will be included in data listings, subject's profiles, and the overall summaries (eg, treatment exposure, AE, concomitant medication, protocol deviation, etc.) for the Double-blind phase.

Table 1a: Time Intervals for Visits for Positive and Negative Syndrome Scale (PANSS), SPSR, PSP, Abbreviated TSQM-9, HRUQ, IEQ, SQLS, and IMR

Analysis Phase	Scheduled Visit Number	Label on Output	Time Interval in Phase Day	Target Time in Phase Day
	1	Screening[a]	Pre-OL dose	-28 to -1 before OL dosing
Trans.[b]	2a, 2b, 2c, 2d or 2e	Baseline (OL.)[b]	≤ 1st Trans. injection date	1
MA[c]	1,2f	Baseline (OL.)[d]	≤ MA injection date	1
		Baseline (MA)[e]		
MA	MA Final Visit	End Point (MA)[f]	≥ 2 (MA day)	30 (PP1M) or 90 (PP3M)
Double-blind	7b	Baseline (DB)[f]	1st OL injection date relative day +1 to ≤1	1
Double-blind	13	Month 3 (DB)	2 to 137	92
Double-blind	20	Month 6 (DB)	138 to 228	183
Double-blind	26	Month 9 (DB)	229 to 319	274
Double-blind	33a or 33b	Month 12 (DB)	320 to DB Day[g] of Visit 33a or 33b if it's ≥ 320	365
Double-blind	DB Final Visit	End Point (DB)	Last record[g] before/on Visit 33a or 33b	

[a] The Screening visit window is defined for PANSS, SPSR and Abbreviated TSQM-9 which are scheduled to be performed at Visit Number 1 (Screening). For PANSS, if there is only 1 pre-dose assessment and it is prior to OL Study Day 1 (ie, Reference Start Date), then the same value will be assigned to the Screening and Baseline (MA) visit windows.

[b] Trans. = Transition Phase, PANSS score only, and only applicable to those who enter Transition Phase.

[c] MA = Maintenance Phase. Only applicable to PANSS and PSP

[d] Only applicable to those who do not enter Transition Phase, and only applicable to PANSS and PSP

[e] Only applicable to those who enter Maintenance Phase, and only applicable to PANSS and PSP

[f] Final post-baseline (MA) assessment during the Maintenance Phase will be used as the value for Baseline (DB) visit.

[g] If the End of DB Phase visit date is after Visit 33b, use the data on or before Date of DB Month 12 that is defined in Section 2.5.1.

OL=Open-label, DB=Double-blind.

Table 1b: Time Intervals for Visits for Prolactin from Laboratory Tests, and EPS (including AIMS, BARS, and SAS)

Analysis Phase	Scheduled Visit Number	Label on Output	Time Interval in Phase Day	Target Time in Phase Day
	1	Screening	Pre-OL Dose	-28 to -1 before OL dosing
Trans.[a]	2a, 2b, 2c, 2d or 2e	Baseline (OL.)[a]	≤ 1st Trans. injection date	1
MA[b]	1,2f	Baseline (OL.)[c]	≤ MA injection date	1
		Baseline (MA)[d]		
MA	MA Final Visit	End Point (MA)[e]	2 to End of MA	30 (PP1M) or 90 (PP3M)
Double-blind	7b	Baseline (DB)[e]	1st OL injection date relative day +1 to ≤1	1
Double-blind	9	Week 3 (DB)	2 to 25	22
Double-blind	10	Week 4 (DB)	26 to 32	29
Double-blind	11	Week 5 (DB)	33 to 47	36
Double-blind	12	Month 2 (DB)[f]	48 to 121	60
Double-blind	20	Month 6 (DB)	122 to 196	183
Double-blind	23	Month 7 (DB)	197 to 226	211
Double-blind	25	Month 8 (DB)	227 to 303	242
Double-blind	33a or 33b	Month 12 (DB)	304 to DB Day[g] of Visit 33a or 33b if it's ≥ 304	365
Double-blind	DB Final Visit	End Point (DB)	Last record[g] before/on Visit 33a or 33b	

[a] Trans. = Transition Phase, only applicable to those who enter the Transition Phase.
[b] MA = Maintenance Phase.
[c] Only applicable to those who do not enter the Transition Phase.
[d] Only applicable to all patients who enter Maintenance Phase. For subjects who do not enter the Transition Phase, Baseline (MA) = Baseline (OL).
[e] Final post-baseline (MA) assessment during the Maintenance Phase will be used as the value for Baseline (DB) visit.
[f] Only applicable to EPS data.
[g] If the End of DB Phase visit date is after Visit 33b, use the data on or before Date of DB Month 12 that is defined in Section 2.5.1.

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OL=Open-label, DB=Double-blind

Table 1c: Time Intervals for Visits for CGI-S, vital signs, and ECG

Analysis Phase	Scheduled Visit Number	Label on Output	Time Interval in Phase Day	Target Time in Phase Day
	1	Screening	<1	-28 to -1 before OL dosing
Trans.[a]	2a, 2b, 2c, 2d or 2e	Baseline (OL.)[a,h]	≤ 1st Trans. injection date	1
MA[b]	1,2f	Baseline (OL.)[c,h]	≤ MA injection date	1
		Baseline (MA)[d]		
MA	MA Final Visit	End Point (MA)[e]	2 to End of MA	30 (PP1M) or 90 (PP3M)
Double-blind	7b	Baseline (DB)[e]	1st OL injection date relative day +1 to ≤1	1
Double-blind	10	Week 4 (DB)	2 to 44	29
Double-blind	12	Month 2 (DB)[f]	45 to 75	60
Double-blind	13	Month 3 (DB)[f]	76 to 105	92
Double-blind	14	Month 4 (DB)[f]	106 to 133	120
Double-blind	15	Month 5 (DB)[f]	134 to 165	148
Double-blind	20	Month 6 (DB)[f]	166 to 196	183
Double-blind	20	Month 6 (DB)[g]	45 to 347	183
Double-blind	23	Month 7 (DB)[f]	197 to 226	211
Double-blind	25	Month 8 (DB)[f]	227 to 257	242
Double-blind	26	Month 9 (DB)[f]	258 to 287	274
Double-blind	27	Month 10 (DB)[f]	288 to 315	302
Double-blind	28	Month 11 (DB)[f]	316 to 347	330
Double-blind	33a or 33b	Month 12 (DB)	348 to DB Day[i] of Visit 33a or 33b if it is ≥ 348	365
Double-blind	DB Final Visit	End Point (DB)	Last record[i] before/on Visit 33a or 33b	

[a] Trans. = Transition Phase, only applicable to those who enter the Transition Phase. For ECG, Baseline (OL) is the average predose ECG value that is defined as the average of all non-missing predose ECG results.
[b] MA = Maintenance Phase.
[c] Only applicable to those who do not enter the Transition Phase. For ECG, Baseline (OL) is the average predose ECG value that is defined as the average of all non-missing predose ECG results.
[d] Only applicable to all patients who enter Maintenance Phase. For subjects who do not enter the Transition Phase, Baseline (MA) = Baseline (OL).
[e] Final post-baseline (MA) assessment during the Maintenance Phase will be used as the value for Baseline (DB) visit.
[f] Only applicable to CGI-S
[g] Only applicable to Vital Sign and ECG
[h] In the analysis, the average predose ECG value will be summarized separately for those who were on oral antipsychotic, on injectable risperidone, PP1M initiation, or on PP1M/PP3M stability at the time of entering the study.
[i] If the End of DB Phase visit date is after Visit 33b, use the data on or before Date of DB Month 12 that is defined in Section 2.5.1.

OL=Open-label, DB=Double-blind

Table 1d: Time Intervals for Visits for Laboratory Tests (other than prolactin)

Analysis Phase	Scheduled Visit Number	Label on Output	Time Interval in Phase Day	Target Time in Phase Day
	1	Screening	<1	-28 to -1 before OL dosing
Trans.[a]	2a, 2b, 2c, 2d or 2e	Baseline (OL)[a]	≤ 1st Trans. injection date	1
MA[b]	1,2f	Baseline (OL)[c]	≤ MA injection date	1
		Baseline (MA)[d]		
MA	MA Final Visit	End Point (MA)[e]	2 to End of MA	30 (PP1M) or 90 (PP3M)
Double-blind	7b	Baseline (DB)[e]	1st OL injection date relative day +1 to ≤1	1
Double-blind	20	Month 6 (DB)	2 to 273	183
Double-blind	33a or 33b	Month 12 (DB)	274 to DB Day[f] of Visit 33a or 33b if it's ≥ 274	365
Double-blind	DB Final Visit	End Point (DB)	Last record[f] before/on Visit 33a or 33b	

[a] Trans. = Transition Phase, only applicable to those who enter the Transition Phase.
[b] MA = Maintenance Phase.
[c] Only applicable to those who do not enter the Transition Phase.
[d] Only applicable to those who enter Maintenance Phase. For subjects who do not enter the Transition Phase, Baseline (MA) = Baseline (OL).
[e] Final post-baseline (MA) assessment during the Maintenance Phase will be used as the value for Baseline (DB) visit.
[f] If the End of DB Phase visit date is after Visit 33b, use the data on or before Date of DB Month 12 that is defined in Section 2.5.1.

OL=Open-label, DB=Double-blind

Table 1e: Time Intervals for Visits for C-SSRS				
Analysis Phase	Scheduled Visit Number	Label on Output	Time Interval in Phase Day	Target Time in Phase Day
	1	Screening	<1	-28 to -1 before OL dosing
MA[a]	1,2f	Baseline (MA)[b]	≤ MA injection date	1
MA	MA Final Visit	End Point (MA)[c]	2 to End of MA	30 (PP1M) or 90 (PP3M)
Double-blind	7b	Baseline (DB)[c]	1st OL injection date relative day +1 to ≤1	1
Double-blind	10	Week 4 (DB)	2 to 44	29
Double-blind	12	Month 2 (DB)	45 to 75	60
Double-blind	13	Month 3 (DB)	76 to 105	92
Double-blind	14	Month 4 (DB)	106 to 133	120
Double-blind	15	Month 5 (DB)	134 to 165	148
Double-blind	20	Month 6 (DB)	166 to 197	183
Double-blind	23	Month 7 (DB)	198 to 227	213
Double-blind	25	Month 8 (DB)	228 to 257	242
Double-blind	26	Month 9 (DB)	258 to 287	274
Double-blind	27	Month 10 (DB)	288 to 319	302
Double-blind	29	Month 11 (DB)	320 to 350	337
Double-blind	33a or 33b	Month 12 (DB)	351 to DB Day[d] of Visit 33a or 33b if it's ≥ 351	365
Double-blind	DB Final Visit	End Point (DB)	Last record[d] before/on Visit 33a or 33b	

[a] MA = Maintenance Phase.
[b] Only applicable to those who enter Maintenance Phase. For subjects who do not enter the Transition Phase, Baseline (MA) = Baseline (OL).
[c] Final post-baseline (MA) assessment during the Maintenance Phase will be used as the value for Baseline (DB) visit.
[d] If the End of DB Phase visit date is after Visit 33b, use the data on or before Date of DB Month 12 that is defined in Section 2.5.1.

OL=Open-label, DB=Double-blind

Table 1f: Time Intervals for Subject Injection Site Rating VAS, and Investigator Injection Site Rating

Analysis Phase	Scheduled Visit Number	Label on Output	Time Interval in Phase Day	Target Time in Phase Day
Trans.[a]	Trans. Final visit	End Point (Trans.)[a]	2 to End of Trans	
MA[b]	MA Final Visit	End Point (MA)[c]	2 to End of MA	30 (PP1M) or 90 (PP3M)
Double-blind	7b	Baseline (DB)[c]	1st OL injection date relative day +1 to ≤1	1
Double-blind	8	Day 3 (DB)	2 to 12	3
Double-blind	9	Week 3 (DB)	13 to 56	22
Double-blind	13	Month 3 (DB)	57 to 105	92
Double-blind	14	Month 4 (DB)	106 to 151	120
Double-blind	20	Month 6 (DB)	152 to 228	183
Double-blind	26	Month 9 (DB)	229 to 287	274
Double-blind	27	Month 10 (DB)	288 to 333	302
Double-blind	33a or 33b	Month 12 (DB)	334 to DB Day[d] of Visit 33a or 33b if it's ≥ 334	365
Double-blind	DB Final Visit	End Point (DB)	Last record[d] before/on Visit 33a or 33b	

[a] Trans. = Transition Phase, only applicable to those who enter Transition Phase.
[b] MA = Maintenance Phase.
[c] Final post-baseline (MA) assessment during the Maintenance Phase will be used as the value for Baseline (DB) visit.
[d] If the End of DB Phase visit date is after Visit 33b, use the data on or before Date of DB Month 12 that is defined in Section 2.5.1.

OL=Open-label, DB=Double-blind

Hemoglobin A1c and urinalysis testing will be summarized at baseline (MA), end point (MA), and end point (DB).

To prevent missing data for subjects who withdraw early in the Double-blind phase and do not provide the data in the Follow-up phase up to the end of Month 12 from their first Double-blind injection, multiple contacts to the subjects by the sites will be made to get the information regarding safety and information related to a relapse event. The number of subjects who agreed to be contacted at the time of withdrawal will be summarized by the 2 treatment groups in the Double-blind phase.

2.2. Pooling Algorithm for Analysis Centers

There will be no pooling for the study sites in the efficacy and safety analyses.

2.3. Analysis Populations

Four analysis populations are defined: the open-label intent-to-treat (OL ITT) analysis population, the double-blind intent-to-treat (DB ITT) analysis population, the all randomized analysis population, and the per-protocol analysis population (PP). The DB ITT analysis populations is the primary analysis population for the primary efficacy endpoint.

2.3.1. Open Label Intent-to-Treat (OL ITT) Analysis Population, and OL Safety Population

The open-label intent-to-treat analysis population, denoted as OL ITT, includes all subjects who have received at least 1 dose of open-label study drug (excluding the first study participation of these re-screened subjects mentioned in the first paragraph), including transition and maintenance phases. The open-label safety analysis population (OL Safety) is the same as the OL ITT analysis population.

Protocol amendment 2 permitted the withdrawal of subjects who had an incomplete injection or received an unintended dosing or administration of study drug during the Transitional Phase or Maintenance Phase, and re-screening of these subjects. For these subjects, only data collected during the second study participation will be included in the data summary. The data collected during the first study participation will only be listed in the subject's profile, and would not be included in the summaries for the OL ITT analysis population.

2.3.2. Double-blind Intent-to-Treat (DB ITT) Analysis Population

The DB intent-to-treat analysis population, denoted as DB ITT, includes all subjects who are randomly assigned to treatment group of either PP6M or PP3M during the Double-blind Phase, receive at least 1 dose of double-blind study drug. The Double-blind safety analysis population (DB Safety) will be the same as the DB ITT population.

2.3.3. All Randomized Analysis Population

The all randomized population includes all subjects who are randomly assigned to treatment group of either PP6M or PP3M during the Double-blind Phase.

2.3.4. Per-Protocol Analysis Population

The per-protocol analysis population includes subjects who are randomly assigned to treatment (PP6M or PP3M) during the Double-blind Phase and receive at least 1 dose of double-blind study drug. Subjects should not have Major Protocol Violations (MPV) up to Visit 33a or 33b of the double-blind phase (DB Month 12 date), that is, major protocol deviations that may impact efficacy such as violations of intended study population, errors in treatment assignment or use of excluded medication.

Criteria to identify MPVs:

The categories and examples for subjects who are considered as having had MPVs, that is, the subjects who are in the intent-to-treat analysis set but are excluded from the per-protocol analysis set (Inclusion/Exclusion/Eligibility Criteria numbers referenced below are those from Amendment 3 of the Protocol) are listed below:

1. Violations of Inclusion and Exclusion Criteria that are deemed to affect the primary efficacy endpoint (time to relapse at Month 12 of the Double-blind phase). Examples are: a full PANSS score ≥ 70 points at screen (violation of Inclusion Criteria 6), diagnosis at screening is not schizophrenia (violation of Inclusion Criteria 3), had attempted suicide within 12 months before screening (violation of Exclusion Criteria 2)
2. Subjects who should not be randomized to enter the Double-blind phase. For example, the PANSS total score at the randomization (Visit 7b) is ≥ 70 (violation of Eligibility Criteria 1), or have scores of > 4 points at the randomization (Visit 7b) for at least one of the following PANSS items P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), P6 (suspiciousness/ persecution), P7 (hostility), G8 (uncooperativeness), and G14 (poor impulse control) (violation of Eligibility Criteria 2)
3. Subjects who have errors in treatment of the Maintenance or Double-blind phases. Examples are: Subjects took the study medication that deviated from the assignment of the IWRS in the Maintenance or Double-blind phases, Study drug was not fully administrated at any visit in the Maintenance or Double-blind phase, Subjects took moderate dose level at maintenance though they were supposed to take high dose level according to the protocol, etc.
4. Use of excluded medication, including subjects that used excluded Long Active Injectable (LAI) antipsychotic during Maintenance or Double-blind phases
5. Others, for example, subjects that had no PANSS score data during the entire Double-blind phase

Subjects with a major deviation and/or a MPV will be determined prior to unblinding the data.

2.3.5. Pharmacokinetics Analysis Population

The Plan of PK Analysis will be addressed in a separate document.

2.3.6. Pharmacodynamics Analysis Population

The Plan of PK-PD Analysis will be addressed in a separate document.

2.4. Definition of Subgroups

Subgroup	Version	Definition
Region	1	EU, US, Non-EU/Non-US
Age Group	1	• 18-25 • 26-50 • 51-65

Subgroup	Version	Definition
		• >65
Race	1	White, Black, Non-black/Non-white
Sex	1	male, female
BMI at DB Baseline	1	• normal <25 kg/m^2 • overweight 25-<30 kg/m^2 • obese ≥30 kg/m^2
Stabilized PP formulation (PP1M or PP3M in Maintenance Phase, for primary efficacy and AE summary) (MAR)	1	• PP1M • PP3M
Dose level: (A stratification factor at randomization that based: Dose Level in Maintenance Phase, for primary efficacy and AE summary) (MADL)	1	This subgroup is only defined for randomized subjects: • moderate • high
Prior antipsychotic use (only applicable to analyses of ECG data)	1	• Oral antipsychotic • Injectable Risperidone • PP1M initiation • PP1M stability • PP3M stability

2.5. Study Day and Relative Day

2.5.1. Study Day Definitions

The study day is defined based on the phase a visit happens. Three phases are considered when the study day is calculated: Transition, Maintenance, and Double-blind. Both Transition and Maintenance Phases are also referred as Open-label phase.

The 'Reference Start Date' or 'Start Day 1' for a subject is the date of the first study injection during the Open-Label Phase. The 'Reference End Date' for a subject is the end-of-study (EOS) visit, the completion/withdrawal date, the last date of study drug administration during the study, or the last OL or DB evaluation date collected in QS, EG, VS, and LB data.

Date of Maintenance injection

There is only one study medication injection for the Maintenance Phase. Date of Maintenance injection is the date of the exposure record for Visit 2f for subjects who enter the Transition Phase, and the date of exposure record for Visit 2 for subjects who enter the Maintenance directly (no Transition Phase) from Screen Phase.

Start and End dates of the Transition, Maintenance, and Double-blind phases

- For subjects who enter the Transition Phase, the Start date of Transition Phase (Trans. Day 1) refers to the date of first injection of the study medication (PP1M) during the Transition Phase; and the Transition Phase end date (denoted as 'Trans. End Date') is one day before the start date Maintenance Phase for subjects who enter the Maintenance Phase, or the trial

disposition date for subjects who do not enter the Maintenance Phase. The Start and end dates are not defined for subjects who do not enter the Transition Phase (those who enter the Maintenance Phase directly from Screen Phase).

- For subjects who enter the Maintenance Phase, the Start date of the Maintenance Phase (MA Day 1) is the injection date of the Maintenance Phase; and the Maintenance Phase end date (denoted as "MA End Date") is one day before the DB Day 1 for subjects who enter the Double-blind phase, or the trial disposition date for subjects who do not enter the Double-blind Phase.
- For randomized subjects who receive Double-blind study medication, the Start date of the Double-blind Phase (DB Day 1) is the first injection date of the Double-blind Phase; and the Double-blind Phase end date (denoted as 'DB End Date') is the same as the date on the Double-blind treatment disposition page. The DB Start Date and the DB End Date are not defined for subjects who do not receive Double-blind Phase study medication.

Data collected after the DB End Date will be allocated to phase of 'FOLLOW-UP'. The Start Date for the Follow-up Phase is one Day after the DB End Date. The End Date for the Follow-up Phase is same as the 'Reference End Day.'

Date of Double-blind Month 12 (DB Month 12)

For 5 subjects who received a Month 12 injection as mentioned in Section 2.1, the date of Double-blind Month 12 (DB Month 12) is defined for the primary efficacy analysis as the date of Visit 33a or 33b from the eCRF. For all other subjects who did not receive a Month 12 injection, their DB Month 12 dates will be missing.

2.5.2. Relative Day for a Visit

There are three types of relative days (Study Day) defined for a visit in this trial – (1) relative to the Date of First Open-Label injection (either in Transition phase or Maintenance Phase), (2) relative to the Date of Maintenance Injection, (3) relative to the DB Start Date. Relative days are defined with respect to the date of Maintenance injection and the DB start date. Days relative to the DB Start Date will only be defined for the Double-blind and Follow-up visits.

Maintenance (MA) Study Day

Days relative to the Date of Maintenance injection are defined as follows (only for subjects who receive Maintenance injection):

MA Study Day = visit date – the Date of Maintenance injection + 1; if visit date ≥ the Date of Maintenance injection;

MA Study Day = visit date – the Date of Maintenance injection; if visit date < the Date of Maintenance injection.

OL Study Day

Days relative to the Date of First Open-Label (either transition or maintenance phase) injection are defined as follows:

- If the subject receives injections in transition phase,

OL Study Day = visit date – the Date of First injection of Transition phase + 1; if visit date ≥ the Date of First injection in Transition phase

OL Study Day = visit date – the Date of First injection of Transition phase; if visit date < the Date of First injection of Transition phase.

- If the subject enters maintenance directly after the screen phase (no transition phase),

OL Study Day = MA Day.

DB Study Day

Days relative to the DB Start Date are defined as follows (only for those who receive Double-Blind injection):

DB Study Day = visit date - the DB Start Date+ 1; if visit date ≥ the DB Start Date,

DB Study Day = visit date – the DB Start Date; if visit date < the DB Start Date.

For all types of relative days, as per the definitions above, there is no 'Day 0'.

2.6. Baseline and Endpoint

2.6.1. Baseline Values

Three kinds of Baseline values are defined in the analyses: Baseline (OL), Baseline (MA), and Baseline (DB).

Baseline (OL):

The 'Baseline (OL)' value is the baseline values that will be summarized in the demographic tables. The 'baseline (OL)' value is defined as the last value collected before administration of any study medication from Open-label phases (Transition and Maintenance Phases).

For ECG, the Baseline (OL) is the average predose value defined in Section 6.4.

Baseline (MA):

The 'Baseline (MA)' value for the Maintenance phase is defined as the last assessment on or before the Maintenance injection date. Note that the Baseline (MA) is defined for each parameter of interest whereas the Maintenance injection Date is defined at subject level and remains the same for all parameters of interest.

The 'C-SSRS Baseline' version is collected on the Screening visit and the 'C-SSRS Since Last Visit' version is collected on all other visits including Visit 2 (or 2a to 2f). To avoid confusion of the meaning of 'baseline', we denote assessment of C-SSRS at Visit 2 or 2f (i.e., the Maintenance Start Date) as 'Day 1 (MA)' (Table 1e), instead of 'Baseline (MA)' because it uses the C-SSRS Since Last Visit version.

Baseline (DB):

The 'Baseline (DB)' value for the Double-blind Phase is defined as the pre-dose (Double-blind) assessment value measured at the day closest to (and including) the DB Start Date. It is defined for all efficacy variables as well as for the safety variables in the Double-blind Phase for subjects who enter the DB phase.

No baseline values are needed for the Transition phase (only baseline values for Open-label phase) and the Follow-up Phase.

2.6.2. Endpoint Values

For each variable measured over time, the 'End Point (MA)' value is defined as the last assessment value (note that the Baseline (MA) value is excluded) during the Maintenance Phase. This value will be the same as the Baseline (DB) value for subjects who continue into the Double-blind Phase.

The 'End Point (DB)' value is defined as the last post-baseline (DB) assessment value (note that the Baseline (DB) value is excluded) before or on the date of DB Month 12, or the disposition date of the treatment disposition if the date of DB Month 12 is missing.

2.7. Imputation Rules for Missing Date and Time

2.7.1. Imputation Rules for Missing AE Date/Time of Onset/Resolution

An AE with an incomplete date will not be considered as treatment-emergent for the open-label phase (including Transition and Maintenance phases).

The following rules will be used to determine if an AE is treatment-emergent for the Double-blind phase when the AE start date is incomplete:

(1) If the month and year are known and day of the month is missing: If the DB study medication started during or prior to that month/year then the AE is considered treatment-emergent for the Double-blind phase. If the DB study medication started after that month/year, then the AE will not be considered treatment emergent for the Double-blind phase.

(2) If the year is known and the month is missing: If the DB study medication started during or prior to that year then the AE is considered treatment-emergent.

(3) If the year is missing: The AE will be considered treatment emergent for the Double-blind phase.

2.7.2. Incomplete/Missing Dates of Most Recent Hospitalization for Psychosis

The duration (days) of the most recent hospitalization for psychosis prior to the start of the study will be calculated as: stop date - start date + 1. If the hospitalization start/stop date is completely missing or the year is missing, no imputation will be performed. If the start/stop dates of hospitalization are partially missing the following rules will apply:

- Hospitalization start date: if only the day is missing, use the first day of the month. If only the month is missing, January will be used. If both the day and month are missing, the imputed date will be January 1.
- Hospitalization stop date will be the minimum between the day before the Screening Visit and the following imputed date:
  - If only the day is missing, then the last day of the given month will be used (eg, if the month is April, then the missing day will be imputed as April 30);
  - If only the month is missing, then December will be used;
  - If both the day and the month are missing, then the imputed date will be December 31.

2.7.3. Incomplete/Missing Dates of Hospitalization Collected in HRUQ

The duration (days) of the hospitalization collected in HRUQ will be calculated as: stop date - start date + 1. If the hospitalization start/stop date is completely missing or the year is missing, no imputation will be performed. If the start/stop dates of hospitalization are partially missing the following rules will apply:

Hospitalization start date:

- if only the day is missing, use the first day of the month.
- If only the month is missing, January will be used.
- If both the day and month are missing, the imputed date will be January 1.

Hospitalization stop date will be the minimum between the day before the date of assessment and the following imputed date:

- If only the day is missing, then the last day of the given month will be used (eg, if the month is April, then the missing day will be imputed as April 30);

- If only the month is missing, then December will be used;
- If both the day and the month are missing, then the imputed date will be December 31.

2.7.4. Incomplete/Missing Dates for Concomitant Medications

No imputation of start/end dates will be done for concomitant medication reported during the follow-up phase, and hence, the following rules do not apply to follow-up phase.

If a partial date is reported, it is assumed medication was taken in both the Open-label and Double-blind phases that overlap with the partial date. If both start and end dates are missing but this concomitant medication was taken both prior to the study entry (OL Day 1) and still ongoing at end of the Double-blind Phase, it is assumed medication was taken both in the Open-label Phase and the Double-blind Phase.

The rules for estimating an incomplete concomitant medication start date are as follows:

If the month of the concomitant medication start date is equal to the month of the start of the Open-label Phase, then the estimated start date is the start date of the Open-label Phase;

If the month of the concomitant medication start date is greater than the month of the start of the Open-label Phase and earlier than the month of the reference end date (i.e. max (the OL End Date, the DB End Date)), then the estimated start date of the concomitant medication is the first day of the month;

If the month of the concomitant medication start date is greater than the month of the reference end date, then no imputation will be done;

If the month and year of the concomitant medication start date are known and the OL Start Date is after the month of the concomitant medication start date, then no imputation will be done;

If both the month and the day of the concomitant medication start date are missing but the year is not, the imputed start date will be the first day of that year.

For the incomplete concomitant medication end date, the rules are:

If the month of the concomitant medication end date is prior to the month of the reference end date, then the estimated the concomitant medication end date is the last day of that month;

If the month of the concomitant medication end date is during the month of the reference end date, then the estimated end date is the reference end date;

If the month of the concomitant medication end date is after the reference end date, then the estimated end date is the last day of that month;

If the month of the concomitant medication end date is missing but the year is not, and if the subject entered the Open-label Phase, then the estimated end date is the minimum of the last day of the year and the reference end date;

If the year is missing then the estimated end date is the reference end date;

If the concomitant medication is continuing, then the estimated end date is the reference end date for the purpose of duration calculation.

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

No interim analyses are planned. There is no unblinded Data Monitoring Committee for this study.

4. SUBJECT INFORMATION

Unless indicated otherwise, the results for subject information will be provided by treatment group and total subjects.

4.1. Demographics and Baseline Characteristics

Table 2 presents the list of demographic variables and baseline characteristics and Table 3 presents the list of diagnosis and psychiatric history variables. Variables will be summarized for the OL ITT (same as OL Safety), DB ITT (same as DB Safety), and per-protocol analysis populations except for smoking history which will be summarized for the OL ITT analysis population only. In addition, these summaries will be presented for the subset of the OL ITT subjects who were not randomized.

The continuous variables will be summarized using descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]). The categorical variables will be summarized using a frequency distribution with the number and percentage of subjects in each category.

Table 2: Demographic Variables and Baseline Characteristics

Continuous Variables:
- Age (years)[a]
- Baseline (OL) weight (kg)
- Baseline (OL) height (cm)
- Baseline (OL) BMI (kg/m^2) calculated as Weight (kg)/[Height (m)]^2
- Baseline (OL) waist circumference (cm)

Categorical Variables:
- Age (18-25 years, 26-50 years, 51-65 years, and >65 years)[a]
- Sex (male, female)
- Race[b] (White, Black or African American, Asian (include Asian subcategories)[c], American Indian or Alaska native, native Hawaiian or other Pacific islander, other, multiple, not reported, unknown)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)
- Country
- Region (European Union, US, Non-EU/Non-US)
- Baseline (OL) BMI (normal: <25 kg/m^2, overweight: 25 kg/m^2 to <30 kg/m^2, obese: ≥30 kg/m^2)
- Nicotine Use at Screening (never used, current/former user)

[a] Age at Screening visit.
[b] If multiple race categories are indicated, then Race is recorded as "Multiple."
[c] Asian subcategories include Chinese, Korean, Japanese, Filipino, Asian Indian, Thai, Malaysian, and Asian (other).

Demographic and baseline characteristics will be summarized by European Union vs. US vs. Non-EU/Non-US, for the per-protocol analysis population.

Table 3: Diagnosis and Psychiatric History Variables at Maintenance and Double-blind Phases

Continuous Variables:
- Age at diagnosis of schizophrenia (years)
- Duration of most recent hospitalization prior to study entry (years)[a,b] calculated as end date of hospitalization for psychosis-start date of hospitalization for psychosis + 1
- Baseline (MA) and Baseline (DB) PANSS total score
- Baseline (MA) and baseline (DB) PSP score

Categorical Variables:
- DSM-5 diagnosis
  1) Number of prior hospitalizations for psychosis within last 24 months (0, 1, 2, 3, ≥4)[a]
- Baseline (MA) and Baseline (DB) CGI-S score

[a] Excludes hospitalization at time of study entry.
[b] Applies only to subjects with prior hospitalizations.

4.2. Disposition Information

Subject disposition will be summarized for both the Open-label (including Transition and Maintenance Phases) and Double-blind phases. For the OL ITT analysis population, the reasons for study discontinuation during the Open-label Phase will be summarized. In addition, the number of subjects continuing into the Double-blind Phase will be summarized. For the DB ITT (same as

DB Safety), and per-protocol analysis populations, the reasons for study completion (i.e. relapse during the Double-blind Phase or completion of Double-blind Phase without a relapse) and the reasons for study discontinuation during the Double-blind Phase will be summarized. The disposition information for the Double-blind Phase is recorded on the treatment disposition "of Double-blind Phase" CRF page. Subjects who discontinue treatment by "disease relapse" will be considered as having completed the Double-blind phase by having a relapse event.

The cumulative number of subjects in the DB ITT analysis population will be presented over time for those who discontinue the Double-blind treatment without a relapse event..

Subject disposition during the Double-blind Phase will also be summarized by remission status during the Double-blind Phase. The remission criteria are provided in Section 5.3.6.

A Kaplan-Meier plot of time to all cause discontinuation (including relapses) during the Double-blind Phase will be presented by treatment group for the DB ITT population.

The number of screen failures will be presented.

4.3. Treatment Compliance

Since the study injection medication will be administered as SC injections by the study site staff, compliance of the injection study medication will not be included as an analysis variable. The number of injections received will be summarized as part of exposure (see Section 4.4.1).

4.4. Extent of Exposure

4.4.1. Injections

The number and percent of subjects who receive 1, 2, 3, etc. injections of double-blind study drug will be summarized by treatment group, both including and excluding the placebo injections in the PP6M group. The number and percent of subjects at each dose level will be summarized. For each 3 months (quarterly) during the Double-blind Phase, a frequency distribution will be presented showing the number of subjects who receive the injection in the gluteal muscle. The treatment exposure (including duration of total exposure), and mean dose (not including placebo injection) will be presented. These summaries will be provided for the DB ITT population.

The duration of total exposure in the Double-blind phase is calculated as the total number of days a subject remains in the Double-blind Phase of the study, that is,

The duration of total exposure in DB phase = treatment disposition date – the DB Start Date + 1

Similar analyses on the exposure during the Open-label Phase will be carried out for the OL ITT analysis population.

4.4.2. Oral Tolerability Test

For those subjects without documented tolerability to oral or injectable risperidone or paliperidone, oral paliperidone ER 6 mg daily or oral risperidone 3 mg daily are to be administered for 4 to 6 consecutive days. Tolerability testing is to occur during the Screening Phase (last dose must be administered by Day -1) and may be concurrent with any required washout.

The number and percent of subjects who receive 4, 5, or 6 consecutive daily doses of paliperidone ER as a tolerability test during the screening period will be summarized for the OL ITT analysis population.

4.5. Protocol Deviations

All major protocol deviations will be summarized for the OL ITT (Same as OL Safety) population and the DB ITT (same as DB Safety) population. Major Protocol Violations (i.e., Major Protocol Deviations that led to exclusion from Per-protocol population) before visits 33a or 33b (Section 2.3.4) will be summarized for the DB ITT population.

The following list of major protocol deviations may have the potential to impact subjects' rights, safety or well-being, or the integrity and/or result of the clinical study. Subjects with major protocol deviations will be identified prior to database lock and the subjects with major protocol deviations will be summarized by category.

- Developed withdrawal criteria but not withdrawn
- Entered but did not satisfy criteria
- Received a disallowed concomitant treatment
- Received wrong treatment or incorrect dose
- Other

4.6. Prior and Concomitant Medications

4.6.1. Prior Psychotropic Medications

The number and percentage of subjects who received psychotropic medications prior to the OL Start Date will be presented by the generic term category within the psychotropic group. Each medication will be categorized into one of the following psychotropic groups (used for Anti-extrapyramidal symptoms [EPS] / akasthesia) : Acetylcholinesterase inhibitors, Antidepressants, Anti- EPS, Antihistamines, Atypical antipsychotics, Benzodiazepines, Beta blockers, Depot antipsychotics, Mood stabilizers and antiepileptics, Non-benzodiazepines hypnotics and anxiolytics, Stimulants, and Typical antipsychotics. These summaries will be presented for the OL ITT (same as OL safety) and DB ITT analysis populations.

Those prior psychotropic medications received by at least 5% of the subjects in either double-blind treatment group will be presented for the safety analysis population.

The number and percentage of subjects who received prior antiparkinsonian medications (beta blockers (used for EPS / akasthesia), anticholinergics [anti-EPS] or antihistamines) will be provided by the generic term category within the psychotropic group. The summary will be presented for the OL ITT (same as OL safety) analysis populations.

4.6.2. Concomitant Benzodiazepines (Sedatives/Hypnotics/Anxiolytics)

The number and percentage of subjects who received benzodiazepines during the Open-label Phase (Transition and Maintenance phases combined) will be provided based on generic term category for the OL ITT (same as OL safety) analysis population. The number and percentage of subjects who received benzodiazepines during the Double-blind Phase will be provided based on generic term category for DB ITT (same as DB Safety) and per-protocol analysis populations.

For each subject, the total duration of each benzodiazepine will be calculated. Descriptive statistics of the duration (days) of benzodiazepine use during the Open-label Phase for the OL ITT analysis population, and during the Double-blind Phase for the safety and per-protocol analysis populations will be presented.

If both start and end dates for benzodiazepines are known, duration of concomitant medication is defined as stop date – start date +1. Otherwise stop and start dates of the concomitant medication during the 2 phases (OL and DB phases) are defined below.

For the summary of duration of benzodiazepines during the Open-label Phase, if the start date of concomitant medication is prior to the OL Start Date, the OL Start Date will be used as concomitant medication start date for duration calculation. If the end date of concomitant medication is after the OL End Date or indicated as continuing, then the OL End Date will be used as the concomitant medication end date for duration calculation.

For the summary of duration of benzodiazepines during the Double-blind Phase, if the start date of concomitant medication is prior to the DB Start Date, then the DB Start date will be used as concomitant medication start date for duration calculation. If the end date of concomitant medication is after the DB End Date or indicated as continuing, then the DB End Date will be used as the concomitant end date in calculating duration.

Additionally, for the summary of duration of benzodiazepines during the combined open-label and double-blind phase, if the start date of concomitant medication is prior to the OL Start Date, then the OL Start date will be used as concomitant medication start date for duration calculation. If the end date of concomitant medication is after the DB End Date or indicated as continuing, then the DB End Date will be used as the concomitant end date in calculating duration. Otherwise, duration in the combined phase = benzodiazepine stop date –start +1.

4.6.3. Concomitant Medications Other Than Benzodiazepines

The number and percentage of subjects who receive concomitant therapies other than benzodiazepines during the study will be provided based on generic term category for the Open-label Phase for the OL ITT analysis population and for the Double-blind Phase for the safety analysis population. Those concomitant medications, other than benzodiazepines, received by at least 5% of the subjects in either double-blind treatment group will be presented for the safety analysis population.

Note that duration in the trial is not calculated for concomitant medications other than benzodiazepines and prior psychotropic medications.

5. EFFICACY

5.1. Analysis Specifications

5.1.1. Level of Significance

Unless otherwise specified, a 2-sided significance level of 5% will be used. No adjustment for multiple testing will be used for the secondary efficacy analyses.

5.1.2. Data Handling Rules

For the efficacy scales PANSS, CGI, and PSP, both observed case (OC) and last observation carried forward (LOCF) values will be determined for Maintenance Visit 2 (for subjects who do not enter transition phase) or 2f (for subjects who enter transition phase), and double-blind Months 3, 6, 9, and so on. These imputed time points will be labeled “Month X LOCF.” Because it is possible for more than 1 visit to occur during the same time interval for a protocol-specified visit, rules for choosing the visit to use for the analysis are those given in Section 2.2. Imputed time points Month XX (MA) LOCF and Month XX (DB) LOCF are not needed as they are essentially equivalent to END POINT (MA) and END POINT (DB), respectively.

If there are multiple visits in a time interval with non-missing values, the visit closest to the protocol-specified time is used as both observed case and LOCF. If there is no visit in a time interval with a non-missing value, then the OC value is missing and the last non-missing, post-baseline value prior to the interval is used for LOCF.

Individual item scores will not be carried forward for PANSS. Refer to Section 5.3.1.1 for handling of missing PANSS item scores.

5.2. Primary Efficacy Estimand

The primary efficacy estimand is defined by the following components:

The *population* is restricted to those who are stabilized on either PP1M or PP3M during the Maintenance Phase and meet the inclusion/exclusion criteria.

The *variable* is time to first occurrence of a relapse event during the Double-blind Phase.

The *intercurrent events and corresponding strategies are the following:*

- Treatment discontinuation – Hypothetical Strategy: After treatment discontinuation, assume similar efficacy for subjects who discontinued as those subjects from the same treatment group who did not discontinue the treatment.
- Major protocol violations – Treatment Policy Strategy: use all relapse events, regardless of whether or not major protocol violations had occurred.

The *population-level summary* is the difference in Kaplan-Meier estimate at Month 12 of relapse-free proportions between the 2 treatment groups.

The primary analysis set is the DB ITT population (see Section 2.3.2.). For consistency to previous studies, same analyses will also be applied to the PP population (see Section 2.3.4.).

Subjects who meet at least 1 of the criteria for a relapse during the Double-blind Phase before DB Month 12 date are considered to have had a relapse event. The definition of a relapse event is presented in Section 5.2.1.1. Under the primary estimand, which applies a hypothetical strategy for treatment discontinuation, only the relapse events occurring during the Double-blind Phase prior to treatment discontinuation will be counted as events in the primary analysis. The details are as follows:

The date of DB Month 12 has been specified in Section 2.5.1.

(1) For a subject who stays in the DB phase up to the date of DB Month 12 without a relapse event, the subject would be considered as censored at the date of the DB Month 12 whether the date is before or after Day 365;

(2) If a subject does not belong in (1), the subject must have discontinued the Double-blind phase before reaching DB Month 12 visit, either by premature withdrawal (i.e. treatment discontinuation) or by having a relapse event.

    - If the subject has a relapse event in the Double-blind Phase before reaching the DB Month 12 date, prior to treatment discontinuation, the subject is considered as having an event
    - If the subject discontinues treatment (and therefore the Double-blind Phase) before Day 365 without a relapse event, the subject is considered as censored at the Day of discontinuation (day of treatment disposition of the Double-blind Phase).

The definition of the time to relapse in the Double-blind Phase is presented in Section 5.2.1.2.

5.2.1. Definition of Time to Relapse

5.2.1.1. Definition of Relapse Event

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 Symptom Scale for Schizophrenia (PANSS)
    - The subject has an increase of 25% in PANSS total score from randomization for 2 consecutive assessments separated by 3 to 7 days if the score at randomization was >40, where

      $$\text{Percent change} = \frac{\text{DB score} - \text{randomization score}}{\text{randomization score} - 30} * 100$$

      or,
    - The subject has a 10-point increase in the PANSS total score from randomization for 2 consecutive assessments separated by 3 to 7 days if the score at randomization was $\leq$40, or
- The subject inflicts deliberate self-injury or exhibits violent behavior resulting in suicide, clinically significant injury to him/herself or another person, or significant property damage, or
    - The 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 $\geq$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 $\leq$ 3 at randomization, or
    - The subject has a score of $\geq$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 relapse will be the date of the first assessment for symptoms of relapse (not the date of confirmation).

5.2.1.2. Time to Relapse During Double-Blind Phase

The time to relapse during the Double-blind phase is defined as follows:

1. Relapse during the Double-blind Phase

   Time to relapse = Date of Relapse - Randomization Date + 1

   censoring indicator variable = "NO"

2. Early withdrawal during the Double-blind Phase

   Time to relapse = Date of early withdrawal - Randomization Date + 1

   censoring indicator variable = "YES".

3. Remained relapse free in the Double-blind Phase (for subjects who received Month 12 injection, their time to relapse will be censored at the DB Month 12 date defined in Section 2.5.1)

   Time to relapse = Date of end of Double-blind Phase - Randomization Date + 1

   censoring indicator variable = "YES".

5.2.2. Primary Efficacy Analysis Performed on the Double-blind Intent-to-Treat Analysis Population

5.2.2.1. Main Analysis

The hypotheses to be tested using a 1-sided α=0.025 level are: H_0:p_6-$p_3 \leq -\delta$ vs. H_1:p_6-$p_3 > -\delta$; where p3 refers to the percentage of subjects who remain relapse free at Month 12 for the PP3M groups and p6 refers to the percentage of subjects who remain relapse free at Month 12 for the PP6M group. The Kaplan-Meier method will be used to estimate the Month 12 cumulative estimate of survival (ie, percentage of subjects remaining relapse-free). Standard Error (SE) estimates will be based upon Greenwood's formula.

Non-inferiority of PP6M to PP3M will be concluded if the lower limit of the 2-sided 95% confidence interval of the difference in the relapse-free rates between PP6M and PP3M exceeds -10%. If the lower limit of the 2-sided 95% confidence interval of the difference in the relapse-free rate between PP6M and PP3M exceeds 0%, then PP6M will be declared superior to PP3M.

5.2.2.2. Sensitivity Analysis

The main analysis relies on the assumption of ignorable censoring. Therefore, sensitivity analyses will be performed to stress-test the robustness of results to deviations from ignorable censoring for the DB ITT analysis population. Specifically, it is assumed that subjects on PP6M who discontinue prematurely from the Double-Blind phase have a higher relapse hazard starting from the discontinuation time, compared with similar subjects who remain in this phase. The higher relapse hazard is determined by the single sensitivity parameter Delta, representing the ratio of subject-specific hazard at any given time point *t* following discontinuation compared to that same subject's hazard at the same time *t* if he or she had remained in the Double-Blind phase. A Kaplan-Meier multiple imputation (KMMI) non-parametric approach will be used for the imputation of relapse events, as described in Taylor et al (2002)[11] and Lipkovich et al (2016)[12]. The number of multiple imputations (MI) will be set to 1000 and a seed equal to 234 will be used for MI. A sequence of Delta values will be used for all subjects with non-administrative censoring from the PP6M group (i.e. subjects censored due to other reasons than the end of Double-Blind phase cut-off), starting with 1 (ignorable censoring) and increasing by 1 until the point when the non-inferiority condition is no more satisfied. For the PP3M group, the sensitivity parameter Delta will be set to one, i.e. maintaining the ignorable censoring assumption.

5.2.2.3. Supplementary Analyses

Three supplementary estimands are defined to support the primary estimand. In their definitions, the only component that changes from the definition of the primary estimand is how the strategy is defined for treatment discontinuation.

For subjects who discontinue treatment during the Double-blind phase and enter the Follow up phase, their last day of the Follow up phase is recorded as the trial disposition date.

Supplementary Estimand S1:

Hypothetical Strategy: After treatment discontinuation (defined as treatment discontinuation **plus 91 days in the Follow-up Phase**), assume similar efficacy for subjects who discontinued as those subjects from the same treatment group who did not discontinue the treatment.

Under the S1 supplementary estimand, all relapse events occurring 91 days (i.e. 3 months) after treatment discontinuation will also count as events in the analysis. Subjects who discontinue treatment and have no relapse event within this timeframe will be considered censored at the 91 days threshold, or the date of trial disposition date, whichever is earlier.

Supplementary Estimand S2:

Hypothetical Strategy: After treatment discontinuation (defined as treatment discontinuation **plus 182 days in the Follow-up Phase**), assume similar efficacy for subjects who discontinued as those subjects from the same treatment group who did not discontinue the treatment.

Under the S2 supplementary estimand, all relapse events occurring 182 days (i.e. 6 months) after treatment discontinuation will also count as events in the analysis. Subjects who discontinue treatment and have no relapse events within this timeframe will be considered censored at the 182 days threshold, or the date of trial disposition date, whichever is earlier.

Supplementary Estimand S3:

Treatment Policy Strategy: use all relapse events, regardless of treatment discontinuation.

Under the S3 supplementary estimand, all relapse events occurring after treatment discontinuation up to the DB Month 12 date will also count as events in the analysis. Subjects remaining relapse-free at the DB Month 12 date will be censored at that date. Subjects who discontinue the study and do not reach the DB Month 12 will be censored at the trial disposition date.

For each of the 3 supplementary estimands, the difference between the PP6M and PP3M groups of the percentage of subjects who remain relapse-free at end of Month 12 based on Kaplan-Meier estimate will be presented, together with the 95% confidence interval of the difference. The analysis dataset is the DB ITT population.

Supplementary Analysis S4:

The primary efficacy analysis will be performed based on S3 estimand for the DB ITT analysis population by excluding 3 subjects in Mexico who were impacted by delay of drug supply.

After changes starting in 2018 at the Ministry of Health in Mexico, new drug import licensing process affected shipments of PP6M. The delays affected three subjects who had to be withdrawn early from the Double-blind phase.

Supplementary Analysis S5:

To evaluate the potential impact of COVID-19, this supplementary analysis is added to censor subjects after their last onsite visits for those who had COVID-19 related remote visits.

A supplementary analysis will be performed based on the estimand in Section 5.2 (for primary efficacy estimand) for the DB ITT analysis population by censoring subjects at their last onsite visit. For other subjects who did not have COVID-19 remote visits, or whose end of DB visits were performed onsite, their time to relapse and censoring status remains the same as the analysis specified in Section 5.2.1.2.

5.2.2.4. Subgroup Analysis

To evaluate the consistency of the results in various subgroups, the Kaplan-Meier estimate of time to relapse will be fit for each of the following subgroups: Dose level (moderate/high) in Maintenance Phase, Dose regimen (PP1M/PP3M) in Maintenance Phase, age group (18-25, 26-50, 51-65, > 65 years), sex, race (White, Black, Other), Baseline (DB) BMI group, and region

(European Union, US, Non-EU/Non-US). The treatment difference between PP6M and PP3M groups at Month 12 and its 95% confidence interval will be reported for each of the subgroups.

A forest plot will be used to evaluate the consistency of effect across these subgroups.

In addition, subgroup analysis will also be performed using the Cox Regression model. To adjust for the effect of baseline covariates, the following variables will be included in the Cox regression model: Dose level (moderate/high) in Maintenance Phase, Dose regimen (PP1M/PP3M) in Maintenance Phase, age group (18-25, 26-50, 51-65, > 65 years), sex, race (White, Black, Other), Baseline (DB) BMI group, region (European Union, US, Non-EU/Non-US), in addition to treatment.

5.2.2.5. Model Diagnostics

To assess the appropriateness of the proportional hazards assumption, a log-log survival plot of Kaplan-Meier estimates will be generated. If the proportional hazards assumption is correct, this plot should present approximately parallel lines corresponding to the two treatment groups. Cumulative sums of Schoenfeld residuals over time may also be used to assess the proportional hazards assumption.

5.2.3. Primary Efficacy Analysis Performed on Per-Protocol Analysis Population

Same main analysis, sensitivity analyses and supplementary analyses specified in Section 5.2.2 will also be conducted on the PP population, defined in Section 2.3.4. The 10% non-inferiority margin specified in Section **Error! Reference source not found.** for the DB ITT population will also be used for the main analysis on the PP population.

5.3. Secondary Efficacy Endpoints

Secondary analyses will be conducted using the DB ITT analysis population. Summaries and/or analyses for PANSS total score, CGI-S, PSP, and PANSS subscales will also be provided for the per-protocol analysis population. No multiplicity adjustments will be made.

5.3.1. PANSS Total Score

5.3.1.1. Definition

The PANSS scale consists of 30 items with a score of 1 to 7. The total score is the sum of all 30 PANSS items and ranges from 30 to 210. Higher scores indicate more severe neuropsychiatric symptoms of schizophrenia. If a PANSS item is missing, it will be imputed with the closest integer to the average of the remaining items within the subscale (positive, negative and general psychopathology) at that time point and then the total will be summed. If more than 15% of the items are missing, i.e., if 5 or more items are missing, no imputation will be performed and the total score and the scores of the subscales that include these items will be left missing. Imputation

of item scores is performed prior to determining the LOCF for the PANSS subscale and total scores.

5.3.1.2. Analysis Methods

At each assessment time point during the Double-blind Phase and at end point (DB), descriptive statistics (mean, standard deviation, minimum and maximum) for the PANSS total score and the change from baseline (DB) will be provided for both the observed case and LOCF data. The change from baseline (DB) at each visit during the Double-blind Phase will be analyzed using an ANCOVA model with factors for treatment and country and baseline score as a covariate. The treatment effects will be estimated based upon least square means (PP6M-PP3M), and the accompanying 95% confidence intervals will be presented.

In addition, descriptive statistics of the PANSS total score and the change from baseline (MA) will be provided for selected visits (see Section 2.1, Table 1a) during the Open-label Phase for the OL ITT analysis population.

5.3.2. Clinical Global Impression - Severity (CGI-S)

5.3.2.1. Definition

The CGI-S is a categorical rating of the subject's severity of illness on a 7-point scale (1=not ill, 2=very mild, 3=mild, 4=moderate, 5=marked, 6=severe, 7=extremely severe).

5.3.2.2. Analysis Methods

At each assessment time point during the Double-blind Phase and at endpoint (DB), frequency counts of CGI-S scores by severity label (mild, moderate, etc.) will be produced for both the observed case and LOCF data. At each visit, descriptive statistics (mean, standard deviation, minimum and maximum) of the numerical scores and change from baseline (DB) will also be presented. The change from baseline (DB) at each visit during the Double-blind Phase will be analyzed using an ANCOVA model with factors for treatment and country and baseline score as a covariate. The treatment effects will be estimated based upon least square means (PP6M-PP3M), and the accompanying 95% confidence intervals will be presented.

In addition, frequency distributions and descriptive statistics of the CGI-S score and the change from baseline (MA) will be provided for endpoint of the Maintenance Phase for the ITT (OL) analysis population.

5.3.3. Personal and Social Performance Scale (PSP)

5.3.3.1. Definition

The PSP scale provides an overall rating of personal and social functioning on a 100-point scale of 1 to 100. The scale defines a continuum from grossly impaired functioning to excellent

functioning. A higher score represents a better level of functioning. The PSP scale assesses the degree of difficulty a subject exhibits over a 7-day period based on 4 domains of behavior: socially useful activities, personal and social relationships, self-care, and disturbing and aggressive behaviors.

5.3.3.2. Analysis Methods

At each assessment time point during the Double-blind Phase and at end point (DB), descriptive statistics (mean, standard deviation, minimum and maximum) of the PSP total score and domain scores and change from baseline (DB) will be provided for both the observed case and LOCF data. The change from baseline (DB) in PSP total score at each visit during the Double-blind Phase will be analyzed using an ANCOVA model with factors for treatment and country and baseline score as a covariate. The treatment effects will be estimated based upon least square means (PP6M-PP3M), and the accompanying 95% confidence intervals will be presented. Shift tables summarizing change from Baseline (DB) in number and frequency of subjects reporting each of the PSP deciles, and 3 PSP categories (Poor (≤ 30), Variable (>30 - ≤ 70), Good (>70)) will be presented. Frequency counts, percentages, and cumulative percentages of subjects at each PSP domain level will be summarized for both observed data and LOCF data by treatment group.

In addition, descriptive statistics of the PSP total score and the change from baseline (MA) will be provided for baseline and endpoint of Maintenance Phase for the OL ITT analysis population.

5.3.4. PANSS Subscale Scores

5.3.4.1. Definition

The sums of the item scores for the following derived subscales based on Marder et al[6] will be calculated:

- Positive symptoms factor (range: 8 to 56): Delusions, Hallucinatory behavior, Grandiosity, Suspiciousness (items 1, 3, 5 and 6 in positive subscale), Stereotyped thinking (item 7 in negative subscale), Somatic concern, Unusual thought content, Lack of judgment and insight (items 1, 9, and 12 in general psychopathology subscale);

- Negative symptoms factor (range: 7 to 49): Blunted affect, Emotional withdrawal, Poor rapport, Passive social withdrawal, Lack of spontaneity (items 1, 2, 3, 4, and 6 in negative subscale), Motor retardation, Active social avoidance (items 7 and 16 in general psychopathology subscale);

- Disorganized thoughts factor (range: 7 to 49): Conceptual disorganization (item 2 in positive subscale), Difficulty in abstract thinking (item 5 in negative subscale), Mannerisms and posturing, Disorientation, Poor attention, Disturbance of volition, Preoccupation (items 5, 10, 11, 13, and 15 in general psychopathology subscale);

- Uncontrolled hostility/excitement factor (range: 4 to 28): Excitement, Hostility (items 4 and 7 in positive subscale), Uncooperativeness, Poor impulse control (items 8 and 14 in general psychopathology subscale);
- Anxiety/depression factor (range: 4 to 28): Anxiety, Guilt feelings, Tension, Depression (items 2, 3, 4, and 6 in general psychopathology subscale).

In addition, the following subscale scores of PANSS will be calculated:

- Positive subscale (range: 7-49): sum of Items P1 to P7 in the positive subscale;
- Negative subscale (range: 7-49): sum of Items N1 to N7 in the negative subscale;
- General psychopathology subscale (range: 16-112): sum of Items G1 to G16 in the general psychopathology subscale.

5.3.4.2. Analysis Methods

At each assessment time point during the Double-blind Phase and at end point (DB), descriptive statistics (mean, standard deviation, minimum and maximum) for each factor and subscale score and change from baseline (DB) will be provided for both the observed case and LOCF data. The change from baseline (DB) at each visit during the Double-blind Phase will be analyzed using an ANCOVA model with factors for treatment and country and baseline score as a covariate. The treatment effects will be estimated based upon least square means (PP6M-PP3M), and the accompanying 95% confidence intervals will be presented.

In addition, descriptive statistics of the score and change from baseline (MA) will be provided for baseline and endpoint of Maintenance Phase for the OL ITT analysis population.

5.3.5. PANSS Response and Cumulative Response Rate

5.3.5.1. Definition

Clinical response based on the PANSS total score is defined as a ≥20% reduction from the baseline (DB) score. The percent change in PANSS total score is calculated as: 100*CHANGE/(BASELINE-30), with 30 being the lowest possible value. If BASELINE is 30, then the percent change is missing.

In addition, a 30% and 40% responder classification will be provided.

5.3.5.2. Analysis Methods

For each treatment group, the number and percent of responders will be tabulated at each time point during the Double-blind Phase. At end point (DB), 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 cumulative response rate, defined as the percentage of subjects experiencing at least a given value of percent reduction from baseline in PANSS total score, will also be presented graphically.

5.3.6. Symptomatic Remission

5.3.6.1. Definition

Remission criterion is defined as having a simultaneous score of mild or less on all 8 selected PANSS items (P1, P2, P3, N1, N4, N6, G5, and G9).

Symptomatic remission is defined for the last 6 months of the Double-blind phase as meeting the remission criterion during the last 6 months with one excursion allowed. The duration of the last 6 months counts back from either the date of DB Month 12 (defined in Section 2.5.1) or the disposition date of the Double-blind Phase, whichever is earlier. For a subject who discontinues the Double-blind phase within 6 months, the subject will be considered as a non-remitter for the Double-blind phase.

The Baseline (DB) remission is defined as meeting the remission criterion at all the visits from the start of Maintenance phase to Day 1 of the DB phase, (there are 3 scheduled visits: Visits 2/2f, 6 and 7b). The point-wise remission status at each double-blind time point is defined as meeting the remission criterion at that particular time point.

5.3.6.2. Analysis Methods

For each treatment group, the number and percent of subjects achieving symptomatic remission in 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.

In addition, the count and frequency of remission status at each double-blind time point will be presented by treatment group for subjects who are Baseline (DB) remitters.

5.4. Other Efficacy Variable(s)

5.4.1. Satisfaction With Participation in Social Roles (SPSR) Short Form 8a

5.4.1.1. Definition

The SPSR Short Form 8a asks subjects to consider the past 7 days and to rate 8 items on 5-point Likert scales, with higher scores representing higher satisfaction.

5.4.1.2. Analysis Methods

As noted in the time and event table of the protocol, the SPSR scales will only be analyzed for subjects who entered the study on an oral antipsychotic.

At each assessment time point during the Double-blind Phase and at end point (DB), descriptive statistics (mean, standard deviation, minimum and maximum) for the SPSR total score and the change from baseline (DB) will be provided for both the observed case and LOCF data.

In addition, descriptive statistics of the SPSR total score and the change from baseline (MA) will be provided for endpoint of the Maintenance Phase for the OL ITT analysis population.

PROMIS - Satisfaction with social roles and activities short form 8a

If 4 items are answered:
SPSR total score = (8*sum) /(# of items answered)

5.4.2. Abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9)

5.4.2.1. Definition

The abbreviated treatment satisfaction questionnaire (TSQM-9) for medication has 9 items. Each item is 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.

5.4.2.2. Analysis Methods

As noted in the time and event table of the protocol, the questionnaire will only be analyzed for subjects who entered the study on an oral antipsychotic.

At each assessment time point during the Double-blind Phase and at end point (DB), descriptive statistics (mean, standard deviation, minimum and maximum) for the abbreviated TSQM-9 Subscale score, and the change from baseline (DB) will be provided for both the observed case and LOCF data.

In addition, descriptive statistics of the abbreviated TSQM-9 Subscale score and the change from baseline (MA) will be provided for endpoint of the Maintenance Phase for the ITT OL analysis set.

Subscale Scoring algorithm for TSQM-9 based on TSQM9_Atkinson_2005 paper[13]

- Effectiveness = 100*[(Item 1 + Item 2 + item 3) -3]/18,

  if one item is missing, Effectiveness = 100*[Sum (remaining 2 items) -2]/12
- Convenience = 100*[(Item 4 + Item 5 + item 6) -3]/18,

  if one item is missing, Convenience = 100*[Sum (remaining 2 items) -2]/12
- Overall satisfaction:

  Recode item 9: item 9_recode = (item 9 -1)*5/6
  Overall satisfaction = 100*[(Item 7 + Item 8 + item 9_recode) -3]/12,
  if one item is missing, Effectiveness = 100*[Sum (remaining 2 items) -2]/8

6. SAFETY

All safety analyses and summaries will be based on the Open-label Safety (OL Safety, same as OL ITT) analysis population for the Open-label Phase and Double-blind safety (DB Safety, same as DB ITT) analysis population for the Double-blind Phase.

6.1. Adverse Events

Adverse events (AEs) are coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 16 or later versions.

A treatment-emergent AE is an event that is new in onset or increased in severity following treatment initiation. An event that starts prior to and ends after the initiation of study drug is to be considered treatment-emergent only if the severity increases after the start of medication. Treatment-emergent flags will be defined separately for the Open-label Phase (including Transition and Maintenance Phases), the Double-blind Phase, and combined Double-blind and Follow-up Phases.

Treatment-emergent AE in the Open-label Phase are defined as the adverse events with onset date on or after the first study injection date and during the Open-label Phase (onset date >= the Date of First Study Injection and <= the OL End Date) or increase in severity during the same period. An event that starts prior to the first study injection and ends afterwards will be considered treatment emergent in the Open-label Phase only if the severity increases on or after the Date of First Study Injection.

Treatment-emergent AE in the Double-blind Phase are defined as the adverse events that start after the initiation of the double-blind medication (onset >= the DB Start Date and <= the DB End Date) or increase in severity on or after the DB Start Date (onset in the Open-label Phase or even at Screening). An event that starts prior to the DB Start Date and ends afterwards will be considered treatment-emergent in the Double-blind Phase only if the severity increases on or after the DB Start Date.

Because the OL End Date is the same as DB Start Date for those who entered the Double-blind Phase, adverse events with onset on this date will be considered to be treatment-emergent during the Double-blind Phase.

Treatment-emergent AE summaries will also be provided quarterly for the Double-blind phase. The entire Double-Blind phase will be divided as for time intervals: Double-blind days 1-91, 92-182, 183-273, 274-end of DB. An event that will be considered as treatment-emergent during that time interval, either if the event starts during that interval, or it starts before the time interval but the severity increases on or after the start date of the interval.

The number (%) of subjects with treatment-emergent AEs, treatment-emergent serious AEs (SAEs), treatment-emergent AEs that lead to study discontinuation, and treatment-emergent AEs resulting in death will be summarized separately by system organ class and preferred term. Treatment-emergent AEs will also be summarized by severity and relationship to study drug as determined by the investigator using the preferred term. Summaries will be provided for both the Open-label Phase and the Double-blind Phase by treatment group. AEs that have an onset date in the Open-label Phase and persist into the Double-blind Phase with no change in severity, and lead to discontinuation from the Double-blind Phase, will be counted in the Open-label Phase summary of treatment-emergent AE leading to discontinuation.

Data listings will be generated for deaths, other SAEs, and discontinuations due to AEs. A listing of AEs with onset prior to Day 1 or post-study will be provided. A listing of AEs with onset during the oral tolerability test will also be provided.

Summaries of treatment-emergent adverse events for categories of clinical interest will be provided as discussed in the following sections. The preferred terms for each category are given in Attachment 1.

6.1.1. EPS-Related Adverse Events

Treatment-emergent AEs that are related to extrapyramidal symptoms (EPS) will be summarized. The EPS AEs will be categorized into 5 subgroups (tremor, dystonia, hyperkinesia, parkinsonism, and dyskinesia) that include the following MedDRA v. 22.1 preferred terms:

Tremor (preferred terms: Tremor, Essential tremor, Intention tremor)

Dystonia (preferred terms: Oculogyration, Oculogyric crisis, Trismus, Tongue spasm, Tongue paralysis, Cervical spasm, Emprosthotonus, Myotonia, Pleurothotonus, Risus sardonicus, Muscle spasms, Blepharospasm, Dystonia, Opisthotonus, Torticollis, Facial spasm, Muscle contracture.

Hyperkinesia (preferred terms: Akathisia, Hyperkinesia, Periodic limb movement disorder, Restless legs syndrome, Restlessness)

Parkinsonism (preferred terms: Hypertonia, Bradykinesia, Cogwheel rigidity, Drooling, Musculoskeletal stiffness, Akinesia, Hypokinesia, Nuchal rigidity, Parkinsonian gait, Parkinsonian rest tremor, Parkinsonism, Muscle rigidity, Muscle tightness, Glabellar reflex abnormal, On and off phenomenon, Parkinson's disease, Parkinsonian crisis, Extrapyramidal disorder, Reduced Facial Expression).

Dyskinesia (preferred terms: Dyskinesia, Muscle contractions involuntary, Movement disorder, Muscle twitching, Athetosis, Chorea, Choreoathetosis, Tardive dyskinesia, Myoclonus, Protrusion tongue, Rabbit syndrome, Buccoglossal syndrome.

The incidence for each EPS subgroup will be calculated.

6.1.2. Diabetes Mellitus and Hyperglycaemia-Related Adverse Events

Treatment-emergent adverse events that may be associated with diabetes mellitus and hyperglycaemia will be summarized. MedDRA preferred terms related to diabetes mellitus and hyperglycaemia are defined as follows:

- Acquired lipoatrophic diabetes, Diabetic hepatopathy, Fulminant type 1 diabetes mellitus, Hyperglycaemic seizure, Hyperglycaemic unconsciousness, Type 3 diabetes mellitus, Blood 1,5-anhydroglucitol decreased, Blood glucose increased, Cardiometabolic syndrome, Diabetes complicating pregnancy, Diabetes mellitus, Diabetes mellitus inadequate control, Diabetes with hyperosmolarity, Diabetic coma, Diabetic hyperglycaemic coma, Diabetic hyperosmolar coma, Diabetic ketoacidosis, Diabetic ketoacidotic hyperglycaemic coma, Fructosamine increased, Gestational diabetes, Glucose tolerance impaired, Glucose tolerance impaired in pregnancy, Glucose urine present, Glycosuria, Glycosuria during pregnancy, Glycosylated haemoglobin increased, Hyperglycaemia, Hyperglycaemic hyperosmolar nonketotic syndrome, Impaired fasting glucose, Insulin resistance, Insulin resistant diabetes, Insulin-requiring type 2 diabetes mellitus, Ketoacidosis, Ketonuria, Ketosis, Latent autoimmune diabetes in adults, Neonatal diabetes mellitus, Pancreatogenous diabetes, Type 1 diabetes mellitus, Type 2 diabetes mellitus, Urine ketone body present.

6.1.3. Potentially Prolactin-Related Adverse Events

Treatment-emergent adverse events that may be associated with changes in serum prolactin levels will be summarized. MedDRA preferred terms considered as being potentially related to serum prolactin levels are defined as below:

Amenorrhoea, Amenorrhoea-galactorrhoea syndrome, Galactorrhoea, Gynaecomastia, Hyperprolactinaemia, Oligomenorrhoea, Blood prolactin increased, Anorgasmia, Ejaculation delayed, Ejaculation disorder, Erectile dysfunction, Female sexual dysfunction, Libido decreased, Libido disorder, Loss of libido, Male sexual dysfunction, Orgasm abnormal, Orgasmic sensation decreased, Sexual dysfunction, Breast discharge, Breast enlargement, Breast pain, Prolactin-producing pituitary tumour, Blood prolactin, Blood prolactin abnormal, Breast tenderness, Menstruation irregular.

These adverse events will also be tabulated separately by sex.

6.1.4. Other Adverse Events of Special Interest

Incidence of other treatment-emergent adverse events of clinical interest will be presented. Search terms relevant to the adverse events of clinical importance are listed in Attachment 1. These terms were classified into the following group names:

Suicidality, Aggression and Agitation, Somnolence and Sedation, Seizures and Convulsions, Neuroleptic Malignant Syndrome, Cardiac Arrhythmias, Orthostatic Hypotension, Adverse Events Suggestive of Proarrhythmic Potential, Ischemia-related, Potential Rhabdomyolysis-related, Overdose-related, Weight Gain-related, Tachycardia-related, Injection-site Related, QT Prolongation Related, and Acute Kidney Injury Related.

6.1.5. Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a clinical interview providing an evaluation of suicidal ideation, intent, and behavior. Data are collected using the C-SSRS Baseline Version at Screening, and all the post-screening data is collected using the C-SSRS 'Since Last Visit Version'.

Using the C-SSRS, potentially suicide-related events will be categorized using the following scores:

Suicidal Ideation (1-5)

- 1: Wish to be dead
- 2: Non-specific active suicidal thoughts
- 3: Active suicidal ideation with any methods (not plan) without intent to act
- 4: Active suicidal ideation with some intent to act, without specific plan
- 5: Active suicidal ideation with specific plan and intent

Suicidal Behavior (6-10)

- 6: Preparatory acts or behavior
- 7: Aborted attempt
- 8: Interrupted attempt
- 9: Non-fatal suicide attempt
- 10: Completed suicide

If no events qualify for a score of 1 to 10, a score of 0 will be assigned (0="no event that can be assessed on the basis of C-SSRS").

A frequency distribution of scores (1 to 10) at each time point will be provided. Shifts from the screening visit to the maximum score during the Open-label Phase and the Double-blind Phase will be summarized.

The maximum score assigned during the Open-label and Double-blind Phases for each subject will be summarized into one of three broad categories: No suicidal ideation or behavior (0), Suicidal ideation (1-5), Suicidal behavior (6-10). Shifts from the screening visit to the maximum category during the Open-label Phase and the Double-blind Phase will be summarized.

6.2. Clinical Laboratory Tests

Descriptive statistics (mean, standard deviation, median, minimum, and maximum) will be provided for the clinical laboratory tests at each time point, end point (MA), and end point (DB). Changes from baseline (OL) will be summarized for the Open-label Phase and changes from baseline (DB) will be summarized for the Double-blind Phase. For the Double-blind Phase, changes from baseline (OL) will also be summarized.

Clinical laboratory test values are to be considered "treatment-emergent markedly abnormal" (TEMA) using the criteria defined by the Sponsor (Janssen R&D) listed in Attachment 2. The identification of TEMA laboratory values is based on the postbaseline value being out of range while the baseline value is either missing or within the range given in Attachment 2. If postbaseline laboratory results are above the upper limit and the baseline value is below the lower limit, then the postbaseline abnormality will also be considered TEMA. The same applies to the postbaseline value being below the lower limit with the baseline value being above the upper limit.

The frequency and percent of subjects with any TEMA laboratory values during the Maintenance Phase (relative to baseline (MA)) and the Double-blind Phase (relative to baseline (DB)) will be presented. For the Double-blind Phase, the TEMA values relative to baseline (MA) will also be summarized. Clinical laboratory tests that meet the criteria for markedly abnormal will be listed by subject.

For prolactin laboratory results, values over time and treatment-emergent abnormal results based on the laboratory reference range will be presented by sex during the Maintenance Phase (relative to baseline (MA)) and the Double-blind Phase (relative to both baseline (MA) and baseline (DB)). Median prolactin values will be plotted over time. To avoid potential unblinding of treatment, the prolactin laboratory results will not be made available to the clinical team members until the final database lock and study unblinding.

6.2.1. Glucose Abnormalities

In addition to standard descriptive summaries for glucose measurements and markedly abnormal changes, treatment-emergent abnormal values will be identified according to guidelines from the American Diabetes Association (ADA) [7] (Table 4):

Table 4: Fasting Glucose Treatment-Emergent Abnormality
ADA Guidelines

	Baseline		Any Postbaseline	
Glucose Tolerance	US Units	SI Units	US Units	SI Units

Normal to high	<100 mg/dL	<5.551 mmol/L	≥126 mg/dL	≥6.994 mmol/L
Impaired to high	≥100 mg/dL and <126 mg/dL	≥5.551 mmol/L and <6.994 mmol/L	≥126 mg/dL	≥6.994 mmol/L
Normal/impaired to high	<126 mg/dL	<6.994 mmol/L	≥126 mg/dL	≥6.994 mmol/L
			≥140 mg/dL	≥7.771 mmol/L
			≥200 mg/dL	≥11.102 mmol/L
			≥300 mg/dL	≥16.653 mmol/L

Note: 1 mg/dL=0.05551 mmol/L.

Shift tables from baseline (MA) to the maximum postbaseline fasting glucose during the Maintenance Phase and from both baseline (MA) and baseline (DB) to the maximum postbaseline fasting glucose during the Double-blind Phase will be presented based on the ADA guidelines.

6.3. Vital Signs and Physical Examination Findings

Continuous variables including orthostatic changes in vital sign measures (orthostatic systolic and diastolic blood pressure), heart rate, blood pressure, and change from baseline, will be calculated for each position at each assessment time point, end point (MA), and end point (DB). Changes from baseline (MA) will be summarized for the Open-label Phase and changes from baseline (MA) and baseline (DB) will be summarized for the Double-blind Phase. Descriptive statistics (mean, standard deviation, median, minimum and maximum) will be presented.

A treatment-emergent abnormality for pulse and blood pressure is defined as a postbaseline value and change from baseline that meet the criteria in Table 5. If the baseline value is missing, the postbaseline value will be compared against the abnormally low/abnormally high criteria. The frequency and percent of subjects with any postbaseline treatment-emergent abnormalities during the Open-label Phase (relative to baseline (MA)) and the Double-blind Phase (relative to baseline (MA) and baseline (DB)) will be tabulated.

Table 5: Treatment-Emergent Abnormality Categories for Blood Pressure (BP) and Pulse Relative to Baseline (MA) or Baseline (DB)

	Postbaseline value outside of normal limit if:	
Vital Sign	Abnormally low	Abnormally high
Systolic BP (mmHg)	A decrease from baseline of ≥20 to a value ≤90	An increase from baseline of ≥20 to a value ≥180
Diastolic BP (mmHg)	A decrease from baseline of ≥15 to a value ≤50	An increase from baseline of ≥15 to a value ≥105
Pulse (beats/min)	A decrease from baseline of ≥15 to a value ≤50	An increase from baseline of ≥15 to a value ≥100

Orthostatic hypotension is defined as a decrease in systolic (>20 mmHg), or diastolic (>10 mmHg), blood pressure after standing for at least 2 minutes relative to supine position with an increase in pulse rate of >15 beats per minute (Table 6). The number and percentage of subjects who experience treatment-emergent orthostatic hypotension at any time during the Open-label

Phase and at any time during the Double-blind Phase and for whom the orthostatic hypotension was not present at baseline (MA) or baseline (DB) for the respective phases will be tabulated.

Table 6: Abnormal Limits for Orthostatic Hypotension Parameters (Changes in Vital Signs in Standing Relative to Supine Position)	
Vital Sign	Outside of normal limit if difference (standing minus supine)
(1) Pulse (bpm)	> 15 bpm
(2a) Systolic blood pressure (mmHg) (SBP)	< -20 mmHg
(2b) Diastolic blood pressure (mmHg) (DBP)	< -10 mmHg
Note: Orthostatic hypotension requires that conditions (1) and [(2a) or (2b)] are met.	

For subjects who are unable to stand and have the vital signs measured in a sitting or supine position instead of the standing position, the difference between standing and supine values will remain missing.

6.3.1. Weight, Waist Circumference, and Body Mass Index

Body mass index (BMI) will be calculated as weight (kg)/(height (m))^2, at each time point that body weight is measured. The screening height measurement will be used in the calculation. Continuous variables including weight, waist circumference, and BMI, and change from baseline will be summarized at each assessment time point, end point (MA) and end point (DB). Changes from baseline (MA) will be summarized for the Maintenance Phase and changes from both baseline (MA) and baseline (DB) will be summarized for the Double-blind Phase. Descriptive statistics (mean, standard deviation, median, minimum and maximum) will be presented.

For body weight, the incidence of increases/decreases from both Open-Label and double-blind baselines $\geq$7% will be summarized by a frequency distribution. BMI will be categorized as normal: BMI <25 kg/m^2, overweight: 25 kg/m^2 $\leq$BMI <30 kg/m^2, obese: BMI $\geq$30 kg/m^2. The frequency and percent of subjects in each category will be presented.

6.4. Electrocardiogram

The blinded central reader will read and analyze the 12-lead ECGs. The ECG variables that will be analyzed are heart rate, RR interval, PR interval, QRS interval, QT interval, and QT corrected (QTc) interval using the following correction methods: QTcLD (Linear Derived), QTcF (Fridericia), QTLc linear (Sagie) and QTcB (Bazett).

The QT corrected interval values are based on the following formulas:

- Linear Derived: QTcLD(ms) = QT(ms) + b * (1-60/HR(bpm)), where b is an estimate of the slope, β, derived from the linear regression model QT(ms) = α + β * 60/HR(bpm), using all observations prior to treatment initiation of all subjects including screen failures;

- Fridericia: QTcF(ms) = QT(ms) * (HR(bpm)/60)$^{1/3}$;
- Sagie: QTLc(ms) = 1000 * (QT(sec) + .154 * (1 - 60/HR(bpm)));
- Bazett: QTcB(ms) = QT(ms) * (HR(bpm)/60)$^{1/2}$.

The corrected QTcF and QTcB intervals will be provided by the ECG central reader. The sponsor will calculate QTcLD and QTLc.

The "Average Predose" ECG value is defined as the average of all non-missing predose (prior to intake of study drug) ECG results. The baseline (MA) and baseline (DB) were defined in the Section 2.6.1 of the SAP.

The average predose ECG value will be compared between three prior antipsychotic use subgroups (as indicated in Section 2.4): oral antipsychotic, injectable risperidone, PP1M initiation, or PP1M/PP3M stability at the time of entering the study.

The change from baseline (MA) and baseline (DB) will be summarized for the Maintenance and Double-blind Phases. The maximum postbaseline values during Maintenance phase and Double-blind phase will be obtained. Descriptive statistics (mean, standard deviation, median, minimum and maximum) will be presented.

The number and percent of subjects with QTc intervals >450 ms, >480 ms, and >500 ms will be presented. The QTc increases relative to Baseline (MA) and relative to Baseline (DB) will be categorized as shown in Table 7. The criteria are based on the classification from the International Conference on Harmonisation (ICH) E14 Guideline (2005) [8].

The descriptive statistics will be presented by time point, for the maximum values, end point (MA), and end point (DB).

QTc increase from baseline as categorized in Table 7 will be summarized for change from baseline (MA) to maximum QTc interval during the Maintenance Phase, change from baseline (MA) to maximum QTc interval during the Double-blind Phase and change from baseline (DB) to maximum QTc interval during the Double-blind Phase.

QTc increase from baseline categories will also be presented over time, showing change from baseline (MA) over the Maintenance Phase, change from baseline (MA) over the Double-blind Phase and change from baseline (DB) over the Double-blind Phase.

Table 7: Criteria for Abnormal QTc Values and Changes From Baseline (MA) or Baseline (DB)		
Clinically significant QTc value	No	≤500
	Yes	>500
QTc increase from baseline (MA) or Baseline (DB)	No concern	≤30
	Concern	>30 – 60
	Clear concern	>60
QTc value	Normal	≤450
	>450	>450 – 480
	>480	>480 – 500
	>500	>500
Note: these criteria are based on ICH E14 Guideline		

The distribution of the average predose QTcLD, baseline (DB), and the maximum QTcLD values in each phase will be presented graphically in a box plot. A box plot of the change from average predose to maximum QTcLD value in the Open-label Phase and of the change from baseline (DB) and baseline (MA) to maximum QTcLD value in the Double-blind Phase will also be produced.

A treatment-emergent abnormality for heart rate, PR interval, QRS interval, and QT interval is defined as a postbaseline value that meets the criteria in Table 8. If an open-label postbaseline ECG result is above the upper limit (abnormally high) and the baseline (MA) value is normal or below the lower limit (abnormally low), then the postbaseline abnormality will be considered treatment-emergent. The same applies to the postbaseline value being below the lower limit (abnormally low) with the baseline (MA) value being normal or above the upper limit (abnormally high). If the baseline (MA) value is missing, the postbaseline value will be compared against the abnormally low/abnormally high criteria. Similar derivations will be presented relative to Baseline (DB) for the Double-blind Phase.

Table 8: Potentially Clinically Important Criteria for ECG Parameters		
ECG Parameter	Abnormally Low	Abnormally High
HR (bpm)	≤50	≥100
PR interval (ms)	--	≥210
QRS interval (ms)	≤50	≥120
QT interval (ms)	≤200	≥500

The number and percent of subjects with any postbaseline treatment-emergent abnormalities will be tabulated.

6.5. Extrapyramidal Symptoms (EPS) Assessment Scales

6.5.1. Abnormal Involuntary Movement Scale

The AIMS rates 10 items for dyskinesia on a 5-point scale from 0 to 4, relating to facial and oral movements, extremity movements, trunk movements, and global judgments. Summing items 1 to

7 produces an AIMS total score (range: 0 to 28). No imputation will be performed for missing items; if any of the items 1 to 7 is not recorded the total score will not be calculated. Global judgment items 8 (global impression), 9 (incapacitation), and 10 (awareness) will be summarized separately. Higher scores indicate more severe condition (or higher awareness for item 10) in abnormal involuntary movements. Two additional items (11 and 12) consist of binary questions (0=no, 1=yes) and are related to the subject's dental status.

Descriptive statistics for the AIMS total score will be presented at each time point, end point (MA), and end point (DB). Changes from baseline (MA) will be summarized for the Open-label Phase and changes from baseline (DB) will be summarized for the Double-blind Phase. The frequency distribution for each item will be presented at each time point, end point (MA), and end point (DB).

6.5.2. Barnes Akathisia Rating Scale

The BARS [9] includes an objective rating and 2 subjective ratings (awareness of restlessness and reported distress related to restlessness) of symptoms of akathisia on a 4-point scale ranging from 0 to 3, and a global clinical rating of akathisia on a 6-point scale ranging from 0 (absent) to 5 (severe). Higher scores denote worsening akathisia.

The frequency distribution for each item will be presented at each time point, end point (OL), and end point (DB).

6.5.3. Simpson and Angus Rating Scale

The SAS rates 10 items for general EPS on a 5-point scale from 0 (normal) to 4 (extreme), including gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, head rotation, Glabellar tap, tremor, and salivation. The SAS global score is the average score (total sum of item scores divided by the number of items) and ranges between 0 and 4. No imputation will be performed for missing items; if any item is left blank the global score will not be calculated. Higher scores denote more severe condition of EPS.

Descriptive statistics for the SAS global score will be presented at each time point, end point (MA), and end point (DB). Changes from baseline (MA) will be summarized for the Open-label Phase and changes from baseline (DB) will be summarized for the Double-blind Phase. The frequency distribution for each item will be presented at each time point, end point (MA), and end point (DB).

6.5.4. Extrapyramidal Symptoms Based on Rating Scales and Use of Anticholinergic Medication

Treatment-emergent EPS will also be assessed by various rating scales' incidence and use of anticholinergic medication. The incidence of dyskinesia is defined as the percentage of subjects with a score ≥3 on any of the first 7 items or a score ≥2 on 2 or more of any of the first 7 items of AIMS at any time. The incidence of akathisia is defined as the percentage of subjects with a BARS global clinical rating score ≥2 at any time. The incidence of parkinsonism is defined as the

percentage of subjects with a SAS global score >0.3 at any time. The incidence of use of anticholinergic medication is defined as the use of anti-EPS medication. The identification of treatment-emergent is based on a value occurring after the first injection during each phase meeting the EPS criteria as defined above while the baseline value is either missing or does not meet the criteria. The frequency summary of the treatment-emergent EPS will be provided for the Open-label Phase and the Double-blind Phase.

6.6. Injection Site Evaluations

The investigator will evaluate the injection site for redness, swelling, and induration (0=absent, 1=mild, 2=moderate, 3=severe) and the subject will assess the intensity of the pain of the injection using a visual analogue scale (VAS 0-100 mm). Frequency distributions will be provided for the investigator evaluations of the injection site and descriptive statistics (N, mean, standard deviation, median, and range) will be provided for the subject evaluation of the injection pain. The results will be presented at each time point, end point (TRANS), end point (MA), and end point (DB).

7. PHARMACOKINETICS/PHARMACODYNAMICS

PK/PD analysis will be documented and described in a separate analysis plan.

8. HEALTH ECONOMICS

Descriptive statistics will be provided based on the Healthcare Resource Utilization Questionnaire (HRUQ), Involvement Evaluation Questionnaire (IEQ), the Illness Management and Recovery (IMR) Scale, and the Schizophrenia Quality of Life Scale (SQLS-R4).

As noted in the time and event table of the protocol, the IMR scale will only be analyzed for subjects who entered the study on an oral antipsychotic.

Out of the 31 items on the IEQ questionnaire, 27 items will be summarized into 4-distinct sub-scales: Tension (9 items), Supervision (6 items), Worrying (6 items), Urging (8 items) and a Sum Score of the 27 items [10]. The descriptive statistics for the IEQ will only apply to those subjects who have a designated caregiver during the study.

Additionally, demographic characteristics of the caregiver and caregiving arrangements will be summarized for the OL ITT and DB ITT analysis populations.

Scoring algorithm for the total SQLS-R4

The self-administered rating scale includes 33 items concerning the subject's symptoms and well-being over the preceding 7 days on a scale of 1 to 5. For all items except item number 7, 12, 14 and 26, score 1 indicates "Never" and 5 indicates "Always". For items 7, 12, 14 and 26, scores should be reversed (1 for "Always" and 5 for "Never"). They will be reversed in the programmatic

calculation of total score, as those item scores were entered in the database without conversion. Only total score for the SQLS-R4 will be analyzed.

Total score is calculated as a percentage from 0 to 100 with 0 indicating “no problem at all” and 100 indicating “the maximum level of problem”.

The total score is calculated as:

100*Sum of scores of each item / (4*33)

If less than 25% items are missing (i.e., less than or equal to 8 items), the total score can be calculated by dividing the sum of scores of the valid items by the maximum possible score (4*number of valid items).

Imputed score = (Sum of scores of each valid item * 100)/(4*number of valid items)

If at least 25% of the items (i.e., more than 8 items) are missing, the total score will not be computed for that visit.

Observed case and LOCF values will be derived according to the rules above.

Changes from Baseline (MA) and Baseline (DB) will be calculated. The SQLS-R4 will be summarized descriptively for the OL ITT and DB ITT analysis populations.

REFERENCES

1. Clinical Study Report R092670PSY3012. A randomized, multicenter, double-blind, relapse prevention study of paliperidone palmitate 3-month formulation for the treatment of subjects with schizophrenia. Janssen Research & Development, LLC (02 Sep 2014).
2. Hough D, Gopal S, Vijapurkar V, et al. Paliperidone palmitate maintenance treatment in delaying the time-to-relapse in patients with schizophrenia: A randomized, double-blind, placebo controlled study. Schizophr Res 2010;116:107–117.
3. Kramer M, Simpson G, Maciulis V. Paliperidone extended-release tablets for prevention of symptom recurrence in patients with schizophrenia. A randomized, double-blind, placebo-controlled study. J Clin Psychopharmacol 2007;27:6–14.
4. Justification of Noninferiority Margin. Paliperidone palmitate 6-month product for the maintenance treatment of schizophrenia. Janssen Research & Development, LLC (02 Aug 2017).
5. 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.
6. Marder SR, Davis JM, and Chouinard G. "The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials". *J Clin Psychiatry*, 1997; 58(12): 538-46. Erratum in: *J Clin Psychiatry* 1998; 59(4): 200.
7. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. 2004. Consensus development conference on antipsychotic drugs and obesity and diabetes, *Diabetes Care* 27(2):596-601.
8. International Conference on Harmonization (ICH) Tripartite Guideline E14. The clinical evaluation of QT/QTc interval prolongation and proarrhythmic for non-antiarrhythmic drugs. London 2005.
9. Barnes T, "The Barnes Akathisia Rating Scale – Revisited", *J Psychopharmacology,* 2003, 17(4): 365-370.
10. van Wijngaarden B, Schene AH, Koeter M, et al. Caregiving in schizophrenia: development, internal consistency, and reliability of the Involvement Evaluation Questionnaire – European Version. Br J Psychiatry 2000;177(suppl.39):s21-s27
11. Taylor M., Murray S., Hsu C-H. Survival estimation and testing via multiple imputation. Statistics and Probability letters. 2002; 58:221-232.
12. Lipkovich I., Ratitch, B., Kelly, M. Sensitivity to censored-at-random assumption in the analysis of time-to-event endpoints. Pharmaceutical Statistics. 2016; 15:216-229.
13. Atkinson M., Kumar R., Cappelleri J., Hass S. Hierarchical Construct Validity of the Treatment Satisfaction Questionnaire for Medication (TSQM Version II) Among Outpatient Pharmacy Consumers. ISOR. 2005; 8: S9-S24.

ATTACHMENTS

Attachment 1: Special Interest Adverse Events

MAGCAT	AEDECOD
AGITATION	Agitation
AGITATION	Psychomotor agitation
AGITATION	Psychomotor hyperactivity
AGGRESSION	Aggression
AGGRESSION	Homicidal ideation
AGGRESSION	Hostility
AGGRESSION	Homicide

MCARCAT	AEDECOD
CARDIOVASCULAR	Torsade de pointes
CARDIOVASCULAR	Sudden death
CARDIOVASCULAR	Ventricular tachycardia
CARDIOVASCULAR	Ventricular fibrillation
CARDIOVASCULAR	Ventricular flutter

MISCCAT	AEDECOD
ISCHAEMIA	Acute coronary syndrome
ISCHAEMIA	Acute myocardial infarction
ISCHAEMIA	Angina pectoris
ISCHAEMIA	Angina unstable
ISCHAEMIA	Subendocardial ischaemia
ISCHAEMIA	Myocardial ischaemia
ISCHAEMIA	Cardiac ischaemia
ISCHAEMIA	Coronary artery disease
ISCHAEMIA	Coronary artery insufficiency
ISCHAEMIA	Myocardial infarction
ISCHAEMIA	Myocardial ischaemia
ISCHAEMIA	Papillary muscle infarction
ISCHAEMIA	Postinfarction angina
ISCHAEMIA	Prinzmetal angina
ISCHAEMIA	Silent myocardial infarction
ISCHAEMIA	Subendocardial ischaemia
ISCHAEMIA	Amaurosis fugax
ISCHAEMIA	Brain stem infarction
ISCHAEMIA	Brain stem ischaemia
ISCHAEMIA	Cerebellar infarction
ISCHAEMIA	Cerebral infarction
ISCHAEMIA	Cerebral ischaemia
ISCHAEMIA	Cerebrovascular accident
ISCHAEMIA	Cerebrovascular disorder
ISCHAEMIA	Cerebrovascular insufficiency
ISCHAEMIA	Embolic cerebral infarction

ISCHAEMIA	Embolic stroke
ISCHAEMIA	Haemorrhagic cerebral infarction
ISCHAEMIA	Haemorrhagic stroke
ISCHAEMIA	Ischaemic cerebral infarction
ISCHAEMIA	Ischaemic stroke
ISCHAEMIA	Subclavian steal syndrome
ISCHAEMIA	Thrombotic stroke
ISCHAEMIA	Lacunar infarction
ISCHAEMIA	Reversible ischaemic neurological deficit
ISCHAEMIA	Transient ischaemic attack
ISCHAEMIA	Vascular encephalopathy
ISCHAEMIA	Vertebrobasilar insufficiency
ISCHAEMIA	Ischaemia
ISCHAEMIA	Ischaemic cardiomyopathy
ISCHAEMIA	Thrombotic cerebral infarction
ISCHAEMIA	Cerebral microangiopathy
ISCHAEMIA	Cerebellar ischaemia

MORTHCAT	**AEDECOD**
Orthostatic Hypotension	Blood pressure orthostatic abnormal
Orthostatic Hypotension	Blood pressure orthostatic decreased
Orthostatic Hypotension	Dizziness postural
Orthostatic Hypotension	Orthostatic hypotension
Orthostatic Hypotension	Orthostatic intolerance
Orthostatic Hypotension	Orthostatic heart rate response increased
SYNCOPE	Syncope
SYNCOPE	Presyncope
SYNCOPE	Circulatory collapse
SYNCOPE	Loss of consciousness

MOVERCAT	**AEDECOD**
Overdose	Accidental overdose
Overdose	Overdose

MQTCAT	**AEDECOD**
TORSADE DE POINTES	Torsade de pointes
SUDDEN DEATH	Cardiac arrest
SUDDEN DEATH	Cardiac death
SUDDEN DEATH	Cardio-respiratory arrest
SUDDEN DEATH	Sudden death
SUDDEN DEATH	Sudden cardiac death
SUDDEN DEATH	Ventricular asystole
VENTRICULAR TACHYCARDIA	Accelerated idioventricular rhythm
VENTRICULAR TACHYCARDIA	Ventricular tachycardia
VENTRICULAR TACHYCARDIA	Ventricular tachyarrhythmia
VENTRICULAR FIBRILLATION AND FLUTTER	Cardiac fibrillation

VENTRICULAR FIBRILLATION AND FLUTTER	Ventricular arrhythmia
VENTRICULAR FIBRILLATION AND FLUTTER	Ventricular fibrillation
VENTRICULAR FIBRILLATION AND FLUTTER	Ventricular flutter

MRHACAT	**AEDECOD**
RHABDOMYOLYSIS	Rhabdomyolysis
RHABDOMYOLYSIS	Blood creatine phosphokinase increased
RHABDOMYOLYSIS	Myoglobinuria
RHABDOMYOLYSIS	Myoglobin urine

MSEIZCAT	**AEDECOD**
SEIZURES	Acquired epileptic aphasia
SEIZURES	Alcoholic seizure
SEIZURES	Atonic seizures
SEIZURES	Atypical benign partial epilepsy
SEIZURES	Automatism epileptic
SEIZURES	Baltic myoclonic epilepsy
SEIZURES	Clonic convulsion
SEIZURES	Focal dyscognitive seizures
SEIZURES	Seizure
SEIZURES	Convulsion in childhood
SEIZURES	Neonatal seizure
SEIZURES	Convulsions local
SEIZURES	Convulsive threshold lowered
SEIZURES	Déjà vu
SEIZURES	Dreamy state
SEIZURES	Drug withdrawal convulsions
SEIZURES	Eclampsia
SEIZURES	Epilepsy
SEIZURES	Epilepsy congenital
SEIZURES	Epileptic aura
SEIZURES	Epileptic psychosis
SEIZURES	Febrile convulsion
SEIZURES	Frontal lobe epilepsy
SEIZURES	Generalised non-convulsive epilepsy
SEIZURES	Grand tonic-clonic seizure
SEIZURES	Hypoglycaemic seizure
SEIZURES	Infantile spasms
SEIZURES	Lafora's myoclonic epilepsy
SEIZURES	Lennox-Gastaut syndrome
SEIZURES	Myoclonic epilepsy
SEIZURES	Myoclonic epilepsy and ragged-red fibres
SEIZURES	Partial seizures with secondary generalisation
SEIZURES	Petit mal epilepsy
SEIZURES	Post-traumatic epilepsy

SEIZURES	Focal dyscognitive seizures
SEIZURES	Seizure anoxic
SEIZURES	Simple partial seizures
SEIZURES	Status epilepticus
SEIZURES	Sudden unexplained death in epilepsy
SEIZURES	Temporal lobe epilepsy
SEIZURES	Tonic clonic movements
SEIZURES	Tonic convulsion
SEIZURES	Uncinate fits

MSOMCAT	**AEDECOD**
SOMNOLENCE	Somnolence
SOMNOLENCE	Sedation
SOMNOLENCE	Lethargy
SOMNOLENCE	Hypersomnia

MSUICAT	**AEDECOD**
SUICIDALITY	Depression suicidal
SUICIDALITY	Intentional self-injury
SUICIDALITY	Poisoning deliberate
SUICIDALITY	Self-injurious ideation
SUICIDALITY	Completed suicide
SUICIDALITY	Suicidal ideation
SUICIDALITY	Suicide attempt
SUICIDALITY	Suicidal behaviour

MNMSCAT	**AEDECOD**
NMS	Hyperthermia malignant
NMS	Neuroleptic malignant syndrome
NMS	Serotonin syndrome
NMS	Body temperature increased
NMS	Hyperpyrexia
NMS	Pyrexia
NMS	Catatonia
NMS	Dyskinesia
NMS	Dystonia
NMS	Freezing phenomenon
NMS	Hyperkinesia
NMS	Hypertonia
NMS	Muscle necrosis
NMS	Muscle rigidity
NMS	Oculogyric crisis
NMS	Opisthotonus
NMS	Rhabdomyolysis

NMS	Altered state of consciousness
NMS	Autonomic nervous system imbalance
NMS	Blood creatine phosphokinase abnormal
NMS	Blood creatine phosphokinase increased
NMS	Blood creatine phosphokinase MM increased
NMS	Blood pressure abnormal
NMS	Blood pressure decreased
NMS	Blood pressure fluctuation
NMS	Blood pressure increased
NMS	Cardiovascular insufficiency
NMS	Coma
NMS	Confusional state
NMS	Consciousness fluctuating
NMS	Delirium
NMS	Depressed level of consciousness
NMS	Disorientation
NMS	Extrapyramidal disorder
NMS	Heart rate abnormal
NMS	Heart rate increased
NMS	Hyperhidrosis
NMS	Hypertension
NMS	Hypotension
NMS	Labile blood pressure
NMS	Labile hypertension
NMS	Leukocytosis
NMS	Loss of consciousness
NMS	Muscle enzyme increased
NMS	Myoclonus
NMS	Myoglobin blood increased
NMS	Myoglobin blood present
NMS	Myoglobin urine present
NMS	Myoglobinaemia
NMS	Myoglobinuria
NMS	Parkinsonian crisis
NMS	Parkinsonian rest tremor
NMS	Parkinsonism
NMS	Parkinson's disease
NMS	Stupor
NMS	Tachycardia
NMS	Tremor
NMS	Unresponsive to stimuli
NMS	White blood cell count abnormal
NMS	White blood cell count increased

MTACCAT	AEDECOD
Tachycardia	Heart rate increased
Tachycardia	Sinus tachycardia
Tachycardia	Tachycardia
Tachycardia	Tachycardia paroxysmal

MWEICAT	AEDECOD
WEIGHT GAIN	Increased appetite
WEIGHT GAIN	Hyperphagia
WEIGHT GAIN	Obesity
WEIGHT GAIN	Overweight
WEIGHT GAIN	Abnormal weight gain
WEIGHT GAIN	Waist circumference increased
WEIGHT GAIN	Weight increased

MINJCAT	AEDECOD
INJECTION SITE	Injection related reaction
INJECTION SITE	Injection site abscess
INJECTION SITE	Injection site abscess sterile
INJECTION SITE	Injection site anaesthesia
INJECTION SITE	Injection site atrophy
INJECTION SITE	Injection site bruising
INJECTION SITE	Injection site calcification
INJECTION SITE	Injection site cellulitis
INJECTION SITE	Injection site coldness
INJECTION SITE	Injection site cyst
INJECTION SITE	Injection site dermatitis
INJECTION SITE	Injection site exfoliation
INJECTION SITE	Injection site discharge
INJECTION SITE	Injection site discolouration
INJECTION SITE	Injection site discomfort
INJECTION SITE	Injection site eczema
INJECTION SITE	Injection site erosion
INJECTION SITE	Injection site erythema
INJECTION SITE	Injection site extravasation
INJECTION SITE	Injection site fibrosis
INJECTION SITE	Injection site haematoma
INJECTION SITE	Injection site haemorrhage
INJECTION SITE	Injection site hypersensitivity
INJECTION SITE	Injection site hypertrophy
INJECTION SITE	Injection site induration
INJECTION SITE	Injection site infection
INJECTION SITE	Injection site inflammation
INJECTION SITE	Injection site injury
INJECTION SITE	Injection site irritation

INJECTION SITE	Injection site ischaemia
INJECTION SITE	Injection site lymphadenopathy
INJECTION SITE	Injection site mass
INJECTION SITE	Injection site movement impairment
INJECTION SITE	Injection site necrosis
INJECTION SITE	Injection site nerve damage
INJECTION SITE	Injection site nodule
INJECTION SITE	Injection site oedema
INJECTION SITE	Injection site pain
INJECTION SITE	Injection site pallor
INJECTION SITE	Injection site papule
INJECTION SITE	Injection site paraesthesia
INJECTION SITE	Injection site phlebitis
INJECTION SITE	Injection site photosensitivity reaction
INJECTION SITE	Injection site pruritus
INJECTION SITE	Injection site pustule
INJECTION SITE	Injection site rash
INJECTION SITE	Injection site reaction
INJECTION SITE	Injection site scab
INJECTION SITE	Injection site scar
INJECTION SITE	Injection site swelling
INJECTION SITE	Injection site thrombosis
INJECTION SITE	Injection site ulcer
INJECTION SITE	Injection site urticaria
INJECTION SITE	Injection site vesicles
INJECTION SITE	Injection site warmth
INJECTION SITE	Musculoskeletal pain
INJECTION SITE	Pain in extremity
INJECTION SITE	Puncture site pain
INJECTION SITE	Administration site pain
INJECTION SITE	Application site pain
INJECTION SITE	Injection site dryness
INJECTION SITE	Injection site dysaesthesia
INJECTION SITE	Injection site exfoliation
INJECTION SITE	Injection site granuloma
INJECTION SITE	Injection site hyperaesthesia
INJECTION SITE	Injection site laceration
INJECTION SITE	Injection site macule
INJECTION SITE	Injection site plaque
INJECTION SITE	Injection site streaking
INJECTION SITE	Injection site vasculitis

MQTPLCAT	**AEDECOD**

QT PROLONGATION	Electrocardiogram QT interval abnormal
QT PROLONGATION	Electrocardiogram QT prolonged
QT PROLONGATION	Long QT syndrome
QT PROLONGATION	Long QT syndrome congenital

MAKICAT	**AEDECOD**
ACUTE RENAL FAILURE (SMQ)	ACUTE PHOSPHATE NEPHROPATHY
ACUTE RENAL FAILURE (SMQ)	ACUTE KIDNEY INJURY
ACUTE RENAL FAILURE (SMQ)	ANURIA
ACUTE RENAL FAILURE (SMQ)	AZOTAEMIA
ACUTE RENAL FAILURE (SMQ)	CONTINUOUS HAEMODIAFILTRATION
ACUTE RENAL FAILURE (SMQ)	DIALYSIS
ACUTE RENAL FAILURE (SMQ)	HAEMODIALYSIS
ACUTE RENAL FAILURE (SMQ)	HAEMOFILTRATION
ACUTE RENAL FAILURE (SMQ)	NEONATAL ANURIA
ACUTE RENAL FAILURE (SMQ)	NEPHROPATHY TOXIC
ACUTE RENAL FAILURE (SMQ)	OLIGURIA
ACUTE RENAL FAILURE (SMQ)	PERITONEAL DIALYSIS
ACUTE RENAL FAILURE (SMQ)	PRERENAL FAILURE
ACUTE RENAL FAILURE (SMQ)	RENAL FAILURE
ACUTE RENAL FAILURE (SMQ)	RENAL FAILURE NEONATAL
ACUTE RENAL FAILURE (SMQ)	RENAL IMPAIRMENT
ACUTE RENAL FAILURE (SMQ)	RENAL IMPAIRMENT NEONATAL

Attachment 2: Criteria of Markedly Abnormal Laboratory Values

Laboratory Parameter[unit]	Markedly Abnormal Limits	
	Low	High
Albumin [g/L]	24	60
Alkaline phosphatase [U/L]	N/A	250
Alanine Aminotransaminase (SGPT) [U/L]	N/A	200
Aspartate Aminotransaminase (SGOT) [U/L]	N/A	250
Bicarbonate [mmol/L]	15.1	34.9
Blood urea nitrogen [mmol/L]	N/A	17.9
Calcium [mmol/L]	1.5	3
Chloride [mmol/L]	94	112
CCI	[redacted]	[redacted]
Creatinine [µmol/L]	N/A	265.2
Gamma glutamyl transferase [U/L]	N/A	300
Glucose [mmol/L]	2.2	16.7
CCI	[redacted]	[redacted]
Lactate Dehydrogenase[U/L]	N/A	500
Phosphate [mmol/L]	0.7	2.6
Potassium [mmol/L]	3.0	5.8
Sodium [mmol/L]	125	155
Bilirubin, total [µmol/L]	N/A	51.3
Protein, total (g/L)	50	N/A
CCI	[redacted]	[redacted]
Urate [µmol/L]	89.2	594.8
Hematocrit (fraction) -- female	0.28	0.5
-- male	0.24	0.55
Hemoglobin [g/L]	80	190
Neutrophils, Segmented [%]	30	90
Monocytes [%]	N/A	20
Eosinophils [%]	N/A	10
Basophils [%]	N/A	6
Lymphocytes [%]	10	60
Platelet count [$x10^9$/L]	100	600
Erythrocytes [$x10^{12}$/L] -- female	3.0	5.5
-- male	3.0	6.4
Leukocytes [$x10^9$/L]	2.5	15.0

Note: The same limits apply to both males and females unless gender is indicated; N/A = Not applicable.