COVER PAGE

Statistical Analysis Plan (SAP)

TITLE: Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Intramuscular Injections of Risperidone ISM® in Patients with Acute Exacerbation of Schizophrenia (PRISMA-3)

PROTOCOL NUMBER: ROV-RISP-2016-01

NCT NUMBER: NCT03870880

SAP VERSION 4.0

DOCUMENT DATE: 15 February 2019

Statistical Analysis Plan

Sponsor Name: Laboratorios Farmacéuticos ROVI, S.A.

Protocol Number: ROV-RISP-2016-01

Protocol Title: Multicenter, Randomized, Double-Blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Intramuscular Injections of Risperidone ISM® in Patients with Acute Exacerbation of Schizophrenia (PRISMA-3).

Protocol Version and Date: (DD-Mmm-YYYY): 7.0 (22-MAR-2018)

Syneos Health Project Code: 1004855

Author:
Gary Smith, Principal Biostatistician

Revision History

Version #	Date (dd-mmm-yyyy)	Document Owner	Revision Summary
1.0	28-JUL-2017	Gary Smith	First Version
2.0	03-JAN-2018	Gary Smith	- Update in line with latest protocol V6.0 - Update to detail potential accidental unblinding issue and corresponding actions: • Define mITT, mPP and mSAF populations (Section 5) • Detail of updated confirmatory testing procedures and additional analysis of new analysis populations (Section 8) - Clarify how to determine the effect size for purpose of sample size re-estimation (Section 12) - Provide more detail on the conditional power calculation to assess futility (Section 12)
3.0	23-FEB-2018	Gary Smith	- Update to CHW analysis using z instead of t as per the reference (Section 8.1.1). - Update to conditional power formula in line with the formula used in the reference (Section 12) - Clarify the outputs to be provided to DMC for sample size re-estimation (Section 12)

Version #	Date (dd-mmm-yyyy)	Document Owner	Revision Summary
4.0	15-FEB-2019	Gary Smith	- Rebranding of INC Research to Syneos Health (all sections). - Added detail of interim analyses 2 and 3 (sections 2.3 and 12) - Update study overview text (section 3) based on Protocol V7 updates for inclusion of de novo subjects. - Added Modified Randomized Population for multiple imputation sensitivity analyses (section 5.5). - Updated PP population definition following blind data review (Section 5.8)) - Added PK evaluable windowing definitions relative to dosing rather than study visits (Sections 5.10 and 9) - Added PGx population (Section 5.11) - Updated the definition for treatment exposure (section 6.2.8) - Ensure that disposition listings and summaries include de novo patients (section 7.1). - Update treatment groupings for OLE summaries (sections 5.10 / 6.1 / 8.2.3) and clarify treatment groups/sorting for listings (section 6.1). - Update definition of concomitant medication to exclude medications taken after treatment discontinuation. The term prior medication replaced with off-treatment medication and definition updated (section 7.4). - Added additional interaction terms including visit into MMRM models for subgroup analyses to enable within subgroup treatment comparisons at each visit (Section 8.1.1) - Added approach to Simpson Angus Scale data collected on the incorrect scale (section 11.7.3) - Clarified baseline for change from baseline endpoints for the C-SSRS (section 11.8)

I confirm that I have reviewed this document and agree with the content.

APPROVALS	
Syneos Health	
Lead Biostatistician Gary Smith Principal Biostatistician	18 FEB 2019 **Date (dd-Mmm-yyyy)**
PK Scientist Hiren Mehta Director of Pharmacometrics	19 FEB 2019, 9:30 am EST **Date (dd-Mmm-yyyy)**
Senior Reviewing Biostatistician John Williams Senior Director, Biostatistics	18 FEB 2019 **Date (dd-Mmm-yyyy)**
Laboratorios Farmacéuticos ROVI, S.A	
Sponsor Contact Begoña Gorostidi Losada Clinical Operations Manager	18/Feb/2019 (16:48h. CET) **Date (dd-Mmm-yyyy)**
Sponsor Contact Jordi Llaudó Clinical Development Manager	18/FEB/2019 (16:47h. CET) **Date (dd-Mmm-yyyy)**

TABLE OF CONTENTS

1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
AST	Aspartate aminotransferase
BARS	Barnes Akathisia Rating Scale
BCVA	Best Corrected Visual Activity
BDRM	Blind Data Review Meeting
BMI	Body Mass index
CGI-I	Clinician Global Impression – Improvement scale
CGI-S	Clinician Global Impression – Severity scale
CI	Confidence Interval
C_{max}	maximum concentration
C_{min}	minimum concentration
CP	Conditional Power
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	Clinical Study Report
CV	Coefficient of Variation
DB	Double-blind
DMC	Data Monitoring Committee
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
ET	End of Study Visit

Abbreviation	Description
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HEOR	Health Economics and Outcomes Research
HRQL	Health-Related Quality of Life
HRU	Healthcare Resource Utilization
ICH	International Conference on Harmonization
ITT	Intent-to-Treat
IM	intramuscular
ISM®	In situ microparticle
IVRS	Interactive Voice Randomization System
IWRS	Interactive Web Randomization System
MAR	Missing at Random
Max	Maximum
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
Min	Minimum
MINI	MINI International Neuropsychiatric Interview
mITT	Modified Intent-to-Treat
MMRM	Mixed Model Repeated Measurement
MNAR	Missing Not at Random
mPP	Modified Per-protocol
mSAF	Modified Safety Population
N/A	Not Applicable
NA	Not Applicable
NCI	National Cancer Institute
OC	Observed Cases
OLE	Open-label extension phase
OLP	Open-label Population

Abbreviation	Description
PANSS	Positive and Negative Syndrome Scale
PK	Pharmacokinetic
PMM	Pattern Mixture Model
PP	Per-protocol
PSP	Personal and Social Performance scale
PT	Preferred Term
QC	Quality Control
QTc	Corrected QT Interval
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	Serious Adverse Event
SAF	Safety Population
SAP	Statistical Analysis Plan
SAS	Simpson-Angus Scale
SD	Standard Deviation
SE	Standard Error
SI	Standard International System of Units
SOC	System Organ Class
SOP	Standard Operating Procedure
SWN-20	Subjective Well-being Under Neuroleptics – Short Form
TEAE	Treatment Emergent Adverse Event
TLF	Table, Listing and Figure
VAS	Visual Analogue Scale
WHO	World Health Organization

2. PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1 RESPONSIBILITIES

Syneos Health will perform the statistical analyses and are responsible for the production and quality control of all tables, figures and listings. Laboratorios Farmacéuticos ROVI, S.A. will review and approve the final tables, figures and listings.

From 4th January 2018, INC Research was re-branded to Syneos Health. Syneos Health will always be referred to in this version of the SAP, even when discussing past activities prior to this date.

2.2 STANDARDS

Statistical analyses are planned and conducted in accordance with the principles outlined by the ICH E9 guidelines. Creation and validation of the clinical database, management of data, and transfer of laboratory data are conducted in accordance with 21 CFR Part 11 and Guidance for Industry on Computerized Systems Used in Clinical Trials.

2.3 TIMINGS OF ANALYSES

The primary analysis of safety, efficacy, and pharmacokinetics is to be conducted when all patients have either completed or terminated early from the DB phase of the study. Unless otherwise specified, the analysis will include all data collected in the database through the time of the database lock for the DB phase, which will also include open label extension (OLE) analyses on incomplete data. A follow-up analysis will be performed when all patients have completed or discontinued from the OLE phase of the study.

An interim analysis to evaluate sample size assumptions will be conducted when 196 randomized patients, for whom the blinding is not compromised (see Section 3.6.3), have either reached day 85 or withdrawn from the DB phase of the study. Only data from these patients will be used in this analysis. An independent statistical center will perform the analyses (as described in Sections 8.1 and 12 of this SAP) to maintain the blinding of the study.

Two further interim analyses will be conducted following the unblinding of the DB phase when approximately 65 and 100 patients are known to have been exposed to either of the active arms for at least 337 days respectively.

A Data Monitoring Committee (DMC) will be formed to monitor patient accrual and to monitor compliance with the protocol at individual investigational sites, review any safety data (including

individual AEs and SAEs), alert and /or make recommendations to the sponsor about any existing or potential problems. The DMC meetings will take place as follows:

DMC Safety Review Meetings will be scheduled as follows:

- Approximately 4 – 6 weeks after:
    - 10% patients have completed (i.e. reached day 85) the DB phase
    - 25%, 50% (including interim analysis*) and 75% of the randomized patients have either completed (i.e. reached day 85) or terminated early from the DB phase of the study.
- After the DB phase is completed, meetings will be planned to review 25%, 50%, 75% of patients completed as applicable (OLE) phase
- Ad hoc at the request of the DMC or Laboratorios Farmacéuticos ROVI, S.A. (e.g. in the event of unexpected SAEs)

* Note: Due to potential accidental unblinding, it was considered that 43 patients were potentially compromised and therefore the interim analysis sample size re-estimation will only include the 196 non-compromised patients (see Section 12) whereas the safety outputs provided for the 50% DMC will include both the 196 non-compromised and 43 compromised patients.

3. STUDY OVERVIEW

3.1 PRIMARY OBJECTIVE

The primary objective of this study is to evaluate the efficacy of Risperidone ISM® as compared with that of placebo in the treatment of patients with acute exacerbation of schizophrenia.

3.2 SECONDARY OBJECTIVE(S)

The secondary objectives of this study are the following:

- To characterize safety and tolerability of Risperidone ISM as compared with that of placebo in patients with acute exacerbation of schizophrenia
- To quantify healthcare resource utilization (HRU), health-related quality of life (HRQL), and social functioning in patients treated with Risperidone ISM versus placebo for an acute exacerbation of schizophrenia
- To explore pharmacokinetic characteristics of Risperidone ISM and associations with efficacy

3.3 BRIEF DESCRIPTION

This is a multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of Risperidone ISM, a new long-acting injectable form of the licensed drug risperidone. Eligible patients will be randomly assigned, under double-blind conditions, to receive Risperidone ISM (75 or 100 mg) or placebo.

The study design includes a screening period (planned duration 1 to 8 days) immediately preceding the DB phase baseline day (designated as DB phase study day 1), a DB phase treatment period (duration 12 weeks), an OLE period (duration 12 months) and a follow-up period (duration 2 weeks [DB] or 4 weeks [OLE]).

The initial planned total number of randomized patients in the DB phase of the study is approximately 393 patients (131 in each of the 3 treatment groups) for whom the blinding is not compromised (see Section 3.6.3). Following confirmation of eligibility, each patient will be randomly assigned under double-blind conditions to receive 1 of the following 3 study drug treatments: Risperidone ISM 75 mg, Risperidone ISM 100 mg, or placebo, with an overall 1:1:1 ratio.

Patients who have never taken risperidone must have a brief trial of oral risperidone 2 mg/day for 3 days during the screening period in order to ensure a lack of any clinically significant hypersensitivity reactions before the first dose of long-acting IM study drug is administered. A trial of oral risperidone is not required for patients who have previously taken any formulation of risperidone.

Study drug will be administered as IM injections. Treatment assignment for each individual patient will remain blinded for patients, investigators, and all study site staff, with the exception of identified

individuals at each study site who will be unblinded in order to prepare and administer study drug for each patient at that study site.

After initial dosing on study day 1, study drug (Risperidone ISM or placebo) will be administered once every 4 weeks during the 12-week treatment period (i.e., at study days 29 and 57).

Patients who complete planned participation in this study through to the end of the DB phase treatment period may be eligible to enter into an optional OLE phase of the study, during which open-label Risperidone ISM (i.e. either 75 or 100 mg) will be administered to all participating patients once every 4 weeks for approximately 12 months. Patients who enter into the OLE phase of the study will begin participation in that phase immediately upon completion of the DB phase end-of-treatment visit assessments and procedures. Patients who do not enter into the OLE phase will have a final safety follow-up phone contact approximately 2 weeks after the DB phase end-of-treatment visit.

In addition to patients continuing from the DB phase of the study (rollover patients), patients not previously enrolled in the study (de novo patients) may be eligible to enter the long-term OLE phase of the study. These patients will be evaluated for eligibility at a screening visit and, if eligible, will be allocated to receive either 75 or 100 mg Risperidone ISM every 4 weeks for approximately 12 months. Approximately 100 de novo patients are planned to be enrolled in the OLE phase of the study, in addition to rollover patients.

3.4 PATIENT SELECTION

To be eligible for participation in the study, at screening each patient must meet all of the inclusion criteria and none of the exclusion criteria.

3.4.1 Eligibility Criteria for Enrollment into the DB Phase of the Study

3.4.1.1 Inclusion Criteria

Inclusion criteria for enrollment in the DB phase of the study are defined in the Study Protocol Section 4.1.1.1.

3.4.1.2 Exclusion Criteria

Exclusion criteria for enrollment in the DB phase of the study are defined in the Study Protocol Section 4.1.1.2.

3.4.2 Eligibility Criteria for Entry into the OLE Phase of the Study (Rollover Patients)

Participation in the OLE phase of the study is optional, and patients who complete participation in the DB phase of the study may opt to not participate. Patients who are interested in participating must meet all eligibility criteria in order to enter into the OLE phase.

3.4.2.1 Inclusion Criteria

Inclusion criteria for the OLE phase for rollover patients are defined in the Study Protocol Section 4.1.2.1.

3.4.2.2 Exclusion Criteria

Exclusion criteria for the OLE phase for rollover patients are defined in the Study Protocol Section 4.1.2.2.

3.4.3 Eligibility Criteria for Entry into the OLE Phase of the Study (De Novo Patients)

To be eligible for entry into the OLE phase of the study, a de novo patient must meet all of the eligibility criteria at the OLE screening visit.

3.4.3.1 Inclusion Criteria

Inclusion criteria for the OLE phase for de novo patients are defined in the Study Protocol Section 4.1.3.1.

3.4.3.2 Exclusion Criteria

Exclusion criteria for the OLE phase for de novo patients are defined in the Study Protocol Section 4.1.3.2.

3.5 DETERMINATION OF SAMPLE SIZE

The overall ratio for the random allocation of the 3 treatments to patients will be 1:1:1 (Risperidone ISM 75 mg: Risperidone ISM 100 mg: placebo) during the DB phase.

The primary efficacy analysis will include all patients for whom the blinding was not compromised (see Section 3.6.3), who receive at least 1 dose of study drug and have both a baseline and at least 1 post-baseline PANSS evaluation (modified intent-to-treat [mITT]) population).

The primary efficacy variable is the PANSS total score mean change from baseline to endpoint, which is assumed to differ between Risperidone ISM and placebo groups by 9 points. The primary efficacy analysis is designed to show superiority of the active treatment groups versus placebo, according to the closed testing procedure (see Section 8.1).

Taking into account that each of the 2 Risperidone ISM groups (i.e. Risperidone ISM 75 mg and Risperidone ISM 100 mg) will be tested separately against the placebo group, a Bonferroni adjustment for the α level was performed. A common standard deviation of 20 in 2-group t-tests was assumed.

A sample size of 124 patients in the mITT population in each treatment-group will have 90% power to detect a difference in means of 9 (standard deviation = 20, effect size = 0.45) with a 2.5% 2-sided

significance level in both Risperidone ISM groups versus the placebo group. The power to show superiority of both Risperidone ISM doses to placebo using the above calculation would be at least 81%. This will be higher due to a high correlation in pharmacokinetic data between doses (see Study Protocol - Section 1) and use of a less conservative multiplicity adjustment than Bonferroni (i.e., Hommel – see Section 8.1.1)..

A relatively low post-randomization dropout rate is anticipated because it is surmised that most patients in the inpatient setting will reach study day 4 (patients who drop out before study day 4 will not be included in the mITT population); therefore, a 5% dropout rate is considered reasonable. Assuming this 5% dropout rate, a randomized sample size of 131 patients per treatment group, or 393 patients total (all 3 treatment groups combined) for whom the blinding was not compromised (see Section 3.6.3), will be required. This assumption will be re-assessed at the interim analysis and used in re-estimating the total number of randomized patients required (see Section 12).

Taking into account the 43 patients for whom blinding was potentially compromised (see Section 3.6.3), 436 randomized patients in total will be required for the DB phase of the study.

Assuming a screening failure rate of 35%, approximately 671 patients will need to be screened in order to achieve the planned 436 patients randomized in the DB phase of the study.

3.6 TREATMENT ASSIGNMENT & BLINDING

3.6.1 Treatment Assignment

Upon confirmation of eligibility for a given patient to participate in the DB phase study, a unique randomization number for that patient will be assigned via an interactive voice or web response system (IVRS/IWRS) that is to be accessed by study site personnel immediately after confirmation of patient eligibility has been recorded.

The randomization number for a given patient will be used to identify the study drug (i.e., blinded Risperidone ISM 75 mg, Risperidone ISM 100 mg, or placebo) which will be administered to that patient.

The randomization scheme will automatically ensure that the study drug assignment for a given patient is random, and that an overall 1:1:1 ratio of assignments to each of the 3 study drug treatments is approximated.

In addition, the randomization scheme will include the following stratification parameters to ensure balanced distribution of assignment to the 3 treatments: country where enrolled and PANSS total score (i.e., ≥ 95 versus < 95) at baseline/randomization.

An independent biostatistician will maintain the randomization scheme key, which will remain unavailable to all other individuals until after completion of the DB phase and subsequent locking of the DB phase data at this point.

Once a randomization number has been assigned, that number must not be used again for any other patient (e.g. when patient is withdrawn from the study, that patients's randomization number must not be reused for any other patient).

In the OLE phase of the study, all participating patients will receive active Risperidone ISM under open-label conditions. However, in order to preserve the blinding condition of the double-blind stage of the study, if a participating patient enters this OLE phase of the study prior to locking the database of the double-blind stage of the study, the allocation to either 75 or 100 mg of this patient will be still blinded at least up to locking the aforementioned database. Patients who had been on active Risperidone ISM in the DB phase of the study will continue to receive active Risperidone ISM at the same dose (i.e., 75 or 100 mg) in the OLE phase. Patients who had been receiving placebo in the DB phase of the study will be randomly assigned to receive either 75 or 100 mg during the OLE phase.

De novo patients participating in the OLE phase of the study will receive either 75 or 100 mg Risperidone ISM depending on their previous oral risperidone dose. Patients on 4 mg of oral risperidone will be assigned to 75 mg Risperidone ISM, and patients on more than 4 mg to a maximum of 6 mg of oral risperidone will be assigned to 100 mg Risperidone ISM. Upon confirmation of eligibility for a given de novo patient, the corresponding IMP kit will be assigned via IVRS/IWRS which will be accessed by study site personnel immediately after confirmation of patient eligibility has been recorded

3.6.2 Blinding

During the double-blind phase of the study, the IM study drug will be administered under double-blind conditions so that investigators, site staff, and patients will not be aware about the identity of the study drug (i.e., blinded Risperidone ISM 75 mg, Risperidone ISM 100 mg, or placebo) administered to any given patient.

The packaging and labelling for placebo or Risperidone ISM 75 or 100 mg will be identical. The placebo and Risperidone ISM doses are practically indistinguishable before or after reconstitution. Reconstitution will follow the same process for placebo or Risperidone ISM. Any small differences in final volumes are not perceptible.

For de novo patients, the corresponding IMP kit will be assigned via IVRS/IWRS based on the criteria stated in Section 3.6.1 (i.e., 4 mg or >4 to 6 mg oral risperidone) so that both investigator and patient will know the treatment administered, which is consistent with the open -label definition of this phase of the study.

Nevertheless, the management of the study drug will only be performed by designated unblinded individuals at sites who will be dealing with the study drug reconstitution and administration of the study drug to the patient, and will not be involved in any clinical evaluation. These individuals will be

appropriately qualified and trained to perform the required study drug reconstitution and study drug administration to patients.

Oral risperidone test doses of 2mg per day for 3 days, if applicable for a given patient, will be administered under open-label conditions during the screening period.

If an investigator deems it necessary to break the treatment assignment blind, he or she should promptly document and explain to the medical monitor or designee the reason of the unblinding (e.g. accidental unblinding, unblinding due to an SAE) of study drug.

Once it has been determined that breaking the blind is necessary, the investigator or other designated study site staff member will contact the IVRS/IWRS to obtain disclosure of the identified patient's treatment assignment.

Breaking the blind for a single patient will not affect the blind for the remaining patients.

All patients who participate in the optional OLE phase of the study will receive active Risperidone ISM (i.e., 75 or 100 mg) under open-label conditions. However, in order to preserve the blinding condition of the double-blind stage of the study, if a participating rollover patient enters this OLE phase of the study prior to locking the database of the double-blind stage of the study, the allocation to either 75 or 100 mg of this patient will still be blinded at least up to locking the aforementioned database.

One unblinded interim analysis will be conducted when 196 randomized patients have either reached day 85 or withdrawn from the DB phase. This interim statistical analysis will be conducted by a designated Syneos Health unblinded team located in a different country to the Syneos Health blinded team. All designated blinded study personnel will remain blinded.

3.6.3 Potential Unblinding

On 28th September 2017, due to a noted error in the IWRS system, potential accidental unblinding of treatment allocation to patients for blinded personnel was reported.

At an ad-hoc DMC meeting on 8th November 2017, it was concluded that there were 43 patients for whom the blinding was potentially compromised due to this error. The following decisions pertaining to the analysis of the study were also agreed:

- Add 43 replacement patients
- Create a modified ITT (mITT) population which will comprise of the ITT population without the compromised patients.
- The mITT population will become the primary analysis population for efficacy. The reasoning would be that this will be the most conservative patient group to demonstrate efficacy. The full ITT analysis would still have to meet the significance levels also in the final analysis.

- Perform the sample size re-estimation at interim based on the mITT analysis (i.e. perform original study plan as if the compromised patients did not exist)
- Keep the planned analysis weightings for the final analysis of the mITT that were in place for the ITT (i.e. 50/50 between pre/post IA) and same analysis methods
- Modify the weightings for the ITT analysis to account for likely greater percentage of patients at interim but otherwise keep all planned analyses.
- Repeat all ITT efficacy analyses using the mITT.
- Add a modified PP (mPP) population to support mITT results (selected endpoints).
- Add a modified SAF (mSAF) population to support SAF results (selected endpoints).
- PK populations and analysis unaffected due to objective data.

These actions were recommended by the Syneos Health Biostatistics team and agreed by ROVI and DMC members prior to first receipt of the unblinded randomization list by Syneos Health Unblinded Statistical personnel (for DMC analyses). This was received on 17th November 2017.

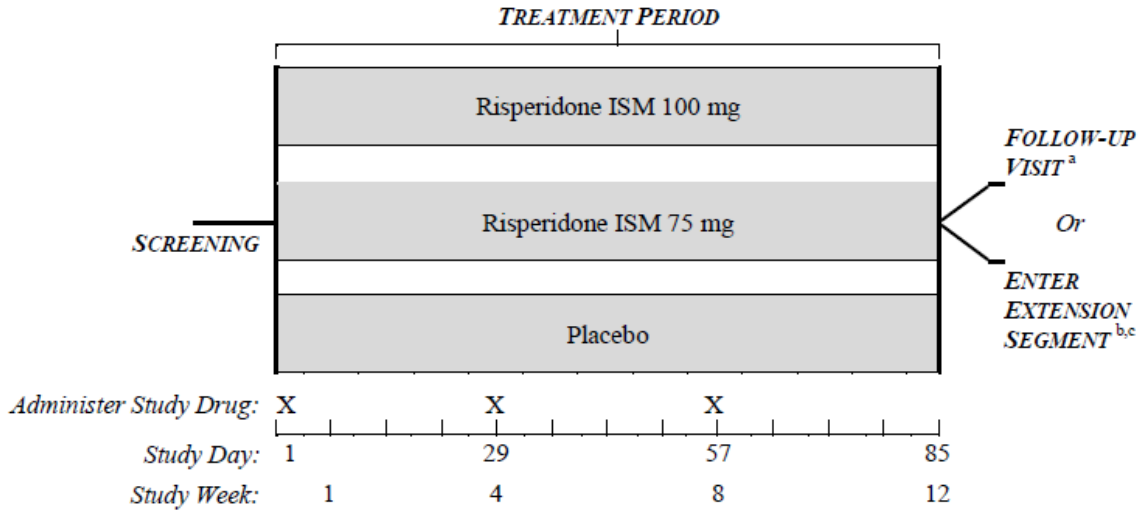
3.7 ADMINISTRATION OF STUDY MEDICATION

The preparation and administration of the study drugs are described in Section 5.1.2 of the Study Protocol.

3.8 STUDY PROCEDURES AND FLOWCHART

The overall study design is depicted schematically in **Figure 1**. A schedule of assessments and procedures is displayed by visit in **Table 1**, **Table 2 and Table 3**.

Figure 1 Schematic of Study Design



[a] If a patient does not enter the extension segment of the study, no additional doses of study drug will be administered to that patient.

[b] Patients who complete planned participation through to the end of the treatment period may be eligible to enter into a long-term extension segment of the study, during which open-label Risperidone ISM (i.e., 75 or 100 mg) will be administered once every 4 weeks for approximately 12 months. However, in order to preserve the blinding condition of the double-blind stage of the study, if a participating patient enters this OLE phase of the study prior to locking the database of the double-blind stage of the study, the allocation to either 75 or 100 mg of this patient will be still blinded at least up to locking the aforementioned database. Patients who enter into the extension segment will begin participation in the extension segment immediately upon completion of scheduled end-of-treatment assessments and procedures at the week 12 time point. Patients who had been on active Risperidone ISM in the double-blind segment of the study will continue to receive active Risperidone ISM at the same dose (i.e., 75 or 100 mg) in the extension segment; patients who had been receiving placebo in the double-blind segment of the study will be randomly assigned to receive either 75 or 100 mg during the extension segment.

[c] De novo patients may also be eligible to enter the long-term extension segment of the study. These patients will be evaluated for eligibility at a screening visit and, if eligible, will be allocated to receive either 75 or 100 mg Risperidone ISM every 4 weeks for approximately 12 months. De novo patients on 4 mg/day of oral risperidone will be assigned to 75 mg Risperidone ISM every 4 weeks, and patients on more than 4 mg/day to a maximum of 6 mg/day of oral risperidone will be assigned to 100 mg Risperidone ISM every 4 weeks.

Table 1 Schedule of Assessments and Procedures During the Double-Blind Phase

	Screening	DB BL	Treatment Period (DB Phase)												FU
DB Phase Visit Number:	**1**	**2**	**3**	**4**	**5**	**6**	**7[1]**	**8**	**9**	**10**	**11**	**12**	**13**	**14[2]**	**15[3]**
DB Phase Study Day[4]:	**-8 to -1[5]**	**1**	**3**	**4**	**8**	**15**	**22**	**29**	**31**	**43**	**57**	**59**	**71**	**85**	**99**
DB Phase Treatment Week:					**1**	**2**	**3**	**4**		**6**	**8**		**10**	**12**	
DB Phase Overall Dosing Sequence:		**1**						**2**			**3**				
Informed Consent	X														
Screening assessments[6]	X														
Eligibility criteria review[7]	X	X													
Inpatient study unit[8]	X	X	X	X	(X)	(X)									
(Test oral risperidone)[9]	(X)														
Randomization[10]		X													
Inject IM study drug[11]		X						X			X				
Efficacy scales:[12]															
PANSS	X	X		X	X	X		X			X			X	
CGI-S	X	X		X	X	X		X			X			X	
CGI-I				X	X	X		X		X	X		X	X	
Socio-demographic information		X						X			X			X	
HRU data collection – center														X	
HRU data collection – patient								X			X			X	
Health outcome scales[13]		X						X			X			X	
PSP (clinician administered)															
SWN-20 (patient reported)		X						X			X			X	
Safety assessments:															
AEs[14]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant meds[15]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X				X	X								X	
Height	X														
Weight and body mass index	X	X			X	X		X			X			X	
Vital signs[16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG[17]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Injection site evaluation[18]		X			X	X		X		X	X		X	X	
Injection site pain VAS[18]		X			X	X		X		X	X		X	X	
Safety scales:[12]															
AIMS	X	X		X	X	X		X		X	X		X	X	
BARS	X	X		X	X	X		X		X	X		X	X	
SAS	X	X		X	X	X		X		X	X		X	X	
C-SSRS	X	X			X	X		X			X			X	

	Screening	DB BL	Treatment Period (DB Phase)												FU
DB Phase Visit Number:	**1**	**2**	**3**	**4**	**5**	**6**	**7[1]**	**8**	**9**	**10**	**11**	**12**	**13**	**14[2]**	**15[3]**
DB Phase Study Day[4]:	**-8 to -1[5]**	**1**	**3**	**4**	**8**	**15**	**22**	**29**	**31**	**43**	**57**	**59**	**71**	**85**	**99**
DB Phase Treatment Week:					**1**	**2**	**3**	**4**		**6**	**8**		**10**	**12**	
DB Phase Overall Dosing Sequence:		**1**						**2**			**3**				
Ophthalmological examination[19]	X													X	
Blood sample for:															
Hematology panel[20]	X	X			X	X		X			X			X	
Chemistry panel[21]	X	X			X	X		X			X			X	
Prolactin	X	X			X			X			X			X	
Pharmacokinetics[22]		X	X		X[23]	X[23]	X[23]	X	X		X	X		X	
Genotype[24]		X													
Serology panel[25]	X														
Pregnancy test (serum)	X														
Urine sample for:															
Pregnancy test[26]		X						X			X			X	
Urinalysis[27]	X	X			X	X		X			X			X	
Drug screen[28]	X	X			(X)	(X)		(X)		(X)	(X)		(X)	(X)	

AE = adverse event; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale;
BL = Baseline; CGI-I = Clinical Global Impression – Improvement; CGI-S = Clinical Global Impression – Severity;
C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; FU = Follow-up;
HRU = healthcare resource utilization; IM = intramuscular; ISM = in situ microparticle;
PANSS = Positive and Negative Syndrome Scale; PSP = Personal and Social Performance Scale;
SAS = Simpson-Angus Scale; SWN-20 = 20-item Subjective Well-Being Under Neuroleptics Treatment Scale;
VAS = visual analog scale; *(X)* = assessment to be done as applicable.

1. Study visit 7 (study day 22) is applicable to patients who participate in pharmacokinetic subgroup only.
2. Visit 14, which is scheduled to occur at the week 12 time point, is the designated end-of-treatment visit. However, if a patient withdraws or is withdrawn early from the study (ie, before the week 12 time point), an early termination visit should occur at which time all assessments for the end-of-treatment visit (as listed for visit 14) will be performed.
3. The follow-up visit will be conducted by telephone. The follow-up visit is to occur 14 (± 3) days after the end-of-treatment visit (ie, the week 12 time point or earlier in the case of an early termination). This visit is not applicable for patients who enter into the OLE phase.
4. The study day 4 (visit 4) must occur 3 days after study day 1. Allowable study visit time windows for treatment period study visits occurring after visit 4 (study day 4) are ± 1 day for study visit 5, ± 2 days for study visit 14, and ± 3 days for each of the other treatment period study visits (ie, study visits 6 through 13, inclusive).
5. If there is a valid reason for a given potential patient to extend the screening period duration beyond the designated 8 days, the investigator may contact the medical monitor to request an extension of up to 14 days; such an extension may be implemented only after medical monitor approval has been obtained.
6. Screening assessments will include the following: informed consent, demographic data, medical and psychiatric history, and a diagnostic interview (which will include completion of the MINI International Neuropsychiatric Interview for Schizophrenia and Psychotic Disorders studies, version 7.0.2).
7. Eligibility will be determined by the investigator, who will assess eligibility by confirming that that all inclusion criteria (see Study Protocol Section 4.1.1.1) have been met and that none of the exclusion criteria have been met (see Study Protocol Section 4.1.1.2).

8. Patients who, after completion of all scheduled assessments on the screening visit day, are considered provisionally eligible will be admitted directly to the inpatient study that day. Patients will subsequently remain on the inpatient study unit for the remainder of the screening period (ie, through study day -1, inclusive). Confirmed eligible patients will remain inpatient on study day 1. No patient should be discharged from the inpatient before study day 2, and it is anticipated that most patients will remain on the inpatient unit through study day 8, and that thereafter patients will be discharged from the inpatient unit when the investigator has assessed the patient and determines that he or she is appropriately clinically stable and otherwise ready for safe discharge. After study day 8, continuation of a patient on the inpatient unit from study day 9 through study day 15, inclusive, is an allowable option, as deemed clinically indicated. If the investigator believes that a given patient should remain inpatient beyond study day 15, the investigator should contact the medical monitor to discuss the proposed inpatient duration extension.
9. Patients who have never taken risperidone must take oral risperidone 2 mg/day for 3 days sometime during the screening period to ensure a lack of clinically significant hypersensitivity before the first IM dose of study drug is administered; this oral risperidone trial is not required for patients who have previously taken any formulation of risperidone.
10. A unique randomization number will be assigned via interactive voice or web response system accessed immediately after eligibility confirmation of a patient. The randomization process will determine (under double-blind conditions) for each individual patient the study drug regimen: an individual patient will receive either active Risperidone ISM or IM placebo.
11. All study drug doses will be administered by deep IM injection (deltoid muscle or gluteal muscle). The IM study drug doses will be prepared and administered by a designated unblinded individual at the study site (see Study Protocol Section 5.1.2). The IM study drug will contain either active Risperidone ISM (75 or 100 mg) or placebo (double blind).
12. See Protocol Appendix C – Rating Scale and Interview Descriptions.
13. Health economics and outcomes research evaluations. To be administered prior to medication dose.
14. Monitoring for AEs will occur throughout a patient's participation in this study, starting from the patient's signature of informed consent form; required details of identified AEs are to be recorded.
15. Information regarding concomitant medications, including new medications and changes to existing medications, will be elicited and recorded.
16. Vital signs will include blood pressure, pulse rate, respiratory rate, and body temperature. At each identified time point, vital signs will be measured after the patient has been resting in a supine position for at least 5 minutes. On days when patients receive an IM injection of study drug, vital signs are to be measured within 1 hour before and then again within 3 hours after the study drug injection; at each of these time points, orthostatic blood pressure and pulse rate will be measured (immediately after completion of supine vital sign measurements) after the patient has risen from the supine to the standing position and has remained standing for approximately 3 minutes (see Study Protocol Section 6.4.3).
17. A 12-lead ECG will be performed at identified visits; on days when patients receive an injection of IM study drug, an ECG will be performed both before and after dosing. Pre-dose ECG is to be completed within 1 hour prior to dosing. The post-dose ECG is to be completed within 3 hours post-dose. All scheduled ECGs are to be performed after the patient has rested quietly for at least 5 minutes in the supine position (see Study Protocol Section 6.4.4).
18. The patient will perform and record self-assessment of pain at the injection site using the injection site pain VAS (see Protocol Appendix D) approximately 1 hour after each study drug injection. The investigator will inspect the recent injection site and all injection sites where IM study drug has been injected on previous visits, also approximately 1 hour after each study drug injection.
19. Ophthalmological examination will include slit-lamp biomicroscopy examination (eyelids, conjunctiva, iris, crystalline lens, sclera, and cornea), best corrected visual acuity, visual field, and intraocular pressure (see Study Protocol Section 6.4.2).
20. The hematology panel includes the following tests: hematocrit, hemoglobin, red blood cell count, white blood cell count and differential count (absolute values for basophils, eosinophils, lymphocytes, monocytes, and neutrophils), and platelets.
21. The chemistry panel will include standard tests as well as hemoglobin A1c, thyroid-stimulating hormone, and a lipid panel.
22. Pharmacokinetic samples will be obtained for all patients in the study on days 1, 3, 29, 31, 57, 59, and 85 (visits 2, 3, 8, 9, 11,12, and 14, respectively). Pharmacokinetic samples will also be collected from patients who have a serious AE.
23. A subgroup of 75 study participants will have additional pharmacokinetic samples collected on days 8, 15, and 22 (visits 5, 6,and 7, respectively).
24. Genotype samples will be obtained only from those patients who sign a separate consent form for genotype sample collection. In these patients, a blood sample for genotype testing may be collected at any time point after randomization (see Study Protocol Section 6.7.5.)

25. A blood sample for a serology panel testing for hepatitis B surface antigen, antihepatitis C antibodies, and human immunodeficiency virus will be performed at screening only.
26. On study day 1 and at identified visits thereafter, onsite dipstick tests will be used for urine pregnancy tests. On each study drug dosing day, the urine pregnancy test must be performed and a negative result confirmed before the schedule dose of study drug for that day is administered.
27. The urinalysis includes the following tests: color, pH, specific gravity, ketones, protein, glucose, bilirubin, nitrite, urobilinogen, and occult blood. Microscopic examination only if urinalysis dipstick results are abnormal.
28. Urine drug screen is mandatory at screening and baseline and is optional thereafter. On these timepoints the sample will also be sent to the laboratory for analysis (see Study Protocol Section 6.4.5.4.3). The urine drug screen will include identification of the presence or absence of amphetamines, barbiturates, cocaine, methadone, opioids, and phencyclidine, as well as for tetrahydrocannabinol, alcohol, and benzodiazepines. In addition, onsite dipstick urine drug screen testing (with the exception of alcohol) may be optionally performed on the sample collected.

Table 2 Schedule of Assessments and Procedures: Optional Open-label Extension Phase for Rollover Patients

	OLE Baseline	OLE Treatment Period (Open-Label)													OLE Follow-up
OLE Phase Visit Number:	**1**[1]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**[2]	**15**[3]
OLE Phase Study Day[4]**:**	**1**[5]	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**393**
OLE Phase Treatment Week:		**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**
OLE Phase Dosing Sequence:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**		
Informed consent[6]	X														
Eligibility criteria review[7]	X														
Inject Risperidone ISM[8]	X	X	X	X	X	X	X	X	X	X	X	X	X		
Efficacy scales:															
PANSS	X[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	
CGI-S	X[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	
CGI-I[10]		X	X	X	X	X	X	X	X	X	X	X	X	X	
Socio-demographic information				X			X			X			X		
HRU data collection - center							X						X		
HRU data collection – patient				X			X			X			X		
Health outcome scales:[11]															
PSP (clinician administered)				X			X							X	
SWN-20 (patient reported)				X			X							X	
Safety assessments:															
AEs[12]	X[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant meds[13]	X[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight and body mass index	X[9]			X			X			X				X	
Vital signs[14]	X[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG[15]	X[9]	X		X		X		X			X			X	
Injection site evaluation[16]	X[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Injection site pain VAS[16]	X[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Safety scales:															
AIMS	X[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	
BARS	X[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	
SAS	X[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	
C-SSRS	X[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood sample for:															
Hematology panel[17]	X[9]			X			X			X				X	
Chemistry panel[18]	X[9]			X			X			X				X	
Prolactin	X[9]			X			X			X				X	
Pregnancy test[19] (serum)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	
Urine sample for:															
Pregnancy test[20]	X[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis[21]	X[9]			X			X			X				X	
Drug screen[22]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	

AE = adverse event; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; CGI-I = Clinical Global Impression – Improvement; CGI-S = Clinical Global Impression – Severity;

C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; HRU = healthcare resource utilization; IM = intramuscular; ISM = in situ microparticle; PANSS = Positive and Negative Syndrome Scale;
PSP = Personal and Social Performance Scale; SAS = Simpson-Angus Scale; SWN-20 = 20-item Subjective Well-Being Under Neuroleptics Treatment Scale; VAS = visual analog scale; *(X)* = assessment to be done as applicable

1. The OLE phase baseline visit may occur on the same day as visit 14 (+ 3-day window) of the main part of the study (i.e., the day on which the designated end-of-treatment visit for the double-blind treatment period of the main part of the study occurs), which is scheduled to occur at the week 12 time point of the main part of the study. However, in order to be eligible for transition into the OLE phase, a patient must first complete all assessments and procedures scheduled for the end-oftreatment visit for the double-blind treatment period of the main part of the study. Patients who withdraw or are withdrawn early from the main part of the study (i.e., before the scheduled week 12 time point) are not eligible for enrollment into the OLE phase.
2. Visit 14 is the designated end-of-treatment visit. However, if a patient withdraws or is withdrawn early from the study, an early termination visit should occur at which time all assessments for the end-of-treatment visit (as listed for visit 14) plus all the socio-demographic information and HRU (center and patient) data collection will be performed.
3. The follow-up visit will be conducted by telephone.
4. The allowable study visit time window for each of the OLE baseline visit is within 3 days after visit 14 of the main part of the study occurs; however, it is generally preferable to conduct the OLE baseline visit assessments and procedures later in the day (i.e., after completion of all assessments and procedures scheduled for the end-of-treatment visit for the double-blind treatment period of the main part of the study) on the same day on which the main study visit 14 occurs. The allowable study visit time window for each of the subsequent OLE visits is ± 3 days (i.e., OLE visits 2 through 15, inclusive).
5. Extension day 1 (the OLE baseline visit time point) is planned to be the same day and date as day 85 of the main part of the study, though a + 3-day window for OLE day 1, as compared with the day and date of the end-of- treatment visit for the main study day 85, is allowable.
6. A separate informed consent form for participation in the optional OLE phase of the study must be signed before any assessments or procedures for the OLE phase are performed for a given patient and before any dose of open-label Risperidone ISM is administered to that patient.
7. Eligibility will be determined by the investigator, who will assess eligibility by confirming that that all OLE phase inclusion criteria (see Study Protocol Section 4.1.2.1) have been met and that none of the OLE phase exclusion criteria have been met (see Study Protocol Section 4.1.2.2).
8. In the OLE phase of the study, all participating patients will receive active Risperidone ISM under open-label conditions. Patients who had been on active Risperidone ISM in the DB phase of the study will continue to receive Risperidone ISM at the same dose (i.e., 75 or 100 mg) in the OLE phase; patients who had been receiving placebo in the DB phase of the study will be randomly assigned to receive either 75 or 100 mg during the OLE phase. All Risperidone ISM doses will be administered by deep IM injection (deltoid muscle or gluteal muscle).
9. For identified assessments at the OLE baseline visit time point (on OLE day 1), results obtained as part of the main study visit 14 (i.e., the designated assessments performed for the end-of-treatment visit for the double-blind treatment period [week 12 time point] of the main part of the study) may be used as the OLE baseline values and do not need to be repeated for the OLE phase baseline visit time point if and only if the OLE baseline visit occurs on the same day and date as the main study visit 14/week 12/end-of-treatment visit. If the OLE baseline visit instead occurs on a day 1 to 3 days after the main study visit 14/week 12/end-of-treatment visit, all of the designated assessments must be performed separately on the day of the OLE baseline visit, and the main study visit 14/week 12/endof- treatment visit assessment results cannot be used as substitutes.
10. Although a CGI-I score in reference to baseline of the main part of the study will be reported as part of the assessments for the end-of-treatment visit for the double-blind treatment period (visit 14 of the main part of the study), no CGI-I score in reference to the OLE phase will be reported at the OLE baseline time point (which may be later on the same day as the visit 14 of the main part of the study). For all subsequent visits in the treatment period of the OLE phase (i.e., OLE phase visits 2 through 14, inclusive), the reference time point for the CGI-I scores will be that patient's overall status at the OLE baseline time point.
11. Health economics and outcomes research evaluations. To be administered prior to medication dose.
12. Monitoring for AEs will occur throughout a patient's participation in the OLE phase of the study, starting from the patient's signature of informed consent form; required details of identified AEs are to be recorded.
13. Information regarding concomitant medications, including new medications and changes to existing medications, will be elicited and recorded.

14. Vital signs will include blood pressure, pulse rate, respiratory rate, and body temperature. At each identified time point, vital signs will be measured after the patient has been resting in a supine position for at least 5 minutes. At each scheduled visit, vital signs are to be measured within 1 hour before and then again within 3 hours after the Risperidone ISM injection; at each of these time points, orthostatic blood pressure and pulse rate will be measured (immediately after completion of supine vital sign measurements) after the patient has risen from the supine to the standing position and has remained standing for approximately 3 minutes (see Study Protocol Section 6.4.3).
15. A 12-lead ECG will be performed at identified visits, both before and after dosing of risperidone ISM (with the exception of visit 14 when only 1 ECG is applicable). Each pre-dose ECG is to be completed within 1 hour before dosing. Each post-dose ECG is to be completed within 3 hours post-dose. All scheduled ECGs are to be performed after the patient has rested quietly for at least 5 minutes in the supine position (see Study Protocol Section 6.4.4).
16. The patient will perform and record self-assessment of pain at the injection using the injection site pain VAS (see Protocol Appendix D) approximately 1 hour after each study drug injection. The investigator will inspect the recent injection site and all injection sites where IM study drug has been injected on previous visits, also approximately 1 hour after each study drug injection.
17. The hematology panel includes the following tests: hematocrit, hemoglobin, red blood cell count, white blood cell count and differential count (absolute values for basophils, eosinophils, lymphocytes, monocytes, and neutrophils), and platelets.
18. The chemistry panel will include standard tests as well as hemoglobin A1c, thyroid-stimulating hormone, and a lipid panel.
19. A blood sample for a serum pregnancy test is not required, but the investigator may order a serum pregnancy test at any time according to the investigator's judgment.
20. On OLE phase day 1 and at each identified visit thereafter, onsite dipstick tests will be used for urine pregnancy tests. At each applicable visit, the urine pregnancy test must be performed and a negative result confirmed before the schedule dose of study drug for that day is administered.
21. The urinalysis includes the following tests: color, pH, specific gravity, ketones, protein, glucose, bilirubin, nitrite, urobilinogen, and occult blood. Microscopic examination only if urinalysis dipstick results are abnormal
22. Urine drug screen is optional at each study site visit. It will include identification of the presence or absence of amphetamines, barbiturates, cocaine, methadone, opioids, and phencyclidine, as well as for tetrahydrocannabinol, alcohol, and benzodiazepines.

Table 3 Schedule of Assessments and Procedures: Open-label Extension Phase for De Novo Patients

	Screening	OLE Baseline	OLE Treatment Period (Open-Label)													OLE Follow-up
OLE Visit Number:	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14[1]**	**15**
OLE Study Day[2]:	**-8 to -1[3]**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**393**
OLE Treatment Week:			**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**
OLE Dosing Sequence:		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**		
Informed consent[4]	X															
Screening assessment*	X															
Eligibility criteria review[2]	X	X														
Arm assignment[5]		X														
Inject Risperidone ISM[3]		X	X	X	X	X	X	X	X	X	X	X	X	X		
Efficacy scales:																
PANSS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CGI-S	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CGI-I			X	X	X	X	X	X	X	X	X	X	X	X	X	
Socio-demographic information		X			X			X			X			X		
HRU data collection – center		X						X						X		
HRU data collection – patient		X	X	X	X	X	X	X	X	X	X	X	X	X		
Health outcome scales:[6]																
PSP (clinician administered)		X			X			X							X	
SWN-20 (patient reported)		X			X			X							X	
Safety assessments:																
AEs[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant meds[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight and body mass index	X	X			X			X			X				X	
Vital signs[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG[10]	X	X	X		X		X		X			X			X	
Injection site evaluation[11]		X	X	X	X	X	X	X	X	X	X	X	X	X		
Injection site pain VAS[11]		X	X	X	X	X	X	X	X	X	X	X	X	X		
Safety scales:																
AIMS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
BARS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
SAS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood sample for:																
Hematology panel[12]	X	X			X			X			X				X	

	Screening	OLE Baseline	OLE Treatment Period (Open-Label)													OLE Follow -up
OLE Visit Number:	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14[1]**	**15**
OLE Study Day[2]:	**-8 to -1[3]**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**393**
OLE Treatment Week:			**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**
OLE Dosing Sequence:		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**		
Chemistry panel[13]	X	X			X			X			X				X	
Prolactin	X	X			X			X			X				X	
Serology panel**	X															
Pregnancy test[14] (serum)	*X*	*(X)*	*(X)*	*(X)*	*(X)*	*(X)*	*(X)*	*(X)*	*(X)*	*(X)*	*(X)*	*(X)*	*(X)*	*(X)*	*(X)*	
Urine sample for: Pregnancy test[15]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis[16]	X	X			X			X			X				X	
Drug screen[17]	*X*	*X*	*(X)*	*(X)*	*(X)*	*(X)*	*(X)*	*(X)*	*(X)*	*(X)*	*(X)*	*(X)*	*(X)*	*(X)*	*(X)*	

AE = adverse event; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; CGI I = Clinical Global Impression – Improvement; CGI-S = Clinical Global Impression – Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; HRU = healthcare resource utilization; IM = intramuscular; ISM = in situ microparticle; PANSS = Positive and Negative Syndrome Scale; PSP = Personal and Social Performance Scale; SAS = Simpson-Angus Scale; SWN-20 = 20-item Subjective Well-Being Under Neuroleptics Treatment Scale; VAS = visual analog scale; (X) = assessment to be done as applicable.

1. Visit 14 is the designated end-of-treatment visit. However, if a patient withdraws or is withdrawn early from the study, an early termination visit should occur at which time all assessments for the end-of-treatment visit (as listed for visit 14) plus all the socio-demographic information and HRU (center and patient) data collection will be performed.
2. The allowable study visit time window for baseline visit 1 is + 4-day window and for each of the subsequent OLE visits is ± 3 days (i.e., OLE visits 2 through 15, inclusive).
3. If there is a valid reason for a given potential patient to extend the screening period duration beyond the designated 8 days, the investigator may contact the medical monitor to request an extension of up to 14 days; such an extension may be implemented only after medical monitor approval has been obtained.
4. An informed consent form for participation in the OLE phase of the study must be signed before any assessments or procedures for the OLE phase are performed for a given patient and before any dose of open-label Risperidone ISM is administered to that patient. Eligibility will be determined by the investigator, who will assess eligibility by confirming that that all inclusion criteria have been met and that none of the exclusion criteria have been met.
5. In the OLE phase of the study, all participating patients will receive active Risperidone ISM under open-label conditions. Patients on 4 mg of oral risperidone will be assigned to 75 mg Risperidone ISM every 28 days. Patients on more than 4 mg to a maximum of 6 mg of oral risperidone will be assigned to 100 mg Risperidone ISM every 28 days. All Risperidone ISM doses will be administered by deep IM injection (deltoid muscle or gluteal muscle).
6. Health economics and outcomes research evaluations. To be administered prior to medication dose.
7. Monitoring for AEs will occur throughout a patient's participation in the extension segment of the study, starting from the patient's signature of informed consent form; required details of identified AEs are to be recorded.
8. Information regarding concomitant medications, including new medications and changes to existing medications, will be elicited and recorded.
9. Vital signs will include blood pressure, pulse rate, respiratory rate, and body temperature. At each identified time point, vital signs will be measured after the patient has been resting in a supine position for at least 5 minutes. At each scheduled visit, vital signs are to be measured within 1 hour before and then again within 3 hours after the Risperidone ISM injection; at each of these time points, orthostatic blood pressure and pulse rate will be measured (immediately after completion of supine vital sign measurements) after the patient has risen from the supine to the standing position and has remained standing for approximately 3 minutes (see Study Protocol Section 6.4.3).
10. A 12-lead ECG will be performed at identified visits, both before and after dosing of risperidone ISM (with the exception of visit 14 when only 1 ECG is applicable). Each pre-dose ECG is to be completed within 1 hour before dosing. Each post-dose ECG is to be completed within 3 hours post-dose. All scheduled ECGs are to be performed after the patient has rested quietly for at least 5 minutes in the supine position (see Study Protocol Section 6.4.4).

11. The patient will perform and record self-assessment of pain at the injection using the injection site pain VAS (see Study Protocol Appendix D) approximately 1 hour after each study drug injection. The investigator will inspect the recent injection site and all injection sites where IM study drug has been injected on previous visits, also approximately 1 hour after each study drug injection.
12. The hematology panel includes the following tests: hematocrit, hemoglobin, red blood cell count, white blood cell count and differential count (absolute values for basophils, eosinophils, lymphocytes, monocytes, and neutrophils), and platelets.
13. The chemistry panel will include standard tests as well as hemoglobin A1c, thyroid-stimulating hormone, and a lipid panel.
14. A blood sample for a serum pregnancy test is not required, but the investigator may order a serum pregnancy test at any time according to the investigator's judgment.
15. On OLE phase day 1 and at each identified visit thereafter, onsite dipstick tests will be used for urine pregnancy tests. At each applicable visit, the urine pregnancy test must be performed and a negative result confirmed before the schedule dose of study drug for that day is administered.
16. The urinalysis includes the following tests: color, pH, specific gravity, ketones, protein, glucose, bilirubin, nitrite, urobilinogen, and occult blood. Microscopic examination only if urinalysis dipstick results are abnormal.
17. Urine drug screen is optional at each study site visit properly identified. It will include identification of the presence or absence of amphetamines, barbiturates, cocaine, methadone, opioids, and phencyclidine, as well as for tetrahydrocannabinol, alcohol, and benzodiazepines.

* Screening assessments will include the following: informed consent, demographic data, medical and psychiatric history, and a diagnostic interview (which will include completion of the MINI International Neuropsychiatric Interview for Schizophrenia and Psychotic Disorders studies, version 7.0.2).
** A blood sample for a serology panel testing for hepatitis B surface antigen, antihepatitis C antibodies, and human immunodeficiency virus will be performed at screening only.

4. VARIABLES

4.1 PRIMARY EFFICACY VARIABLES

Positive and Negative Syndrome Scale (PANSS)[1] total score mean change from baseline to endpoint. In this context, endpoint is defined as study day 85 or the last post-baseline double-blind assessment.

4.2 SECONDARY EFFICACY VARIABLES

Key Secondary Efficacy Variable:

- Clinician Global Impression – Severity scale (CGI-S) score mean change from baseline to endpoint

Other Secondary Efficacy Variables:

- CGI-I score mean at endpoint
- Overall response rate at endpoint
    - Overall response is defined as either of the following:
        - PANSS total score ≥ 30% decrease (improvement of symptoms) from baseline to endpoint
        - Clinician Global Impression – Improvement scale (CGI-I) score of 2 (much improved) or 1 (very much improved) at endpoint
- PANSS response rate at endpoint
    - PANSS response is defined as the following:
        - PANSS total score ≥ 30% decrease (improvement of symptoms) from baseline at endpoint
- Time to reach PANSS response
- PANSS total score mean change from baseline at each post-baseline assessment time point
- PANSS subscale score mean change from baseline at endpoint and at each post-baseline assessment time point for each of the positive, negative and general psychopathology subscales
- Overall response rate at each post-baseline assessment time point
- Time to reach overall response
- PANSS response rate at each post-baseline assessment time point
- CGI-S score mean change from baseline at each post-baseline assessment time point
- CGI-I score mean at each post-baseline assessment time point

4.3 EFFICACY VARIABLES IN THE OLE PHASE OF THE STUDY

The following efficacy parameters will be summarized in the OLE phase of the study for the Open – Label Population (OLP – see section 5.13) by treatment group and overall.

Durability of effect evaluations:

- Positive and Negative Syndrome Scale (PANSS) total score
- Positive, negative, and general psychopathology subscale scores
- CGI-I score
- CGI-S score
- Overall response (as defined in Section 4.2)
- PANSS response (as defined in Section 4.2)
- Relapse, defined as
    - PANSS total score increase of ≥ 30% from baseline or
    - Re-hospitalization for psychotic symptoms or use of adjunctive antipsychotic medication after stabilization
- Remitters, defined as
    - The simultaneous attainment of a score of ≤ 3 for 6 months or more on 8 main items of the PANSS (delusions, conceptual disorganization, hallucinations, blunted affect, passive apathetic social withdrawal, lack of spontaneity and flow of conversations, mannerisms and posturing, unusual thought content)
- Time to discontinuation.

Other evaluations include HRU, PSP, SWN-20 and concomitant antipsychotic medication use.

All analyses of data from the OLE phase of the study will be of descriptive nature only.

4.4 HEALTH ECONOMICS AND OUTCOMES RESEARCH (HEOR) VARIABLES

Endpoint is defined as study day 85 or the last post-baseline double-blind assessment.

- HRU data will be collected both inside and outside the treating center with the aim to establish resource use patterns that are as complete as possible and to generate more accurate cost estimates. HRU categories include:
    - Medication
    - Inpatient hospital services
    - Emergency/A&E visits
    - Outpatient hospital services (i.e. specialist outpatient visits and day hospital visits)
    - Outpatient hospital care contacts (i.e. other allied healthcare professional contacts)

  - Community-based day services (patient-reported only)
  - Primary and community care contacts (patient-reported only)
  - Therapy
  - Criminal justice services (patient-reported only)

- HRU and cost variables include the following:
  - For each item, total quantity of resources used within and outside the participating center at endpoint. For each item, the mean number at endpoint and rate of use per 3 months will be calculated.
  - By resource use category (e.g. inpatient services, outpatient services) and total direct medical costs (reflecting resources used within and outside the participating center) at endpoint and average cost per 3 months will be calculated.
  - For all resource use categories combined, total medical costs at endpoint and average cost per 3 months will be calculated.
  - Indirect costs (days absent from work due to illness) at endpoint.
- Personal and Social Performance Scale (PSP) score mean change from baseline at each post-baseline assessment time point.
- PSP[2] domain score mean change from baseline at each post-baseline assessment time point.
- Subjective Well-being Under Neuroleptics – Short Form (SWN-20) total score mean change from baseline at each post-baseline assessment time point.
- SWN-20 subscale score mean change from baseline at each post-baseline assessment time point.

4.5 SAFETY VARIABLES

Safety variables include the following:

- Occurrence, nature, duration, intensity, and relationship to study drug of injection site reactions:
  - Injection site pain, assessed by patients using a visual analog scale (VAS) after each dose
  - Injection site evaluation of redness, swelling, and induration, evaluated by designated study site personnel after each injection
- Occurrence (incidence), nature, onset time, duration, intensity, action taken, and relationship to study drug of treatment-emergent AEs
- Occurrence, nature, time to onset, duration, seriousness criteria, relationship to study drug, and outcome of treatment-emergent SAEs
- Occurrence of extrapyramidal symptoms, as assessed using the SAS[3], BARS, and AIMS
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Physical examination, vital signs, weight, body mass index, clinical laboratory test results, and ECG findings

- Time to early termination

4.6 PHARMACOKINETIC VARIABLES

Pharmacokinetic variables include the following:

- Summary plasma concentrations of risperidone, its active metabolite (9 OH-risperidone), and the active moiety (ie, risperidone plus 9-OH-risperidone) by injection site (gluteal and deltoid) and by study drug dose level
- Trough and estimated C_{max} concentrations and accumulation index for steady state by injection site (gluteal and deltoid) and by study drug dose level
  - Estimated C_{max} for all doses (days 3, 31 and 59)
  - C_{min} for all doses (days 29, 57 and 85) including C_{ss} after last dosing interval (day 85)
  - C_{ss}/D after last dosing interval (day 85)
  - R_{Cmin} and R_{Cmax}
- Exploratory associations of pharmacokinetic results with efficacy results
- Non-compartmental PK parameters will be derived for a subset of patients:
  - Derived C_{max} for dose 1
  - Derived C_{max}/D for dose 1
  - t_{max} for dose 1
  - T_{last} for dose 1
  - C_{last} for dose 1
  - AUC_{last} for dose 1
  - AUC_{tau} for dose 1
  - AUC_{tau}/D for dose 1
  - C_{avg} for dose 1
  - $t_{1/2}$ for dose 1
  - AUC_{inf} for dose 1
  - CL/F for dose 1
  - V/F for dose 1

4.7 OTHER VARIABLES

Genotypes for cytochrome P450 enzymes, and/or genes that are potentially related to efficacy response and/or adverse effects. These will be used to provide subgroup analyses for PK and efficacy and will be of exploratory nature only for both.

5. ANALYSIS POPULATIONS

Protocol deviations will be captured throughout the study. Those that may significantly impact the completeness, accuracy, and/or reliability of the study data or may significantly affect a patient's rights, safety, or well-being will be classed as an important protocol deviation.

A blinded data review meeting (BDRM) will be held before database lock and unblinding of the DB phase to clarify any open questions or doubts and agree upon the exclusions from the PP and Pharmacokinetic (PK) populations and analyses as defined below. All patients satisfying the ITT and mITT population definitions will be included in the respective efficacy analyses. Attendees will include appropriate individuals from the sponsor and contract research organization. Additional details will be provided in a separate blinded data review meeting plan document. Reasons for excluding patients from the PP or PK population will be determined and documented before database lock, except mistakes regarding randomization procedures or based on non-quantifiable PK concentrations which are not available before unblinding. All decisions will be documented.

5.1 SCREENED POPULATION

The screened population will include all patients that signed the informed consent form. The screened population will include screen failures. Unless specified otherwise, this set will be used for patient listings and summaries of patient disposition.

5.2 SAFETY POPULATION

The safety population (SAF) will include all patients who receive at least 1 dose of study drug. Analyses performed on the safety population will be as treated. The safety population will be used for analyses of all safety endpoints and all patient listings unless specified otherwise.

5.3 MODIFIED SAFETY POPULATION

The modified safety population (mSAF) will consist of all patients in the SAF population for whom blinding was not compromised (see Section 3.6.3). Analyses performed on the mSAF population will be as treated. This population will be used for selected safety analyses.

5.4 RANDOMIZED POPULATION

The randomization population will consist of all patients that are randomized in the study. Analyses performed on the randomization population will be as randomized. This population will be used for

sensitivity analysis of the primary variable and for summaries/listings of patient disposition post-screening.

5.5 MODIFIED RANDOMIZED POPULATION

The modified randomized population will consist of all patients in the randomized population for whom blinding was not compromised (see Section 3.6.3). This population will be used for sensitivity analysis of the primary variable.

5.6 INTENT-TO-TREAT POPULATION

The intent-to-treat (ITT) population will consist of all randomized patients who receive at least 1 dose of study drug with a baseline measurement and ≥ 1 post-baseline evaluation of the PANSS. Analyses performed on the ITT population will be as randomized. The ITT population will be used for analyses of efficacy endpoints.

5.7 MODIFIED INTENT-TO-TREAT POPULATION

The modified intent-to-treat (mITT) population will consist of all patients in the ITT population for whom blinding was not compromised (see Section 3.6.3). Analyses performed on the mITT population will be as randomized. The mITT population will be used for analyses of efficacy endpoints, including health economics and outcomes research endpoints.

5.8 PER PROTOCOL POPULATION

The per-protocol (PP) population will consist of patients from the ITT population who receive ≥ 2 injections of study drug (active or placebo) during the DB phase and have no important protocol deviations that may impact the primary efficacy variable (PANSS).

Additionally, if a patient receives < 2 injections due to early treatment discontinuation with a reason related to an adverse event or lack of efficacy (i.e. insufficient clinical response, hospitalization for worsening, relapse, or exacerbation of Schizophrenia symptoms or other reason related to lack of efficacy or worsening, relapse, or exacerbation of Schizophrenia symptoms) then they will not be excluded from the PP population for this reason.

Additionally, if a patient has a protocol deviation which is deemed to have only affected the PANSS data following the third dose, then only the affected data will be excluded from the PP analysis and the patient will not be excluded from the PP population for this reason.

Analyses performed on the PP population will be as treated. The PP population will be used for supporting analyses of all efficacy endpoints.

Table 4 provides examples of important protocol deviation for which the patient would be excluded from the PP population. Patients to be excluded from the PP population will be determined prior to database lock.

Table 4 Examples of Important Protocol Deviations that would result in exclusion from PP population

Type of deviation	Description of Deviation
Failed inclusion/exclusion	Patient failed to meet at least 1 inclusion criterion, or met at least 1 exclusion criterion for the DB phase of the study.
Dosing error	Patient received incorrect study medication during the DB phase of the study
Other investigational drug	Patient took any experimental or investigational drug or agent after enrollment in the current study, other than investigational treatment for Study ROV-RISP-2016-01 during the DB phase of the study
Substance abuse	Patient took prohibited substances include amphetamines, barbiturates, cocaine, methadone, opioids, and phencyclidine during the DB phase of the study.
Prohibited Therapy	Patient took one of the following prohibited medications during participation in the DB phase of the study: • Cytochrome P450 3A4 Inducers and Inhibitors and 2D6 Inhibitors are prohibited during the course of the study and within 30 days before study day 1 • Antipsychotic medications, other than the study drugs administered according to this protocol, are not permitted during a patient's participation in the DB phase of this study. Existing antipsychotic medication must be discontinued during the screening period (while the patient is admitted to the inpatient study unit), if deemed clinically appropriate by investigator judgment. • Monoamine oxidase inhibitors • Lithium and mood stabilizers • Nicotine replacement therapy varenicline (Chantix®) is not permitted. • Prohibited non-medication therapy

5.9 MODIFIED PER PROTOCOL POPULATION

The modified per-protocol (mPP) population will consist of all patients in the PP population for whom blinding was not compromised (see Section 3.6.3). Analyses performed on the mPP population will be as treated. This population will be used for selected efficacy analyses.

5.10 PHARMACOKINETIC POPULATION

Out of 393 patients randomized into the study, approximately 262 will receive active treatment of Risperidone ISM 75 or 100 mg. Such patients will be considered for the Pharmacokinetic (PK)

population. Patients on placebo treatment will also have PK samples taken to prevent unblinding but will not have the plasma analyzed and will not be included in the PK population.

The PK population will include patients in the safety population who have at least 1 measured plasma concentration value. In cases where a protocol deviation is identified to potentially effect plasma concentration data, or if the sample was taken out of the required window (see section 9.2) the identified concentration values will be flagged and excluded from summarization as indicated, and in some cases may be excluded from the pharmacokinetic analysis overall; excluded concentration values will be identified before database lock based on a protocol deviations log and a listing of sample times verus dosing and confirmed with sponsor. Actual PK concentrations will not be reviewed by any blinded study personnel until after database lock of the DB phase.

This population will be used for the analysis of trough and estimated C_{max} concentrations over the DB phase.

Intense PK Subset

The PK population will consist of a further subset of patients defined as the intense PK subset.

A subset of 75 patients will be identified (in eCRF) to undergo additional PK sampling on days 8, 15, 22. This will include approximately 50 patients from the PK population (i.e. those who receive active treatment) though the exact number will not be known. The patients will be included in the intense PK subset.

This population will be used for the analysis of non-compartmental PK parameters over the DB phase.

5.11 PHARMACOGENOMIC POPULATION

The pharmacogenomic (PGx) population will consist of all patients in the SAF who have a blood sample taken for genotyping in the DB phase.

5.12 MODIFIED PHARMACOGENOMIC POPULATION

The modified pharmacogenomic (mPGx) population will consist of all patients in the PGx population for whom blinding was not compromised (see Section 3.6.3).

5.13 OPEN-LABEL POPULATION

The OLP will consist of all patients who received at least 1 dose of study drug in the OLE phase of the study and will be used for presentation of OLE analyses and listings. Analyses performed on the OLP will be as treated, and by DB phase treatment arm / de novo entry at time of the OLE phase (see section 6.1).

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1 GENERAL METHODS

Statistical methodology and analyses are in accordance with the principles outlined by the ICH E9 guidelines. All statistical analyses will be done using SAS statistical software version 9.3 or higher.

Tables, listings and figures (TLFs) will be produced in accordance with the principles outlined by the International Conference on Harmonization (ICH) E3 guidelines. For most summary statistics, data from the DB phase will be analyzed by the following treatment groups: Placebo, Risperidone ISM 75 mg, Risperidone ISM 100 mg, and All Risperidone ISM. The treatment groupings to be employed for OLE efficacy and safety summaries (excluding adverse events, see Section 11.2) will be as follows in respect to DB/OLE treatments:

1) Placebo / Risperidone ISM 75mg
2) Risperidone ISM 75mg / Risperidone ISM 75mg
3) De novo / Risperidone ISM 75mg
4) All / Risperidone ISM 75mg
5) Placebo / Risperidone ISM 100mg
6) Risperidone ISM 100mg / Risperidone ISM 100mg
7) De novo / Risperidone ISM 100mg
8) All / Risperidone ISM 100mg
9) All / Risperidone ISM

All available data for all patients from the relevant analysis population will be presented in the patient listings. Unless stated otherwise, listings will be sorted by treatment group and then patient number. Listings showing only data from the DB phase will be sorted by the DB treatment groups only, whilst all other listings will be sorted by the DB/OLE combination group (i.e. 1, 2, 3, 5, 6 and 7 from above, and Risperidone ISM 75mg / NA or Risperidone ISM 100mg / NA for patients not dosed in the OLE phase).

With regards to HRU, PSP, and SWN-20 endpoints, data will be analyzed for All Risperidone ISM doses pooled. The reason for this is (1) HEOR data are not primary endpoints in this study and the study is not powered to detect differences between risperidone doses in these endpoints; (2) there is no hypothesis stated in the protocol and study design around the higher dose of risperidone having a significant influence on HEOR endpoints compared to the lower dose; (3) pooling of the two risperidone arms will increase the sample size and therefore the precision around the estimates. This in turn will have an influence on finding statistically significant differences in HEOR endpoints compared to placebo, i.e. lower p-values; and finally, (4) often HEOR endpoints are even pooled between treatment arms (i.e. pooling of risperidone and placebo) for use in economic models when no difference is found between the arms. Economic modelling always differentiates the efficacy by treatment arm and treatment dose, but once a specific health state is reached (for example a health

state based on the PANSS), patients incur the same "utility value" and incur the same type of follow-up care (i.e. same costs). So, pooling between the two risperidone doses is acceptable.

In general, summary statistics (n, mean, standard deviation, median, minimum, and maximum values for continuous variables, and number and percentage of patients in each defined category for categorical variables) will be provided by treatment group for all variables. Unless otherwise specified, the denominator for percentages will be the number of patients in the treatment group. Source data for the summary tables and statistical analyses will be presented as patient data listings.

Scheduled visit assessment data will appear in summary tables and figures. Unscheduled visit assessment data will not be summarized. Both scheduled and unscheduled visit assessment data will appear in the patient listings.

In the case of multiple or repeat assessments at a scheduled visit, the latest value at the visit will be used for summarization and analyses unless otherwise specified.

No data imputation will be applied for missing values, unless otherwise specified (e.g. HEOR endpoints, see Section 8.2.4).

6.2 KEY DEFINITIONS

6.2.1 DB and OLE Phases

The terms DB and OLE will be used to represent the item of interest in the DB and OLE phases respectively.

6.2.2 Stage 1 and Stage 2

Those patients included in the interim analysis (see section 12) will constitute stage 1 patients with all subsequent patients being stage 2 patients for purpose of the primary and key secondary efficacy analyses.

6.2.3 First Dose Date

Two "first dose dates" will be required – one for the DB phase and one for the OLE phase. The first dose date for the DB phase will be the date that the first dose of randomized, double-blind study medication is administered, and the first dose date for the OLE phase will be the date of the first administration of Risperidone ISM in the OLE phase. Both first dose dates will be obtained from the CRF.

6.2.4 Double-Blind Study Day

Patients will be randomized and the first dose of randomized, double-blind study medication will be administered on Day 1. There is no study day 0. Study day for event dates prior to the date of the first dose will be determined as Study Day = Event Date –DB First Dose Date. Study day for event dates

on or after the date of first dose will be determined as Study Day = Event Date – DB First Dose Date + 1.

6.2.5 Open-Label Extension Study Day

The first dose of medication in the OLE phase will be administered on OLE day 1. OLE study day for event dates during the OLE phase will be determined as OLE Study Day = Event Date – OLE First Dose Date + 1.

6.2.6 Baseline Values

Unless otherwise specified, baseline values are the last non-missing measurement or assessment prior to the first dose of study medication in each phase. The DB baseline will be used for summaries during the DB phase and the OLE baseline will be used for summaries during the OLE phase.

For rollover patients, OLE baseline is planned to be the same day as day 85 of the DB phase of the study; in which case, DB Day 85 assessments will serve as the OLE baseline. A ± 3 days window for OLE day 1 is allowed. If the OLE baseline visit occurs later than the date of Visit 14 (see Section 3.8, Table 1) of the DB phase, all the designated assessments must be repeated.

6.2.7 Last Dose Date

Two "last dose dates" will be required – one for the DB phase and one for the OLE phase. The last dose date for the DB phase will be the date on which a patient takes the last dose of randomized, double-blind study medication. Last dose date for OLE phase will be the date on which a patient takes the last dose of the open-label study medication.

6.2.8 Duration of Exposure

Duration of DB treatment will be determined as DB Duration = Last DB Dose Date – First DB Dose Date + 28. Duration of OLE treatment will be determined as OLE Duration = Last OLE Dose Date – First OLE Dose Date + 28. Duration of Risperidone ISM treatment = Date of last administration of Risperidone ISM – Date of first administration of Risperidone ISM +1.

6.2.9 End of Study

Two 'end of study' dates will be required. The end of DB study is defined as the date of early termination or the date of completion of DB treatment through Day 85. The end of OLE phase is defined as the date of early termination or the date of completion of OLE treatment through OLE Day 365.

6.2.10 Endpoint

For the DB phase, endpoint is defined as study day 85 or the last post-baseline DB assessment. For the OLE phase, endpoint is defined as study day 365 or the last post-baseline OLE assessment.

6.3 MISSING DATA

No imputation of missing data will be used unless specified in the subsequent sections.

6.4 VISIT WINDOWS

The screening period is planned for Days -8 to -1, and the randomization is planned for Day 1, Visit 2. Visit 4 must occur 3 days immediately after study day 1. The allowable study visit time windows for DB phase study visits occurring after Visit 4 are as follows:

- ± 1 day for study visit 5,
- ± 2 days for study visit 14 and
- ± 3 days for each of the other DB phase study visits (i.e. study visits 6 through 13, inclusive)

The follow-up telephone visit is to occur 14 (± 3) days after the DB phase end-of-treatment visit (i.e. the week 12 time point, or earlier in the case of an early termination) for patients who do not enter the OLE phase.

For rollover patients, the OLE phase day 1 is planned to be the same day and date as Visit 14 of the DB phase though a +3-day window for OLE phase day 1, as compared with the Visit 14 of the DB phase of the study is allowable. The allowable study visit time window for each of the subsequent visits is ± 3 days.

For de novo patients, the allowable study visit time window for baseline visit 1 is + 4-day window and for each of the subsequent extension visits is ± 3 days (i.e., extension visits 2 through 15, inclusive).

Nominal visit will be used for all efficacy and visit-wise safety data. No visit mapping will be used. For patients withdrawing early, the end of study data (ET visit) will be mapped to the closest planned scheduled visit, based on the day of assessmement relative to first dose in the corresponding phase (DB or OLE) for summarization and analysis. If the closest planned scheduled visit was actually already performed then for efficacy analyses, the result will be mapped to the next scheduled visit (to enable inclusion of the endpoint result in the MMRM analyses), whilst for safety analyses the result will not be mapped to a scheduled visit (although this result will be used in end of treatment summaries).

6.5 POOLING OF CENTERS

The randomization used in this study is stratified by country. Patients will not be pooled based on center size, but rather by country, to ensure a sufficient number of patients per treatment arm per country in both ITT and PP populations for analysis stratified by country.

6.6 SUBGROUPS

The primary and key secondary efficacy analysis will be repeated to assess the treatment differences within country and baseline PANSS total score (≥ 95 versus < 95).

There will be an exploratory evaluation of genotypes for cytochrome P450 enzymes and/or genes considered potentially related to response and the correlation with primary efficacy, key secondary efficacy and PK outcomes (see Section 10).

7. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

7.1 PATIENT DISPOSITION AND WITHDRAWALS

A disposition table will presented by treatment group and overall, the number and/or percentage of patients who signed the informed consent and entered the study (i.e. were screened, screen failed, and randomized), completed the study with post-baseline efficacy assessments, and withdrew early from the study after randomization. The reasons for early withdrawal after randomization and the duration until completion or withdrawal from the double blind phase will be summarized. A separate table will display the number of patients who were not randomized with a summary of the reasons for non-randomization. Similar tables will be repeated for the OLE phase (including whether the patient was a rollover or de novo patient).

Assignment to the analysis populations (SAF, mSAF, ITT, mITT, PP, mPP, PK, and OLP [rollovers only]) will be summarized for the Randomized population. The assignment to the OLP in terms of rollover / de novo patients will be summarized. A listing will be provided for patient disposition including all patients that are either in the Randomized population or are a de novo patient.

A CONSORT figure showing all patient disposition during the study will be provided in the CSR.

All protocol deviations will be listed and important protocol deviations will be summarized by category and whether they lead to exclusion from the PP or PK population.

7.2 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and personal characteristics will be summarized by treatment group and overall. Sex, race, ethnicity, country, age (years), height (cm), weight (kg) and body mass index (BMI, kg/m^2). BMI (kg/m^2) is calculated as BMI = 100^2 x Weight (kg)/ [Height (cm) ^{2}].

Age will be calculated as the number of complete years between the date of birth and the informed consent date. For the OLE phase summary, age will be derived using the respective date of informed consent for that phase.

Demographic and baseline characteristics will be summarized for the SAF, ITT, mITT, PP, mPP, PK, Intense PK subset and OLP populations and listed. The details of diagnosis of schizophrenia will be summarised (years since diagnosis and weeks since Acute Exacerbation or relapse) and listed.

Socio-demographic data will be displayed as per Section 8.2.4.8.

7.3 MEDICAL, SURGICAL AND PSYCHIATRIC HISTORY

Medical, surgical and psychiatric history will be collected. Each condition will be recorded along with verbatim term, date of onset, date resolved, and a checkbox that indicates ongoing conditions. Medical, surgical and psychiatric history and concomitant diseases will be coded using the most up to date version of MedDRA at the time of data analysis.

Medical, surgical and psychiatric history and concomitant diseases will be summarized for the safety population by treatment group, system organ class, and MedDRA preferred term, overall and by country. The SOC and preferred terms will be displayed in alphabetical order and patients will be counted only once for each SOC and preferred term.

7.4 MEDICATION

Medications (off-treatment and concomitant) will be coded based on the most up to date version of World Health Organization (WHO) Drug dictionary and Anatomical Therapeutic Chemical (ATC) codes at the time of data analysis; the version number will be given in a footnote to the applicable displays.

Medication summaries based on ATC classes 1 and 3 and the preferred term will be produced for the Safety Population. Summaries will present the frequency and percentage of patients who used any medication in an ATC classes 1 and 3, or any medication based on a single preferred term, by treatment group. Medications will be sorted alphabetically and patients will be counted only once for each distinct medication class and preferred term.

For patient listings, medications will be reported based on ATC classes 1 and 3 and preferred term; multiple medications for an individual patient will be listed by start date and then by stop date, from earliest to latest medications.

Concomitant medications and medications taken whilst off-treatment will be presented together in a single listing and flagged to identify the classification. Off-treatment medications will be presented separately from concomitant medications in summary tables.

7.4.1 Off-Treatment Medication

A medication will be classed as off-treatment if either 1) it has a confirmed stop date prior or equal to the first dose date of study drug in the study or 2) a start date equal to or after the day of treatment discontinuation in the study. In the case of a partial stop date, missing day will be considered as the last day of the month, missing month will be considered as December, and missing month and day will be considered as December 31st. In the case of a partial start date, missing day will be considered as the first day of the month, missing month will be considered as January, and missing month and day will be considered as January 1st.

7.4.2 Concomitant Medication

A medication will be classed as concomitant during the DB/OLE phase if 1) it had a confirmed stop date after the first dose date of study drug in the DB/OLE phase or a missing stop date and 2) the start date was prior to the day of treatment discontinuation in the DB/OLE phase

In the case of a partial stop date, missing day will be considered as the last day of the month, missing month will be considered as December, and missing month and day will be considered as December

31st. In the case of a partial start date, missing day will be considered as the first day of the month, missing month will be considered as January, and missing month and day will be considered as January 1st.

8. EFFICACY

Efficacy variables from the double-blind part of the study will be summarized by treatment group for the mITT, ITT and PP populations using descriptive statistics. The analyses of primary and key secondary endpoints will also be provided for the mPP population. Although any confirmatory findings related to efficacy must be substantiated in both the mITT and ITT populations (see sections 8.1.1 and 8.2.1), the mITT will be used as the primary population to describe efficacy results in the CSR.

Efficacy variables from the OLE phase of the study will be summarized similarly for the OLP, as applicable, for descriptive purposes.

All efficacy assessments will be listed.

With regard to efficacy variables that refer to endpoint, to account for post-baseline endpoints occurring before study day 85 (i.e. at the time when the last post-baseline double-blind assessment was performed) a mixed model for repeated measurements (MMRM) using an unstructured covariance matrix approach will be used as the primary method and the estimates from the model at day 85 will be used for the primary efficacy analysis. It is assumed that a majority of the missing values will be the following

- "Missing Completely At Random", i.e., probability of an observation being missing does not depend on observed or unobserved measurements. or
- "Missing At Random", i.e. probability of an observation being missing depends only on observed measurements.

In such situations, likelihood-base methods like MMRM are appropriate (EMA, 2010[4]), and already were use previously as per Kane et al (2014)[5] and Nasser et al (2016)[6].

8.1 PRIMARY EFFICACY VARIABLES AND ANALYSIS

The primary efficacy variable is PANSS total score mean change from baseline to endpoint. The PANSS will be performed at screening, DB phase study days 1 (pre-dose), 4, 8, 15, 29, 57, and 85 and OLE phase study days 1, 29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, and 365.

The PANSS is a well-known and validated rating scale used in numerous drug evaluation trials. This 30-item scale provides a total score (sum of the scores of all 30 items) and scores for 3 subscales. The subscales include the positive subscale (7 items), negative subscale (7 items), and general psychopathology subscale (16 items). The severity of each of the 30 items of the PANSS is rated on a scale of 1 (absent) to 7 (extreme). Higher scores represent greater symptom severity. The maximum total score equals 210 and the total minimum score equals 30, when all items are completed.

If a patient has a PANSS assessment recorded, but any of the 30 items are missing, the last nonmissing score for the respective item from previous assessments will be carried forward. If the total or subscale

score has > 30% of the items missing at a particular visit, the respective total or subscale score at the visit will not be calculated and will be treated as missing data in the analysis.

8.1.1 Primary Efficacy Analyses

The primary efficacy analysis is designed to show superiority of active treatment versus placebo in the PANSS total score mean change from baseline to endpoint.

Two hypotheses will be tested:

a. $H_{0,A}$: $\mu_{\text{Risperidone 75 mg}} - \mu_{\text{placebo}} = 0$ vs $H_{1,A}$: $\mu_{\text{Risperidone 75 mg}} - \mu_{\text{placebo}} \neq 0$
b. $H_{0,B}$: $\mu_{\text{Risperidone 100 mg}} - \mu_{\text{placebo}} = 0$ vs $H_{0,B}$: $\mu_{\text{Risperidone 100 mg}} - \mu_{\text{placebo}} \neq 0$

with μ = PANSS total score mean change from baseline for the identified treatment group.

An MMRM will be fitted for patients in the mITT population with country where enrolled, visit, treatment, and treatment-by visit interaction as fixed effects and baseline PANSS total score as a covariate. This model will be applied separately for patients in stage 1 and stage 2 of the study (see Section 12) as well as overall patients. The treatment differences from the model at study day 85 will be evaluated to test the hypotheses above, maintaining a 2-sided type 1 error rate of 5%. Model results from each stage and overall will be presented.

In order to maintain the type 1 error rate for the primary efficacy analysis, each hypothesis will be tested using a weighted test statistic in accordance with Cui, Hung, Wang[7] (CHW) methodology which comprises of combining the z-statistics from the respective study day 85 treatment comparison at each stage. The weighting will be equal for each stage and pre-defined as sqrt (0.5) such that:

$$Z_{CHW} = \sqrt{0.5}\, z_1 + \sqrt{0.5}\, z_2$$

where z_n is the cumulative normal density function for the two-sided p-value divided by 2 (i.e. one-sided p-value) from the study day 85 treatment comparison at stage n, n=1 and n=2.

The nominal 2-sided p-value for each hypothesis will be calculated for the respective weighted CHW statistic using the cumulative normal distribution.

Point estimates and 95% CI will be obtained using methodology suggested by Hung and Lawrence[8]:

Point estimate:

$$\hat{\delta} = \frac{t_1 \hat{\delta}^{(1)} + \sqrt{1 - t_1}\,\sqrt{t^* - t_1}\,\hat{\delta}^{(2)}}{t_1 + \sqrt{1 - t_1}\,\sqrt{t^* - t_1}}$$

where

$t_1 = 0.5$

t^* = (Re-estimated sample size per group for analysis)/124

$\hat{\delta}^{(1)}$ = Least square mean difference from stage 1 analysis

$\hat{\delta}^{(2)}$ = Least square mean difference from stage 2 analysis

95% CI:

$$\hat{\delta} \pm \left(\frac{\delta}{z_{CHW}} * 1.96 \right)$$

To account for multiplicity of testing and to keep the type 1 error rate at 5%, the Hommel's closed testing correction procedure[9] as implemented in SAS software (PROC MULTTEST) will be used to provide adjusted p-values to assess for superiority of either dose.

For the MMRM, an unstructured covariance structure shared across treatment groups will be used to model the within-patient errors and the Kenward-Rogers[10] correction to degrees of freedom will be applied. Model assumptions will be checked.

In case of difficulties with initially fitting this unstructured (UN) covariance matrix, the following approaches will be undertaken to improve chances of convergence with the UN structure: 1) Covariance matrix estimated from empty model with no covariance will feed into the full model as the initial values; 2) Fisher scoring will be used to begin the iterative fitting (by specifying a SCORING=5 option in the PROC MIXED statement); 3) initial values for the covariance parameters will be specified based on covariance estimates from a simpler covariance structure. For the last approach, the simpler covariance structure will be compound symmetry (TYPE=CS option in the REPEATED statement) and the corresponding estimates of the covariance parameters will be captured in the ODS Output dataset CovParms from PROC MIXED. These estimates will then be passed as the initial values for the estimation of the UN structure using the PARMS statement in PROC MIXED. In the event the convergence cannot be attained with these approaches, the following alternative structures will be attempted in the specified order: heterogeneous Toeplitz structure (TOEPH), heterogeneous autoregressive(1) (ARH(1)), heterogeneous compound symmetry (CSH), No Diagonal Factor Analytic (FA0(q), with q equal to the number of time points), Toeplitz structure (TOEP), autoregressive(1) (AR(1)), and compound symmetry (CS). If either ARH(1) or AR(1) structure is used, a random patient intercept will also be included in the model (using RANDOM INT statement in PROC MIXED).

Sample SAS code for MMRM analysis:

```
proc mixed data=all3 covtest;
title1 "MMRM with PANSS"
    class country trt visit subjid ;
    model panss = country trt visit trt*visit baseline / s chisq ddfm=kr;
    repeated visit / type=un subject=subjid r;
    lsmeans trt*visit / cl diff;
run;
```

Sample SAS code to compute Hommel's adjusted p-value:

```
proc multtest inpvalues=xx hommel;
run;
```

The results from the MMRM using all patients will be presented with least squares means and differences between active and placebo least squares means (with 95% confidence intervals (CI) and p-value) for each timepoint. The Day 85 contrast will include the CHW adjusted p-values for each comparison (and Lawrence-Hung estimate for the treatment differences with 95% CIs) and the Hommel adjusted p-values for each comparison (to assess superiority).

The results from the MMRM for each stage will also be presented separately with least squares means and differences between active and placebo least squares means (with 95% confidence intervals (CI) and p-value) for each timepoint.

Descriptive statistics of the absolute values and change from baseline (n, mean, median, standard deviation, minimum, and maximum) will be reported by treatment group and visit.

All analyses described above will be repeated for the ITT population. However, to account for extra 43 patients included in Stage 1, the CHW statistic will be derived as:

$Z_{CHW} = \sqrt{0.55}\, z_1 + \sqrt{0.45}\, z_2$

and in the Hung and Lawrence calculations:

$t_1 = 0.55$

$t^* =$ (Re-estimated sample size per group for mITT analysis + 14)/138

Confirmatory findings from the Hommel adjusted CHW analyses will only remain so for a particular dose if $p<0.05$ in both the mITT and ITT analyses.

All analyses described above for the ITT and mITT population will also be repeated for the PP and mPP population respectively.

The descriptive statistics summary will be presented for each country and by the baseline PANSS total score (< 95 v ≥ 95) for both the mITT and ITT population. In addition, the MMRM (without CHW or

Hommel adjustments) will be repeated in the mITT and ITT population incorporating all main effects and interactions between treatment, visit and the subgroup (i.e. country or baseline PANSS total score [< 95 v ≥ 95]) in order to explore the treatment differences within subgroups. The model assessing treatment differences within the baseline PANSS total score (< 95 v ≥ 95) will have the continuous baseline PANSS covariate removed.

The LS means and standard errors of the change from baseline over time from the MMRM including all patients will be presented graphically both overall (from the primary analysis) and by the baseline PANSS total score (< 95 v ≥ 95) (from the interaction models).

8.1.2 Sensitivity Analyses

Sensitivity analyses will include:

- Analysis of PANSS total score mean change from baseline to endpoint, in the mITT population using observed cases (OC) only (i.e. when the last post-baseline double-blind assessment was performed). For this analysis, change from baseline at endpoint will be analyzed using an Analysis of Covariance (ANCOVA) model with country where enrolled and treatment as fixed effects and baseline PANSS total score as a covariate.

- Analysis of the PANSS total score mean change from baseline to day 85, in the modified randomized population using an ANCOVA model with country where enrolled and treatment as fixed effects and baseline PANSS total score as a covariate. Missing data from patients with the last post-baseline double-blind assessment performed prior to day 85 (or no post-baseline double-blind assessment) will be imputed using a standard multiple imputation (MI) analysis. Imputed data for the PANSS total score in each step will always be rounded to the nearest integer corresponding to a possible PANSS total score (i.e. 30 to 210). Data will be imputed in the framework of a pattern mixture model (PMM) for missing visits, following a general three-step approach as outlined below (Ratitch B and O'Kelly M, 2011[11]):

    1. Non-monotone (intermediate visits) missing data will be imputed first using the Monte Carlo Markov Chain method under the Missing at Random (MAR) assumption in all treatment arms (using the MCMC statement in PROC MI). Multiple chains option (CHAIN=MULTIPLE option in the MCMC statement of PROC MI) will be used. For the non-monotone imputation of the PANSS missing data, a multivariate normal model will be used including variables for the PANSS at baseline and all post-baseline visits within each treatment group and the randomization stratification variables (country where enrolled, as well as PANSS total score [ie, ≥ 95 versus < 95] at baseline/randomization). One hundred imputations will be generated.

    2. After the non-monotone missing data have been imputed, the remaining monotone missing data will be imputed under the Missing Not at Random (MNAR) assumption that

patients who withdraw from the Risperidone ISM treatment groups (75 mg and 100 mg) will have correlations with future (post-withdrawal) visits similar to patients in the placebo group, adjusted for baseline covariates and observed outcomes prior to withdrawal. Monotone missing data of withdrawn patients from the placebo group will be imputed under the MAR assumption and will follow the pattern of placebo completers. In other words, monotone missing values of the PANSS will be imputed for all patients who withdrew from the study (regardless of treatment group) using an imputation model at each time point estimated from patients with available data in the placebo group only. A regression imputation model for the PANSS at each time point will include the stratification factors at randomization and PANSS at all previous time points, including baseline. The input dataset will include all placebo patients and only those patients from Risperidone ISM groups that have values at that time point missing. Imputations will be performed using a sequence of regression-based imputations (using PROC MI statement MONOTONE REG) for each post-baseline time point suggested by Ratitch B and O'Kelly M, 2011[11].

3. Imputed data in each of the multiple imputed datasets will be analyzed using an ANCOVA model. The model will include country where enrolled and treatment as fixed effects and baseline PANSS score as a covariate. The results from all imputed datasets will be combined using the Rubin's combination rule (PROC MIANALYZE).

The sensitivity analyses described above will employ the same CHW and Hommel adjustments and results will be presented both by stage (Stage 1 and 2) and with both stages combined. Each analysis will also be repeated for the ITT (randomized for MI analysis), PP and mPP population. The weighting for the CHW and Hung and Lawrence calculations for the modified populations will be the same as the mITT, whilst the non-modified poulations will be the same as the ITT population.

8.2 SECONDARY EFFICACY VARIABLES AND ANALYSES

8.2.1 Key Secondary Efficacy Variable Analyses

The key secondary variable is mean change from baseline to endpoint in CGI-S during the DB phase. The CGI-S will be performed at Screening, DB phase study days 1 (pre-dose), 4, 8, 15, 29, 57, 85 and OLE phase study days 1, 29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, and 365.

The CGI-S severity of illness scale requires the clinician to rate the severity of illness on a 7-point ordinal scale (0=Not assessed, 1= Normal, not at all ill; 2=Borderline mentally ill; 3=Mildly ill; 4=Moderately ill; 5=Markedly ill; 6=Severely ill; 7=Among the most extremely ill patients).

Similar analyses and summary as for the primary efficacy variable will be performed.

As per the primary efficacy analysis, the CGI-S will be analyzed taking the interim assessment into account by using CHW methodology and the multiplicity of testing into account using Hommel's closed-testing correction procedure as implemented in SAS (PROC MULTTEST).

CGI-S will be analyzed using hierarchical ordering such that if, and only if, the primary efficacy analysis shows the superiority of both doses of Risperidone ISM treatment versus the IM placebo treatment at day 85 in both the mITT and ITT, then the confirmatory testing will be performed sequentially on the mITT and ITT population with regard to the key secondary efficacy variable at day 85. In similar fashion to the primary efficacy variable, only the testing of these hypotheses for the key secondary efficacy variable from the MMRM (with CHW and Hommel adjustments) will provide confirmatory evidence of efficacy (if proven in both mITT and ITT populations) with all other analyses providing exploratory or supporting evidence only.

OC and MI will be conducted as sensitivity analyses and all analyses will be repeated for the ITT, PP and mPP populations in a similar fashion to the primary efficacy variable.

Descriptive statistics of the absolute values and change from baseline (n, mean, median, standard deviation, minimum, and maximum) and the distribution across categories will be reported by treatment group and visit.

8.2.2 Other Secondary Efficacy Variables Analyses

Other secondary efficacy variables will be summarized and tested in the mITT, ITT and PP populations. The nominal p-values without adjustment for interim assessment or multiple comparisons will be used and they will only be considered as exploratory analysis.

8.2.2.1 CGI-I score at each post-baseline assessment and endpoint

The CGI-I will be performed at DB phase study days 4, 8, 15, 29, 43, 57, 71, 85 and OLE phase study days 29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, and 365.

The CGI-I global improvement scale requires the clinician to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the intervention. The clinician rates the degree of change observed on a 7-point ordinal scale (1= Very much improved; 2= Much improved; 3= Minimally improved; 4= No change; 5= Minimally worse; 6= Much worse; or 7= Very much worse). This CGI degree of change scores will be dichotomized into 2 categories, Improved and Not Improved, with scores of 1 (very much improved) and 2 (much improved) in the Improved category and scores of 3 (minimally improved) to 7 (very much worse) in the Not Improved category.

Descriptive statistics of the absolute values and change from baseline (n, mean, median, standard deviation, minimum, and maximum) and the distribution across categories will be reported by treatment group and visit.

Analysis will be conducted using the MMRM model in Section 8.1.1 as a template. The fixed effects will include country where enrolled, visit, treatment, and treatment-by-visit interaction and baseline CGI-S score will be used as a covariate.

8.2.2.2 Overall and PANSS Response Rate

PANSS response is defined as PANSS total score ≥ 30% decrease (improvement of symptoms) from baseline.

The overall response is defined as satisfying either criterion below:

- Response on PANSS or
- CGI-I score of 2 (much improved) or 1 (very much improved)

The response rate at each visit will be presented twice using differing approaches for a patient that has withdrawn early from treatment: 1) will be considered as a non-responder at all time points following early withdrawal, 2) will be excluded from the analysis at all relevant time points following early withdrawal.

The overall and PANSS response will be presented by treatment for each visit and at endpoint using frequency of responses, rate in percentage, along with the exact (Clopper-Pearson) 95% confidence limits. Pairwise comparisons of each dose level of Risperidone ISM to placebo will be conducted using a Mantel-Haenzel test stratified by country where enrolled and baseline PANSS total score [≥ 95 or < 95]. The 95% stratified Newcombe CIs will also be presented.

8.2.2.3 Time to Reach Overall or PANSS Response

Time to reach overall or PANSS response will be presented by cumulative frequencies and percentages of patients achieving a response up to each assessment for both DB and OLE phases separately. The median and 95% confidence limits for median will be estimated using Kaplan-Meier method. Kaplan-Meier plots will be presented by treatment group. If the patient does not achieve a response, the time of response will be censored at the date of treatment discontinuation in the DB phase. A log-rank test between the treatment groups will be performed, adjusted on the stratification factors at randomization.

8.2.2.4 PANSS subscale score mean change from baseline at endpoint and at each post-baseline assessment time point

The PANSS subscales include the positive subscale (7 items; range 7 - 49), negative subscale (7 items; range 7 - 49), and general psychopathology subscale (16 items; range 16 -112). Descriptive statistics of the subscale scores and change from baseline (n, mean, median, standard deviation, minimum, and maximum) will be presented.

Analysis will be conducted using the MMRM model in Section 8.1.1 as a template. The fixed effect will include country where enrolled, visit, treatment, and treatment-by-visit interaction and appropriate baseline score will be used as a covariate.

8.2.3 Efficacy Variables Analyses in the Open-Label Extension Phase of the Study

Efficacy scales PANSS, CGI-S are collected at baseline and all efficacy scales (PANSS, CGI-S, and CGI-I) are collected at all post-baseline time point during the OLE phase. All efficacy analyses in the OLE phase of the study will use the OLP.

Efficacy variables PANSS, PANSS subscale scores, CGI-I, CGI-S, Overall response, PANSS response in the OLE phase of the study will be summarized and listed similarly as in the DB phase of the study, although none of the formal testing between treatment groups will be conducted.

Relapse in the OLE phase is defined as either a PANSS total score increase of $\geq$ 30% from baseline, re-hospitalization for psychotic symptoms or use of adjunctive antipsychotic medication after stabilization.

Remitters in the OLE phase are defined as the simultaneous attainment of a score of $\leq$ 3 for 6 months or more on 8 main items of the PANSS (delusions, conceptual disorganization, hallucinations, blunted affect, passive apathetic social withdrawal, lack of spontaneity and flow of conversations, mannerisms and posturing, unusual thought content).

Relapse and remitters will be analyzed two ways: by rate during the OLE phase and by time to relapse or remittance. Similar summary statistics will be provided as for overall response and time to reach overall response (including Kaplan Meier methods) in DB phase.

The frequency of responses and percentage rate for patients with the following during the OLE phasewill be presented:

- PANSS total score increase of $\geq$ 30% from baseline

- Re-hospitalization for psychotic symptoms

- Use of adjunctive antipsychotic medication after stabilization

Time to discontinuation will be summarized by n, mean, standard deviation, median, and 95% confidence limits for median estimated from Kaplan-Meier method. They will be displayed graphically by treatment group.

8.2.4 Health Economics and Outcomes Research (HEOR) Variables Analyses

8.2.4.1 General comments

All HEOR data will be used and analyzed by ITT – no patients or measurements will be discarded from the analysis. The analysis will include all data from the start of the study until the end of the study.

All analyses are exploratory in nature and not hypothesis driven, therefore no adjustment will be made to the threshold of significant value for multiple testing.

Additionally, the analyses will document missing data for select outcomes as a proportion of all responses collected, and the analysis method will take incomplete data (i.e., partially completed instruments) into account.

8.2.4.2 Exploration of missing data

It is expected there will be some missing data due to missed visits, non-completion of HRU and SWN-20 and PSP forms, loss to follow-up and due to the patient being in an exacerbation and unable to complete the instruments. Missing data can impact on the validity of the analysis, especially if

(1) the missingness is related to the occurrence of an exacerbation (= not missing at random): in this case missingness will lead to an under-estimation of resources and also to a missed 'drop' in the SWN-20 and PSP instruments which will affect the estimated impact of an exacerbation in terms of costs and quality of life.

AND

(2) the frequency of exacerbations is treatment-related: when comparing total costs and quality of life between treatments the estimated difference between treatments will be smaller than the true difference, with fewer statistically significant results found between arms.

The number of patients in the study at each visit will be summarized. Similarly, completeness of HRU and SWN-20 and PSP data will be summarized by visit, as the number of patients with responses at each visit. We will also estimate the total follow-up time of each patient in the study: overall and by treatment phase.

Furthermore, the relationship between the missingness in resource use and SWN-20 and PSP instruments and the occurrence of a relapse will be investigated, in order to assess whether the data are missing at random or not. For this particular assessment, the focus will be on fully missed visits only (i.e. all of the HRU items reported by the patient or all of the SWN-20 or PSP items for a visit are missing). This will be done with a logistic regression, with missingness as a dependent variable, and exacerbation as an independent variable, as well as treatment arm, age, gender, education, living situation and employment indicators.

Regarding missing data in resource utilization: When analyzing cost data particular attention needs to be given to the fact that total costs are composed of many individual cost items, each with their variation and with a different pattern of missing data. When analyzing the sum of these costs it is important to acknowledge that not imputing missing items in this total cost will result in under-estimation. Therefore, the amount and the pattern of missing data for each item need to be investigated and an imputation procedure needs to be selected that will result in correct estimation of the missing values. This relates only to the case where a few items for an assessment time point are missing; in case all HRU items reported by the patient are missing for a particular time point then no imputation will take place for that time point.

Regarding SWN-20 and PSP instruments: The impact on analysis of a missing item in a questionnaire (incompletion) will be different from missing a visit (missed assessment). A missing observation at the item level still allows the other items and domain scores to be documented. A missing observation at the patient level implies that none of the questions and domains was scored. No imputation is planned for SWN-20 and PSP instruments. Changes from baseline and distribution of patients across levels of the SWN-20 and the PSP will be calculated based on available data only.

8.2.4.3 Healthcare Resource Utilization (HRU)

Healthcare Resource Utilization data will be collected in two ways: site-based reporting and patient-(or proxy/caregiver)-based reporting.

Study site staff will retrospectively record any HRU that occurred within the clinical trial center into the applicable forms of the eCRF. Detailed resource use will be collected in the categories detailed in Section 4.4. During the DB phase, clinician-reported data will be recorded once at the end of that phase (at 12 weeks). During the OLE phase, data will be recorded every six months for a total of two measurement points (at weeks 36 and 60 counted from the start of the study).

Study site staff will administer a survey to patients (or their proxy/caregiver) to report any HRU that occurred outside the clinical trial center. The patient survey will be administered at the clinical trial site by designated study site staff. Detailed resource use will be collected in the categories detailed in Section 4.4. During the DB phase, patient (or proxy/caregiver)-reported data will be administered every month for a total of three measurement points (weeks 4, 8 and 12). During the OLE phase, the survey will be administered every three months for a total of four measurement points (weeks 12, 24, 36 and 48 counted from the start of the study).

The number of days missed from work will be recorded at the end of the DB phase and at the end of the OLE phase. The data will be summarized by treatment group.

Clinician-reported HRU (within the participating site) and patient (or proxy/caregiver)-reported HRU (outside the center) will be cross-validated and combined for analysis.

The patients are hospitalized at the start of the study for at least 2 days after which they can be discharged at the discretion of the treating specialist. It may be possible that patients on Risperidone ISM have a different length of hospitalization than placebo patients; therefore, this resource use, although protocol-driven, will also be included in the analysis and added to the total health care utilization.

Depending on the amount of missing data, missing values for time points where some categories of resources are missing may be imputed. When all data are missing for a time point; however, no imputation will take place. Reliable imputation is only possible, if a distinction was made during the data collection phase between a missing value (i.e., we do not know whether the patients used a category of resources) and a zero value (i.e., we know the patient did not use this category). Otherwise, the resources will be over-estimated due to the imputation process. It is therefore important at data collection to distinguish, to the extent possible, between "0" and "missing".

For each resource category and each time period, the non-zero missing data will be imputed. Data will be imputed using the Fully Conditional Specification procedure. This imputation method for missing data uses a regression approach to provide an estimate for the missing value on a specific item of resources. The missing value for each category of resources will be predicted using the patient's health state (based on PANSS) and his use of other categories of medical resources use data, plus a random term.

Data will be analyzed by the following treatment groups: Placebo and all Risperidone ISM. The steps and objectives of the HRU analysis are the following:

1. Describe the types and amounts of resources used by patients per study Phase (DB phase versus OLE phase) expressed as a rate per 3 months
2. Report indirect costs (days absent from work due to illness) per study Phase
3. Test for differences in resource utilization between treatment groups
    - For each resource use item separately
4. Calculate total costs for each Phase of the study (DB phase and OLE phase) and generate confidence intervals
    - For each resource use item separately
    - By resource use category (e.g. inpatient hospital services, outpatient services, drugs)
    - For all resources combined (i.e. total medical costs)
5. Test for differences in total costs between treatment arms

8.2.4.4 Statistical analysis of healthcare resource utilization

Combining resource use:

Results for each HRU variable will be summarized by treatment group for the ITT populations using descriptive statistics, including 95% confidence interval.

Clinician-reported and patient (or proxy/caregiver-) reported HRU will be combined for analysis. For each individual item of resources, total quantity used will be calculated as the sum of resources both within and outside the participating center during the DB and OLE phases, respectively. Patient's exposure time will be calculated and a "rate of use per 3 months" will be computed for all types of resources, per patient. This rate will then be averaged across all patients per treatment arm. A general linear model with the rate as dependent variable, treatment as independent variable and a log link and gamma distribution will be estimated to test for differences between treatment arms.

The reason for choosing a rate as the "unit of measurement" for reporting resource utilization and testing for differences between groups is that (1) resources are measured at different intervals during the study: the physician is reporting HRU at 3 months whereas patients are reporting HRU on a monthly basis in the DB phase. In the OLE phase, the physician is reporting HRU every 6 months and the patient every 3 months. The resources reported for the longer units of time cannot reliably be distributed over the shorter periods. (2) In addition, some patients will have missed visits and therefore the observation time will be different for each patient. The analysis needs to take into account that longer observation times inevitably imply accumulation of more resources, and not taking observation time into account would bias against treatments that keep patients longer in the study (longer follow-up time and fewer drop-outs). Reporting resources in 3-monthly rates remediates both problems: it rescales all resources to the same time period and it divides total resources by the total patient-years of follow-up which takes the length of observation into account.

Calculating total costs:

For the comparison of Total Costs, patient-level all resource counts will be multiplied with their unit cost, summed up and then divided by the patient's exposure time to obtain a total cost per 3 months. The average cost per 3 months by treatment arm will be calculated and non-parametric confidence intervals around the mean cost per treatment arm will be generated using bootstrapping. Bootstrapping is the suitable method for generating non-symmetrical confidence intervals around total costs, this variable taking only non-negative values and being highly skewed to the right.

Statistical comparison between groups will be done with a general linear model with a log link and gamma distribution, where "total cost per patient per 3 months" is the dependent variable, and treatment allocation the independent variable.

Analysis by country:

Analyses by country may be considered in light of potential country clustering due to differences in disease management patterns. Country will be included as a covariate in the regression analysis when testing for differences in the rate of resource use.

8.2.4.5 Social Functioning

Social functioning will be assessed by the clinician-administered Personal and Social Performance Scale (PSP). The PSP will be evaluated at time points: at the DB phase study days 1, 29, 57, 85 and OLE phase study days 1, 85, 365.

The PSP score (Morosini 2000[2]) is a 100-point single-item rating scale, subdivided into 10 equal intervals. The ratings are based mainly on the assessment of patient's functioning in four main areas: 1) socially useful activities; 2) personal and social relationships; 3) self-care; and 4) disturbing and aggressive behaviors. Operational criteria to rate the levels of disabilities have been defined for the above-mentioned areas.

The steps for analysis of the PSP are as follows:

1. Describe the distribution of patients at baseline across the items and domains of the PSP, provide baseline summary scores
2. Describe changes from baseline in PSP at each post-baseline assessment time point: describe the distribution of patients across the levels of PSP, as well as the summary scores over time
3. Test for difference between treatment arms in the total scores of the PSP at each time point jointly

Analyses of the PSP scale will be according to instrument-specific guidance, as specified by the licensing agencies. Domain scores and total scores will be calculated for each assessment point. For the PSP the scoring is as follows:

- Family and social functioning: Absent, Mild, Manifest, Marked, Severe, Very Severe
- Self-care: Absent, Mild, Manifest, Marked, Severe, Very Severe
- Work and socially useful activities: Absent, Mild, Manifest, Marked, Severe, Very Severe
- Disturbing and aggressive behaviours: Absent, Mild, Manifest, Marked, Severe, Very Severe
- Overall score: ranges from 0 to 100, where scores from 0-30 reflect a poorly functioning patient requiring intensive support or supervision, scores from 31-70 reflect varying degrees of disability, and scores from 71-100 reflect only mild difficulties

8.2.4.6 Health-related Quality of Life (HRQL)

Health-related Quality of Life will be assessed by the patient-completed Subjective Well-being Under Neuroleptics – Short Form (SWN-20). Within the SWN-20 the patient is asked to rate well-being items that have been identified as related to antipsychotic treatment on a 6-point scale ranging from

"Not at all" to "Very much." The SWN-20 is scored on a scale ranging from 20 to 120, with higher scores indicating better HRQL.

The SWN-20 contains five 4-item sub-scales: mental functioning, self-control, emotional regulation, physical functioning, and social integration. Each sub-scale score ranges from 4 to 24, with higher scores indicating better HRQL. The SWN-20 will be performed at scheduled time points throughout the treatment period as indicated in Table 1.

The baseline administration of the SWN-20 should occur prior to the administration of the medication dose on Study Day 1 of the DB phase.

The steps for analysis of the SWN-20 are as follows:

1. Describe the distribution of patients at baseline across the items and domains of the SWN-20, provide baseline summary scores
2. Describe changes from baseline in SWN-20 at each post-baseline assessment time point: describe the distribution of patients across the levels of SWN-20, as well as the summary scores over time
3. Test for difference between treatment arms in the total scores of the SWN-20 at each time point jointly

Analyses of the SWN-20 data will be according to instrument-specific guidance, as specified by the licensing agencies. Domain scores and total scores will be calculated for each assessment point. For the SWN-20 the domain scores are calculated as follows: Rating categories scores for items with a ` + ': not at all (1), a little (2), somewhat (3), noticeable (4), much (5), very much (6); for items with a `-' scores have to be reversed, i.e. 6 =1, 5 =2, 4 =3, 3 =4, 2 =5, 1 =6.

Subscales: combining the following items:

- Mental functioning: 3 (+), 7 (+), 11 (-), 17 (-)
- Self-control: 15 (+), 19 (+), 1 (-), 12 (-)
- Emotional regulation: 18 (+), 20 (+), 4 (-), 10 (-)
- Physical functioning: 2 (+), 5 (+), 9 (-), 16 (-)
- Social integration: 8 (+), 13 (+), 6 (-), 14 (-)
- Total score: sum of all items

8.2.4.7 Statistical Analysis of the SWN-20 and the PSP

PSP and SWN-20 scores will be summarized by treatment group for the ITT population and using descriptive statistics for data obtained during the DB phase of the study. PSP and SWN-20 scores from the OLE phase of the study will be summarized similarly for the OLP, as applicable, for descriptive purposes.

At baseline:

At first, univariable analyses will be presented, cross-tabulating the SWN-20 and PSP summary scores at baseline by quantiles of the PANSS and CGI-S values at baseline. In addition, these summary scores will be presented by patient age, gender, country, by history of exacerbations (any other covariates that might be of interest).

Frequency tables will show the proportion of patients falling in each response category for each question of the SWN-20 and the PSP. The denominator for calculating the frequencies will be the number of patients with non-missing data for each variable. Statistical difference between the treatment groups of the summary scores at baseline will be estimated with a general linear model (GLM) with the summary score as dependent and treatment allocation as independent variable. The GLM will have an identity or log link and a normal distribution and gamma distribution will be fitted. The best-fitting model parameterization will be determined by the AICC statistic.

Evolution over time:

In a second step, the values of these summary scores will be summarized (means) by treatment group over time. The evolution of the summary scores will be plotted over time by treatment arm (including 95% confidence intervals). Furthermore, changes from baseline to each assessment point of the summary scores will be tabulated as well.

P-values for differences between treatment groups over time will be estimated with a repeated measurement model which takes the inter-patient as well as the intra-patient correlation into account. A repeated measurement regression framework takes into the account the repeated measures structure of the data and, if appropriate, additionally allows regression coefficients to vary across specified subgroups. We will initially try to fit a random effects model, which is designed to estimate a population level intercept and hence provides distilled estimates of the coefficient. The model will initially be fitted with 3 random effects (intercept, slope and slope^2). We will gradually test for the inclusion of the three random effects in the model using a Likelihood Ratio test. The model will also specify the correlation matrix of the repeated measurements by estimating the most efficient VARCOV matrix. The correlation of the measurements over time will be modelled through the specification of that variance-covariance matrix. It is assumed that the residual errors are homoscedastic and uncorrelated. We will start with an unstructured matrix and test for more reduced version of the variance-covariance matrix such as Toeplitz, compound symmetry and the independent structure.

Furthermore, the analysis will test for different distributions and link functions that would fit the data, such as:

- Normal model: Link = ID, distribution = normal
- Lognormal model: Link = log, distribution = normal
- Gamma model: Link = log, distribution = gamma

These different specifications will be tested against each other using the Likelihood Ratio test.

Depending on convergence of the model and on goodness-of-fit, specific random effects may be retained and a more structured version of the variance-covariance matrix possibly with a non-normal distribution will be considered. These type of models tend to have problems with convergence due to the unbalanced nature of the data and non-convergence will lead to more simplified models whilst still retaining the repeated measurement nature of the data.

8.2.4.8 Socio-demographic Variables

The objectives of the socio-demographic analysis are as follows:

1. By treatment group and per study phase (DB phase versus OLE phase), document the distribution of patients for education, living arrangement, housing and employment at baseline
2. By treatment group and per study phase (DB phase versus OLE phase), document changes from baseline in education, living arrangement, housing and employment at the end of the DB phase and the OLE phase.

All data will be summarized for each visit as follows: n, mean, standard deviation, median, min, max, and normal approximation 95% confidence limits.

9. ANALYSIS OF PHARMACOKINETICS

9.1 PLASMA PK ENDPOINT

The pharmacokinetic endpoints for all patients on Risperidone ISM 75 mg or 100 mg (PK population) will be the following:

- Summary plasma concentrations of risperidone, its active metabolite (9 OH-risperidone), and the active moiety (ie, risperidone plus 9-OH-risperidone) by injection site (gluteal and deltoid) and by study drug dose level
- Trough concentrations and accumulation index for steady state by injection site (gluteal and deltoid) and by study drug dose level
  - C_{min} for all doses (days 29, 57 and 85 including C_{ss} after last dosing interval (day 85)
  - C_{ss}/D after last dosing interval
  - R_{Cmin} and R_{Cmax}
- Estimated C_{max} by injection site (gluteal and deltoid) and by study drug dose level – measured on days 3, 31 and 59

Additionally, data from the patients in the intense PK subset with additional PK sampling points on days 8, 15, 22 will be used to derive the following non-compartmental parameters by injection site (gluteal and deltoid) and by study drug dose level:

- Derived C_{max} for dose 1
- Derived C_{max}/D for dose 1
- t_{max} for dose 1
- T_{last} for dose 1
- C_{last} for dose 1
- AUC_{last} for dose 1
- AUC_{tau} for dose 1
- AUC_{tau}/D for dose 1
- C_{avg} for dose 1
- $t_{1/2}$ for dose 1
- AUC_{inf} for dose 1
- CL/F for dose 1
- V/F for dose 1

In addition, there will be exploratory associations of pharmacokinetic results with efficacy results.

9.2 COLLECTION SCHEDULE AND ALLOWED WINDOWS FOR SAMPLING OF CMAX, TROUGH LEVELS AND DENSE PHARMACOKINETICS FOR RISPERIDONE AND 9-OH-RISPERIDONE

Venous blood samples with corresponding sampling times are shown relative to dosing days and dose number in the DB phase in Table 5 below.

Table 5 Venous blood samples with corresponding times post-dose

DB Phase Day	**1**	**3**	**8**	**15**	**22**	**29**	**31**	**57**	**59**	**85**
Dose number	1					2		3		
Day relative to dosing	1	3	8	15	22	29	3	29	3	29
Inject IM Study drug	+					+		+		
All patients	+	+				+	+	+	+	+
Subset of patients with intense PK sampling	+	+	+	+	+	+	+	+	+	+

The samples at days 29, 57 and 85 are planned to be used to represent the trough concentrations. In order for a sample to be evaluable as a trough concentration corresponding to a particular dose, the day relative to dosing must lie between days 26 and 32 inclusive. If multiple samples lie within this window then the closest sample to day 29 (later sample if two are same proximity either side) will be used.

The samples at days 3, 31 and 59 (2 days after dosing) are planned to be used to represent the estimated C_{max}. In order for a sample to be evaluable as a C_{max} concentration corresponding to a particular dose, the day relative to dosing must lie between days 2 and 4 inclusive. If multiple samples lie within this window then the closest sample to day 3 (later sample if two are same proximity either side) will be used. This may be different to the derived C_{max} for dose 1 for those patients undertaking the intense sampling regime.

For the intense PK samples, all samples collected relative to Dose 1 between days 1 and 32 will be evaluable for PK parameter derivations, apart from C_{max} which must lie between days 2 and 4 inclusive similar to the sparse PK C_{max} to be evaluable. For summaries over time, the sample must be collected within +/- 2 days of the respective planned day 8, 15, 22 time point (later sample if two are same proximity either side), with the same window as above for the days 3 and 29 time points.

Visit 14 concentrations from patients that discontinue early from treatment will be included in the above mapping considerations but only patients identified in the Intense PK subset from the eCRF will be included in Intense PK analyses.

9.3 HANDLING OF MISSING DATA

Missing concentration data for all patients who are administered scheduled study treatments will be considered as non-informative missing and will not be imputed. No concentration estimates will be provided for missing sample values.

For the derivation of AUC and related parameters, the following rules will apply:

- The sampling time of pre-dose samples relative to dosing will be treated as zero;
- BLQ values for pre-dose 1 concentration and before the 1st quantifiable concentration will be set to 0
- All below limit of quantification (BLQ) values after the 1st quantifiable point will be set to missing.
- If the actual time of sampling is missing, the planned time may be used.
- Samples taken outside the sampling windows may be excluded from by-time point summary statistics; this will be determined prior to unblinding.

For the plasma concentration summary and for the individual concentration versus time curves and mean concentration versus time graphs, the following rules will apply:

- Plasma concentration BLQ values in all samples will be set to zero except when they are flanked by quantifiable concentrations.
- BLQ values when they are flanked by quantifiable concentration will be set to missing.
- No further imputation will be applied to any missing values.

9.4 LISTING AND PRESENTATION OF INDIVIDUAL PK DATA

The actual sampling time of PK blood sample collection will be listed for all patients in the PK population and will include the deviation in time from the protocol scheduled time, if applicable.

Individual patient plasma risperidone, 9-OH-risperdone and active moiety (risperidone + 9-OH risperidone) concentration data will be listed by patient, time point and treatment for patients in the PK population.

Individual plasma trough (day 29 following dosing) and estimated C_{max} (day 3 following dosing) concentration profiles vs dose number will be presented for each patient in the PK population with the

three analytes combined in the same figure on linear and log-linear scales. Profiles will be grouped according to injection site and dose level.

Individual plasma concentration profiles vs actual time for dose 1 (days 3, 8, 15, 22 and 29) will be presented for each patient in the intense PK subset with three analytes combined in the same figure on linear and log-linear scales. Profiles will be grouped according to injection site and dose level.

9.5 SUMMARY OF PK CONCENTRATIONS IN PLASMA

Summaries of plasma concentrations over time for dose 1 (days 3, 8, 15, 22 and 29) will be presented by dose level (75 mg and 100 mg) and injection site (deltoid, gluteal and overall) for patients in the intense PK sampling subset. Imputation rules for summary statistics of PK concentrations are described in Section 9.3.

Summarization of PK parameters from trough and estimated C_{max} concentration values are described in the Section 9.6 of the SAP

Samples taken outside the allowed time windows for scheduled time points may be excluded from summarization. This will be determined prior to database lock.

The following conventions will be used for the presentation of the descriptive statistics of plasma concentrations for patients in the intense PK sampling subset:

Variable	Summarized with:
Plasma concentration at each nominal time point	n, number BLQ, arithmetic mean, SD, coefficient of variance (CV) %, minimum, median, and maximum

PK Reporting Precision:

Statistics	Degree of Precision
Minimum, Maximum	3 significant digits or as needed based on actual measured values (for example PK concentrations)
Mean (arithmetic and geometric), Median	4 significant digits or as needed based on actual measured values (for example PK concentrations)
Standard deviation	5 significant digits or as needed based on actual measured values (for example PK concentrations)
CV% and Geometric CV%	1 decimal point or as needed based on actual measured values (for example PK concentrations)

Mean ± SD plasma concentrations for patients in the intense PK sampling subset will be presented by time point relative to start of the 1st dose up to day 29. Curves for the three analytes will be combined on the same figure, separately for injection site (deltoid, gluteal and overall) and dose level (75 mg and 100 mg).

9.6 PK PARAMETERS DERIVATION

For all patients in the PK population, the following parameters will be derived for risperidone, 9-OH risperidone and active moiety (risperodone + 9-OH risperidone):

PK population	
Estimated C_{max}	Maximum observed plasma concentration for all doses measured on day 3 relative to each dose
Estimated C_{max}/D	Maximum observed plasma concentration dose normalized for all doses measured on day 3 relative to each dose
R_{Cmin} and R_{Cmax}	Accumulation ratios based on trough concentrations and estimated C_{max}
C_{min}	Trough concentration after each dose (1, 2, 3), same as C_{ss} for dose 3
C_{min}/D	Trough concentration after each dose (1, 2, 3), same as C_{ss} for dose 3, dose normalized
C_{ss}	Trough concentration at steady state (after last dosing interval)
C_{ss}/D	Trough concentration at steady state (after last dosing interval), dose normalized

For patients in the intense PK sampling subset (as data allow), the following parameters will be derived for risperidone, 9-OH risperidone and active moiety (risperodone + 9-OH risperidone):

Intense PK subset	
Derived C_{max}	Maximum observed plasma concentration for dose 1only
Derived C_{max}/D	Maximum observed plasma concentration dose normalized for dose 1only

t_{max}	Time of maximum observed concentration during dosing interval for dose 1
AUC_{tau}	Area under the plasma concentration-time curve from time zero to the end of dosing interval for dose 1 only
AUC_{tau}/D	Area under the plasma concentration-time curve from time zero to the end of dosing interval for dose 1, dose normalized
C_{avg}	AUC_{tau} divided by tau for dose 1
$t_{1/2}$	Terminal elimination half-life
AUC_{inf}	Area under the plasma concentration-time curve from time zero extrapolated to infinity
λ_z	Elimination constant
CL/F	Apparent terminal plasma clearance
V/F	Apparent volume of distribution

The PK parameters will be estimated as follows:

- AUCs will be calculated using the linear/log trapezoidal rule.
- The apparent C_{max} and the corresponding t_{max} will be read directly from the concentration-time plot (observed data, not predicted data by a program);

Elimination parameters ($t_{1/2}$, AUC_{inf}, CL/F, V/F) may be estimated if data allow with all applicable PK acceptance criteria included to judge the reliability of the resulting parameters:

- number of points excluding C_{max} to calculate $\lambda_z \geq 3$
- R^2 adjusted >0.85
- interval for λ_z calculation > than $t_{1/2}$
- AUC_{extrap} >25%.

Unreliable elimination PK parameters, if calculated, will be flagged and will be excluded from summarization and statistical analyses. Secondary PK parameters R2adj, number of points to calculate λ_z, upper and lower limits of interval for the calculation of λ_z, AUC_{extrap}% will be listed but not summarized.

9.7 PK PARAMETERS SUMMARIZATION

Pharmacokinetic parameters and plasma concentration data will be summarized by injection site (deltoid, gluteal and overall) and dose level (75 mg and 100 mg) using the following descriptive statistics:

Variable	Summarized with:
AUC_{tau}, AUC_{tau}/D, $AUC_{inf,}$ C_{max} (estimated and derived), C_{max}/D (estimated and derived), C_{avg}, C_{ss}, C_{ss}/D, R_{Cmin}, R_{Cmax}, C_{min}, C_{min}/D	n, arithmetic mean, SD, CV%, minimum, median, maximum, geometric mean, and geometric CV%
$t_{1/2}$, $\lambda_{Z,}$ CL/F, V/F	n, arithmetic mean, SD, CV%, minimum, median, and maximum
t_{max} (actual time)	n, minimum,Q1, median, Q3, and maximum

Note: CV% = SD/mean in %.

Dose normalized parameters for dose 1 will additionally be summarized just by injection site and overall.

Mean ± SD plasma trough (day 29 relative to dosing) and estimated C_{max} (day 3 relative to dosing) concentrations vs dose number will be presented for all patients in the PK population combining the curves for the three analytes within the same figure, on linear and log-linear scales separately for each injection site (deltoid and gluteal) and dose level (75 mg and 100 mg).

Box-plots will be presented showing dose normalized PK parameters with a bar for each injection site (deltoid and gluteal) and analyte (risperidone, 9-OH risperidone and active moiety) on the same plot (i.e. 6 bars).

9.8 PLANNED STATISTICAL MODELS FOR PK PARAMETERS AND CONCENTRATIONS

The PK parameters of risperidone, 9-OH risperidone and active moiety related to steady state (estimated C_{max}/D from dose 1 and C_{ss}/D for all active patients, derived C_{max}/D and AUC_{tau}/D for intense sampling PK subset) will be compared between injection sites and dose levels using an ANOVA model with injection site (deltoid or gluteal), dose level (75 mg or 100 mg) and injection site by dose level interaction as fixed effects, based on existing guidance on bioequivalence from EMA[13] and FDA [Food and Drug Administration (FDA)][14]:

The following hypotheses will be tested:

H_{01}: $\mu_T/\mu_R \leq 80\%$ vs. H_{A1}: $\mu_T/\mu_R > 80\%$ and H_{02}: $\mu_T/\mu_R \geq 125\%$ vs. H_{A2}: $\mu_T/\mu_R < 125\%$where T and R are the two groups being compared.

The following 6 contrasts involving the interaction between injection site (deltoid, gluteal) and dose level (75 mg, 100 mg) will be evaluated:

1) Deltoid v Gluteal overall
2) Deltoid v Gluteal within each dose level
3) 75 mg v 100 mg overall
4) 75 mg v 100 mg within each injection site

```
PROC MIXED DATA =data_set_name;
CLASS injection_site dose_level;
MODEL PK_Parameter = injection_site|dose_level/ddfm=kr;
LSMEANS injection_site / CL diff alpha=0.1;
LSMEANS dose_level / CL diff alpha=0.1;
LSMEANS injection_site*dose_level / CL diff alpha=0.1;
RUN;
```

9.9 PK / PD EXPLORATORY ANALYSIS

The relationship between the time matched trough concentrations for risperidone, 9-OH risperidone and active moiety (risperidone + 9-OH risperidone) and the change from baseline in the Total PANSS score at DB phase study days 29, 57 and 85 will be assessed. A scatter plot with regression line will be presented for each visit and analyte (9 plots). The Pearson and Spearman correlation (r coefficient with 95% CI and p-value) will be presented, along with the ratio between the Pearson and Spearman correlation coefficients.

The relationship between C_{max} concentrations (sparse sampling) and the change from baseline in the Total PANSS score in the DB phase for the same doses on different study days will be assessed using the same methods as follows:

- C_{max} for dose 1 on day 3 relative to dosing will be compared to the available PANSS scores for the dose 1 on days 4, 8, 15 and 29
- C_{max} for dose 2 on day 3 relative to dosing will be compared to the available PANSS score for the dose 2 on day 57 (pre-dose 3)
- C_{max} for dose 3 on day 3 relative to dosing will be compared to the available PANSS score for the dose 3 on day 85 (end of dosing)

Total 18 plots will be produced for 6 comparison points and 3 analytes.

10. EXPLORATORY ANALYSIS OF PHARMACOGENOMICS

10.1 CYP2D6 ACTIVITY SCORE

The results of pharmacogenetics testing will be listed for PGx population. Any exploratory analyses of efficacy and PK in subsequent sections will be based on patients in both the corresponding analysis populations and the PGx population.

The results will include listing of alleles of CYP2D6 per subject with corresponding activity score derived based on the following Table 6 using the methods stated by Gaedigk et al (2008)[15] to produce an activity score (AS) for the patient. The AS will be categorized into one of four phenotypic classess as follows: AS = 0 (Poor Metabolizer), AS of 0.5 to 1 (Intermediate metabolizer), AS of 1.5 to 2 (Extensive metabolizer) and AS > 2 (Ultra Metabolizer).

Table 6 Activity Score Values Assigned to CYP2D6

Value assigned to allele	Alleles[a] AS-Model A
0	**3, *4, *4xN, *5, *6, *7, *16, *36, *40, *42, *56B*
0.5	**9, *10, *17, *29, *41, *45, *46*
1	**1, *2, *35, *43, *45xN*
2	**1xN, *2xN, *35xN*

AS, activity score. The AS of a genotype is the sum of the values assigned to each allele (*e.g., CYP2D6*1/*1* and *CYP2D6*2/*5* genotypes have AS of 2 and 1, respectively). [a]Only observed alleles are listed.

In case of alleles which were not characterized to their activity score the investigation of the latest literature data will be performed to relate the allele to activity of CYP2D6. The results will be recorded in a separate document with related references and described in the Clinical Study Report (CSR). The results will be also included in the listing with the explanation in the footnote.

The AS and phenotypic classification will be summarized by treatment group, injection site and overall for SAF, mSAF, ITT, mITT, PP, mPP, PK and OP populations as well as the Intense PK subset.

10.2 EFFICACY SUBGROUP ANALYSES

The primary and key secondary endpoint will be summarized within each phenotypic classification defined above. In addition, an MMRM model will be fitted as per the primary and key secondary analyses (see Section 8.1) with the addition of fixed effects for the CYP2D6 phenotype class and a term for each of the treatment by visit by CYP2D6 phenotype class interaction levels. The LS mean of each treatment and treatment contrasts of interest (Risperidone ISM v placebo) will be presented within each CYP2D6 phenotype class.

For the primary and key secondary endpoint, the relevant change from baseline at endpoint within each phenotypic classification will be presented using box-plots.

10.3 PK SUBGROUP ANALYSES

Correlation between CYP2D6 and bioavailability of oral risperidone and risperidone ISM may be explored graphically on box plots for molar ratio of risperidone to 9-OH risperidone. Bioavailability PK parameters for different activity groups will be summarized separately and compared if sufficient number of data will be available for different activity scores. Effect of CYP2D6 metabolism on bioavailability of oral risperidone and risperidone ISM will be compared using descriptive statistics as described in Novalbos et al 2010[16].

The dose normalized PK parameters of risperidone, 9-OH risperidone and active moiety related to steady state (estimated C_{max}/D for dose 1 and C_{ss}/D for all active patients, AUC_{tau}/D and derived C_{max}/D for the intense sampling PK subset) will be compared between phenotype classifications. An ANOVA model as described in section 9.8 will be fitted but with additional fixed effects for phenotype class and the additional interaction terms between phenotype class, injection site and dose level .

The following contrasts will be explored within each of the 9 combinations of injection site (deltoid, gluteal and overall) and dose level (75 mg, 100 mg and overall):

- Poor metabolizers (AS=0) vs extensive metabolizers (AS=1.5-2)
- Intermediate metabolizers (AS=0.5-1) vs extensive metabolizers (AS=1.5-2)
- Ultrafast metabolizers (AS=>2) vs extensive metabolizers (AS=1.5-2)

11. SAFETY

All safety variables will be displayed as described in Section 4.5 separately for the SAF (and mSAF for selected endpoints) population in the main (double-blind) part of the study, and the OLP in the OLE phase of the study.

Safety and tolerability will be evaluated based on the incidence of treatment-emergent AEs, incidence of AEs leading to discontinuation, vital sign measurements, physical examination findings, weight, abnormal laboratory test results, ECG findings, abnormal movement scale results (AIMS, BARS, and SAS), C-SSRS results, use of concomitant medications, and injection site reactions. Additionally, time to early termination results will be summarized descriptively.

11.1 EXTENT OF EXPOSURE

Exposure to study drug and duration of exposure will be summarized by treatment group separately for the DB phase and OLE phase as well as over both phases.

A listing including study drug administration information from the CRF will be presented. Since all IM study drug is administered in clinic under supervision, no compliance summary is needed.

11.2 ADVERSE EVENTS

Collection of AE data will begin after a patient signs the informed consent form and will continue until completion of the final follow-up visit. Any AE having an onset after the final safety follow-up visit will not be collected or reported unless the investigator feels that the event may be related to the IM study drug.

Preferred AE terms (PT) and system organ class (SOC) will be coded using terminology from the most up to date version of the Medical Dictionary for Regulatory Activities (MedDRA) at the time of data analysis. Summaries will be presented by SOC and then PT in alphabetical order.

A treatment-emergent adverse event (TEAE) is defined as an AE that is first identified, or is identified to have worsened in intensity, at a time point occurring on or after first dose date. All reported adverse events will be listed, but only TEAEs will be summarized in tables.

Completely missing or partially missing AE start dates will be imputed as described in Table 7 below after due diligence to obtain accurate AE information has failed. The imputed dates will be used to determine TEAEs.

TEAE onset day is calculated as (date of TEAE start – date of latest dose + 1). The onset day will be missing if the start date is missing or partially missing.

The duration of a TEAE will be calculated from the start date and time until the end date and time of the TEAE.

All summaries of AEs will be provided separately for the DB and OLE phases as well as over both phases combined (for active treatment only).

An overall summary table will provide, by treatment group and overall (both SAF and mSAF populations separately), the number and percentage of patients who reported:

- Any TEAE
- Any severe TEAEs
- Any treatment-related TEAE (causal relationship suspected)
- Any treatment-related and severe TEAEs
- Any SAE
- Any serious treatment-related adverse event
- Any adverse event leading to study drug discontinuation
- Any adverse events leading to death.

Separate summaries of TEAEs by SOC and PT will be presented for all TEAEs, treatment-related TEAEs, TEAEs leading to study drug discontinuation, and serious TEAEs (for both SAF and mSAF populations separately). Each will include the number of TEAEs and the number and percentage of patients reporting each TEAE at least once. These SAF population summaries (excluding serious TEAEs) will be repeated separately for each dose (i.e. 1, 2 or 3), site of administration (i.e. deltoid or gluteus) and day of onset (≤ 7, 8-14, 15-21, ≥ 22).

In addition, TEAEs will be summarized separately by severity and relationship to study drug. An additional table of TEAEs will be provided for PT's that occurred in ≥2% of patients who received any Risperidone ISM during the respective period.

In the summary tables, patients may be counted under multiple system organ classes and preferred terms, but for each system organ class and preferred term, patients are only counted once. If a patient has the same adverse event on multiple occasions, the highest severity (severe> moderate > mild) or drug relationship (Causal relationship suspected > Causal relationship not suspected) recorded for the event will be presented.

Listings will be provided for all AEs, SAEs, AEs leading to drug discontinuation, and deaths. All reported AEs (including non-treatment-emergent adverse events) will be listed.

No formal hypothesis-testing analysis of AE incidence rates will be performed.

Table 7 Imputation of Missing Adverse Event Data

Missing Data Element	Imputed Value
Intensity/severity	Severe
Relationship to study drug	Causal relationship suspected
Action taken	No imputation
Serious?	No
Date of Onset	Missing day If different month from the date of first dose of study drug, then impute last day of the month; else if same month as the date of first dose of study drug, then impute as date of first dose of study drug Missing day and month If different year from the date of first dose of study drug then impute 31st December; else if same year as the date of first dose of study drug then impute as date of first dose of study drug Completely missing Impute as date of first dose of study drug; If the stop date is prior to this, use the 31st December of the year in the stop date [Note: Any imputed date of onset must fall on or prior to the corresponding event stop date.]
Treatment emergent	Yes, if imputed start date >= first dose date
Date of outcome	No imputation
Outcome	Not recovered/ not resolved

11.3 LABORATORY EVALUATIONS

Laboratory tests of hematology panel, chemistry panel, and urinalysis testing will be performed at the following time points: at the screening visit (Day - 8 to Day -1), on DB phase study days 8, 15, 29, 57 and 85, and OLE phase study days 1, 85, 169, 253, and 365. Prolactin assessments will be performed at the screening visit (Day - 8 to Day -1), on DB phase study days 8, 29, 57, and 85, and OLE phase study days 1, 85, 169, 253, and 365. On days when study drug is administered, assessment sample will be taken pre-dose. Baseline assessment are scheduled on Day 1 of each phase of the study; if a Day 1 value is not available then baseline will be the latest value obtained prior to Day 1. Change from baseline for all continuous parameters will be calculated as the post-baseline value minus the baseline value.

Comparison to the normal ranges and assignment of a flag that will indicate a high, normal, or low value will be accomplished by the central laboratory. Each out-of-range laboratory value will be assessed by the investigator as either clinically significant or not clinically significant. Clinically significant values should be considered AEs and recorded as such. Partial dates/times related to the occurrence of clinically important abnormalities will use the same rules as imputation of TEAE start dates (see Section 11.2).

All scheduled and unscheduled results will be considered in tables that assess maximum grade or toxicity.

Observed values (in SI units) and change from baseline over time will be summarized by treatment group using descriptive statistics (n, mean, median, standard deviation, minimum and maximum) for each continuous clinical laboratory parameter.

All laboratory data will be listed. For hematology and chemistry, columns will be included for normal ranges and individual abnormal laboratory values will be flagged and clinical significance will be indicated. A listing for the microscopic examination will be provided for patients who have a positive result from the urinalysis dipstick evaluation.

The hematology panel includes hematocrit, hemoglobin, red blood cell count, white blood cell count and differential count (absolute values for basophils, eosinophils, lymphocytes, monocytes, and neutrophils), and platelets. The chemistry panel includes sodium, potassium, glucose, creatinine, creatinine clearance [Estimated Glomerular Filtration Rate (eGFR) using Modification of Diet in Renal Disease (MDRD) formula], total protein, blood urea nitrogen, albumin, total bilirubin, ALT, AST, lactic dehydrogenase, gamma-glutamyl transferase, alkaline phosphatase, creatine phosphokinase, prolactin, HbA1c, thyroid stimulating hormone, lipid panel low-density lipoprotein, high-density lipoprotein, total cholesterol, and triglycerides. The urinalysis includes color, pH, specific gravity, ketones, protein, glucose, bilirubin, nitrite, urobilinogen, occult blood, and microscopic examination only if urinalysis dipstick results are abnormal. Prolactin will be summarized with chemistry panel.

Hematology and chemistry test will be summarized by treatment and overall at each time point for the absolute value itself and for changes from baseline. Tables showing the shift in terms of the Low/Normal/High indication (minimum and maximum) from baseline will also be presented.

Other lab tests include serology, serum/urine pregnancy testing, and drug screening. Serology, serum pregnancy testing will be conducted at the screening visit. Urine drug screen is mandatory at screening and baseline, and is optional thereafter. Urine pregnancy test will be performed prior to dose administration on study days 1, 29, 57, and 85, and all time points in OLE phase of the study.

The complete laboratory test results will be listed. In these listings, values outside the reference range will be flagged. Pregnancy testing and drug testing will be listed separately.

11.4 VITAL SIGNS

Vital signs will include blood pressure, pulse rate, respiratory rate, and body temperature and will be measured at each of the following time points: at the screening visit, on DB phase study days 1, 3, 4, 8, 15, 22 (Intense PK subset only), 29, 31, 43, 57, 59, 71, 85, and OLE phase study days 1, 29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, and 365. At each of these time point, vital signs will be measured after the patient has been resting in a supine position for at least 5 minutes. On days when patient receive IM injections of study drug, vital signs are to be measured within 1 hour before and then again within 3 hours after the study drug injection; at each of these time points, orthostatic blood pressure and pulse rate will be measured (immediately after completion of supine vital sign measurements) after the patient has risen from the supine to the standing position and has remained standing for approximately 3 minutes.

For blood pressure (supine, standing and orthostatic change), pulse rate (supine, standing and orthostatic change), respiration rate, body temperature and body weight, observed values and change from baseline will be summarized by treatment group and nominal visit using descriptive statistics (n, mean and median, standard deviation, minimum and maximum). For assessments 3 hours post-dose, baseline will be the pre-dose values at the respective visit, otherwise, baseline will be the latest value obtained prior to the first dose of the study drug in each phase.

Body weight and BMI will be measured at the screening visit, DB phase study days 1, 8, 15, 29, 57, and 85, and OLE phase study days 1, 85, 169, 253, and 365. On days when the patient receives IM injections, weight will be measured pre-dose. Height (cm) will be measured at the screening visit only. Weight and BMI will be summarized at each time point for the absolute value and for changes from baseline by treatment group and overall.

All vital sign measurements will be included in patient listings.

11.5 ECG

The standard 12-lead ECG will be obtained at each of the following time points: at the screening visit, on DB phase study days 1, 3, 4, 8, 15, 22 (Intense PK subset only), 29, 31, 57, 59, 85, and OLE phase study days 1, 29, 85, 141, 197, 281 and 365. For assessments 3 hours post-dose, baseline will be the pre-dose values at the respective visit, otherwise, baseline will be the latest value obtained prior to the first dose of the study drug in each phase.

The following ECG parameters will be recorded: heart rate (bpm), PR interval (msecs), QRS interval (msecs), QT interval (msecs), and corrected QT (QTc) intervals (msecs). QT will be corrected for heart rate using Bazett's (QTcB) interval and Fridericia's (QTcF) interval. On days when patients receive injections of IM study drug, an ECG will be performed both within 1 hour before dosing and within 3 hours after dosing. All scheduled ECGs must be performed after the patient has rested quietly for at least 5 minutes in the supine position.

Interval data will be summarized at each time point for the absolute value and for changes from baseline by treatment group and overall. Overall assessment of ECG will also be summarized by treatment group using counts and percentage. Additionally, QTcF values will be categorized and summarized, using the following QTcF value categories:

- Increase from baseline >30 msec;
- Increase from baseline >60 msec;
- Absolute values > 450 msec for males or > 470 msec for females.

All ECG data will be listed.

11.6 PHYSICAL EXAMINATION

A physical examination will be performed at time point: at the screening visit, on study days 8, 15, and 85 during the DB phase, and OLE phase study days 1, 29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, and 365. The physical examination will include assessment of the following: skin, lymphatic, eyes, ears, nose, throat, neck, respiratory, cardiovascular, gastrointestinal, musculoskeletal, and neurological. Physical examination will be listed.

11.7 ABNORMAL MOVEMENT SCALES

Abnormal movement scales will include the following: Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and Simpson-Angus Scale (SAS)[3]. All abnormal movement scales will be completed at screening, and on DB phase study days 1, 4, 8, 15, 29, 43, 57, 71, 85, and OLE phase study days 1, 29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, and 365. After administration of the first dose of study drug, if a patient complains of extrapyramidal symptoms on days when the abnormal movement scales are not scheduled to be performed, an unscheduled assessment will be performed.

For all abnormal movement scales, total scores and subscale scores will be summarized by treatment group and overall at each visit for the absolute value and for changes from baseline.

A listing will be provided for every abnormal movement scale.

11.7.1 Abnormal Involuntary Movement Scale (AIMS)

The Abnormal Involuntary Movement Scale (AIMS) is composed of 12 items and used to assess dyskinesia. Items related to severity of orofacial, extremity, and trunk movements, global judgment about incapacitation, and patient awareness are rated using a 5-point scale (0=none to 4=severe). Two items related to dental status are scored using “yes” or “no” responses. Overall AIMS scores range from 0 to 42.

11.7.2 Barnes Akathisia Rating Scale (BARS)

The Barnes Akathisia Scale (BARS) is a tool used for diagnosis of drug-induced akathisia (Barnes, et. al, 2004). The BARS consists of items that assess the objective presence and frequency of akathisia, the level of an individual's subjective awareness and distress, and global severity. The objective rating is made using a 4-point scale (0=normal limb movement, 1=restlessness for less than half the time observed, 2=restlessness for at least half of the time observed, 3=constant restlessness). The BARS subjective component consists of two items, both rated using 4-point scales. One is Awareness of Restlessness (0=absent, 1=non-specific sense, 2=complaints of inner restlessness, 3=strong desire to move most of the time) and the other is Distress Related to Restlessness (0=none, 1=mild, 2=moderate, 3=severe). The BARS Global Clinical Assessment of Akathisia is rated using a 6-point scale (0=absent, 1=questionable, 2=mild, 3=moderate, 4=marked, 5=severe). The BARS will be summarized and listed.

11.7.3 Simpson-Angus Scale

The SAS is a brief clinician administered rating scale taking approximately 10 minutes and measuring EPS in patients (Simpson and Angus, 1970). The 1970 version of this scale was later updated and modified by the authors to include the following 10 items: gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, head rotation, glabella tap, tremor, salivation, and akathisia. Item scores range from 0 to 4 with higher scores representing more severe symptoms. The total score is calculated as the sum of the 10 item scores; the range of possible total scores is 0 to 40, with 0 representing a normal response on all items. The modified SAS is typically used in schizophrenia studies to measure the presence of side effects in patients taking antipsychotic medications. The SAS will be summarized and listed.

During the study, it was noted that 26 patients were administered the incorrect SAS scales which included "Head dropping" instead of "Head rotation" and "Leg pendulousness" instead of "Akathisia". For such patients, across all assessments, these items will be imputed as the mean of the other 8 item scores for calculating the total score.

11.8 Columbia Suicide-Severity Rating Scale (C-SSRS)

The C-SSRS will be completed at screening, and on DB phase study days 1, 8, 15, 29, 57, 85, and OLE phase study days 1, 29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, and 365.

The C-SSRS is a suicidal ideation rating scale used for assessment of suicidal ideation and behavior in clinical and research settings. The C-SSRS defines 4 types of suicidal behavior (actual, interrupted, and aborted attempts, and preparatory acts or behavior) and an overall suicidal behavior assessment. The C-SSRS also defines 5 types of suicidal ideation (death wish, active thoughts, active ideation without intention to act, active ideation with some intent to act without a plan, and active ideation with a specific plan and intent) and an overall suicidal ideation, defined as a 'yes' response to any of the 5

types.

The investigator or qualified designee will complete the Columbia Suicide-Severity Rating Scale (C-SSRS). A "baseline" version of the C-SSRS will be administered at screening. At subsequent visits, a "since last visit" version of the C-SSRS will be administered.

For each behavior type, the frequency and percent of patients with a 'yes' response to each behavior type will be reported at each time point. The denominator for percent will be the number of patients with a C-SSRS assessment at the time point. Patients with a 'yes' response at any post baseline time point will be given a 'yes' response for the behavior type over the full treatment phase, which will also be summarized.

For each ideation type, the frequency and percent of patients with a 'yes' response to each behavior type will be reported at each time point. The denominator for percent will be the number of patients with a C-SSRS assessment at the time point. Patients with a 'yes' response at any post baseline time point will be given a 'yes' response for the ideation type over the full treatment phase, which will also be summarized.

As recommended in the C-SSRS manual for evaluation of safety, the following items will be derived from the C-SSRS based on data collected throughout the study and reported in a table:

- The number and percent of patients who had treatment-emergent suicidal behavior
- The number and percent of patients who had treatment-emergent suicidal ideation
- The number and percent of patients who had treatment-emergent suicidal behavior or suicidal ideation
- The number and percent of patients whose suicidal behavior worsened from baseline (lifetime)
- The number and percent of patients whose suicidal ideation worsened from baseline (past 2 months)
- The number and percent of patients whose suicidal behavior or suicidal ideation worsened from baseline
- The number of suicide attempts, aborted attempts, and interrupted attempts
- The mean of the per- patient lethality total scores
- Mean changes from baseline in per-patient lethality total scores
- The mean of the per-patient suicidal ideation intensity score
- Mean changes from baseline (past 2 months) in per-patient suicidal ideation intensity scores.

For OLE rollover patients, any worsening from baseline in suicidal behaviour recorded during the DB phase will be used as the OLE baseline for suicidal behaviour. For suicidal ideation, the maximum suicidal ideation and suicidal ideation intensity score from the DB days 57 and 85 will be considered as the OLE baseline.

Summary tables will be produced for the SAF population (DB phase) and OLP (OLE phase) by treatment group, by country and overall.

Data, as collected, will be included in patient listings.

11.9 INJECTION SITE REACTIONS

The injection site and surrounding area will be evaluated on DB phase study days 1, 8, 15, 29, 43, 57, 71 and 85, and OLE phase study days 1, 29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, and 365.

Injection site reactions (overall and by specific reaction subtype) and pain VAS score will be summarized for the mSAF and SAF populations (DB phase) and OLP (OLE phase) by treatment group and overall at each visit. The number and percentage of patients having reactions at each visit and at any visit within the respective phase will be presented. The pain VAS score at each visit will be summarised as both a categorical and continuous variable (additionally including 95% CI and inter-quartile range). An additional summary of the maximum VAS score recorded for the patient across the respective phase will be presented.

11.10 OTHER SAFETY VARIABLES

Ophthalmological examination including slit lamp biomicroscopy examination (eyelids, conjunctiva, iris, crystalline lens, sclera and cornea), visual field, best correction visual acuity (BCVA), and intraocular pressure will be performed at any time during screening period and at study day 85 (or early termination) of the DB phase. They will be summarized and listed.

12. INTERIM ANALYSES

An unblinded interim analysis will be conducted when 196 (approximately 50%) randomized patients, for whom the blinding was not compromised (see Section 3.6.3), have either reached study day 85 or withdrawn from the study; to re-estimate the sample size required for the final analysis up to 558 patients (186 patients per arm) in the mITT population. Only data collected up to and including the date that the Data Management function become aware of this event from the database will be used in the interim analysis.

Those patients included in the interim analysis (as well as those for whom the blinding was compromised) will constitute stage 1 patients with all subsequent patients being stage 2 patients for purpose of the primary and key secondary variable analyses. There will be no overlap of patients between stages. Only those patients meeting the criteria for inclusion in the mITT population will be included in the interim analysis for purpose of sample size re-estimation.

For stage 1 patients meeting the criteria for inclusion in the mITT population, the effect size (mean difference/pooled standard deviation) will be calculated for each dose compared to placebo separately for the primary efficacy variable (change from baseline to endpoint in total PANSS score). The mean difference will be repesented by the difference between LS means from the primary MMRM model at Day 85 (see Section 8.1.1) and the pooled standard deviation will be derived from the standard error of the difference between LS means divided by sqrt($1/n_r + 1/n_p$) where n_r and n_p are the sample size included in the interim analysis for the risperidone and placebo group respectively.

If one or both of the effect sizes are less than the expected effect size of 0.45, the lowest effect size will be used to derive the new sample size per group for the mITT population (M2) as suggested by Cui et al. (1999)[7] as follows:

M2 = 124 * (0.45/lowest effect size) up to a maximum of 186 patients per group in the mITT population.

If the lowest effect size is greater than or equal to 0.45, the target sample size for the mITT population will be maintained at 124 patients per arm.

The dropout rate at interim (from the randomization population to the ITT population) will be used to re-calculate the number of patients required to be randomized in stage 2 to meet the required total number in the mITT.

From an ethical point of view, there will be an early stopping for futility for a particular dose when the conditional power[17] at interim <10%. The conditional power (c_p) will be calculated for each risperidone dose as follows:

$$Cp = 1 - \varphi\left(\frac{2.2414 - \sqrt{0.5}\ \varphi^{-1}(1 - \frac{p_1}{2})}{\sqrt{0.5}} - \frac{\delta}{\sigma}\sqrt{31}\right)$$

where p_1 is the two-sided p-value from the primary analysis (MMRM Day 85 comparison) for stage 1 (interim), δ and σ are the difference between least square means and the corresponding standard error divided by sqrt($1/n_r + 1/n_p$) respectively from stage 1 (n_a and n_p are the sample sizes for risperidone and placebo in the interim analysis), and φ is the normal cumulative density function.

The DMC will receive one of the following from the unblinded statistician in a letter relative to each risperidone group comparison to placebo:

1. The number of patients to be randomized per group in stage 2
2. Confirmation that the conditional power <10%

The DMC will receive an analysis table (ensuring that the blinding of the DMC is not compromised) detailing the MMRM results compared to placebo, including the effect sizes and conditional powers.

The DMC will communicate to the sponsor this decision from the interim analysis.

Two further interim analyses will be conducted following the unblinding of the DB phase when approximately 65 and 100 patients are known to have been exposed to either of the active arms for at least 337 days respectively.

13. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

The following updates have been made to section 7.2 Analysis Populations from the Protocol V7.0 (22nd March 2018) in this version of the SAP:

- The protocol section 7.3.4 states that the MI sensitivity analyses will be performed on the mITT and ITT populations. This SAP clarifies that these analyses will be performed to test the sensitivity of the mITT and ITT analyses using MI techniques for the Modified Randomized and Randomized populations respectively. This was the intention of the Randomized population as stated in the Analysis Populatons section 7.2 of the protocol. The use of MI allows the implementation of the true ITT principle and ability to impute missing data for all randomized patients in the study in an unbiased manner. The addition of the mITT population in the updated protocol requires a Modified Randomization Population also to present sensitivity analyses for the mITT analyses, so this was added to this SAP.

- The definition of the PP analysis was updated following the blind data review meeting such that:

  1) those patients with < 2 doses would not be excluded if they withdrew early due to lack of efficacy and/or AE.

  2) those patients with protocol deviations deemed to have affected the PANSS after the third dose will remain in the PP population but any data following the third dose will be excluded from the PP analysis.

- The PK population and Intense PK subset will not be finalized until after database lock of the DB data when it can be checked if a patient has at least 1 measured plasma concentration value. Evaluability of PK concentrations due to protocol deviations and allowed sample windows will be conducted and agreed prior to data lock.

- Additional interaction terms including visit by subgroup and visit by treatment by subgroup were added into the MMRM models for subgroup analyses. Only the treatment by subgroup interaction was mentioned in the protocol but as this is an MMRM model, in order to compare treatments within each subgroup at each visit, such interactions in the model are required.

14. REFERENCE LIST

1. Kay, SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bulletin 1987; 13:261-276.
2. Morosini P-L, Magliano L, Brambilla L, Ugolini S, Pioli R. Development, reliability and acceptability of a new version of the DSMIV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social funtioning. Acta Psychiatr Scand 2000: 101: 323-329.
3. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl. 1970; 212:11-9.
4. EMA: Guideline on Missing Data in Confirmatory Clinical Trials, Committee for Medicinal Products for Human Use (CHMP), EMA/CPMP/EWP/1776/99 Rev. 1, 2 July 2010
5. Kane JM, Peters-Strickland T, Baker RA, Hertel P, Eramo A, Jin N, Peryy PP, Gara M, McQuade RD, Carson WH, Sanchez R: Aripiprazole once Monthly in the Acute Treatment of Schizophrenia: Findings from a 12-Week, Randomized, Double-Blind, Placebo-Controlled Study, J Clin Psychiatry, 2014
6. Nasser AF, Henderson DC, MD, Fava M, Fudala PJ, Twumasi-Ankrah P, Kouassi A, Heidbreder C: Efficacy, Safety, and Tolerability of RBP-7000 Once-Monthly Risperidone for the Treatment of Acute Schizophrenia, An 8-Week, Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase 3 Study, Journal of Clinical Psychopharmacology • Volume 36, Number 2, April 2016
7. Cui L, Hung HM, Wang SJ. Modification of sample size in group sequential clinical trials. Biometrics, 1999, 55:853-857.
8. Lawrence J, Hung H.M. Estimation and Confidence after Adjusting the Maximum Information". Biometrical Journal, 2003, 45, 143–152
9. Hommel G: A stagewise rejective multiple test procedure based on a modified Bonferroni test, Biometrika, 1988, 75, 383-386
10. Kenward, M. G. and Roger, J. H. Small Sample Inference for Fixed Effects from Restricted Maximum Likelihood," Biometrics, 1997, 53, 983–997.
11. Ratitch B., and O'Kelly M., Implementation of pattern-mixture models using standard SAS/STAT procedures, SUGI 2011.
12. Xin Yan and Xiao Gang (2010). Stratified Wilson and Newcombe Confidence Intervals for Multiple Binomial Proportions. Statistics in Biopharmaceutical Research, 2:3, 329-335.
13. EMA: Questions & Answers: positions on specific questions addressed to the Pharmacokinetics Working Party (PKWP), EMA/618604/2008 Rev. 13, 19 November 2015
14. FDA Guidance for Industry: Statistical Approaches to Establishing Bioequivalence, January 2001
15. A Gaedigk, SD Simon, RE Pearce, LD Bradford, MJ Kennedy and JS Leeder. The CYP2D6 Activity Score: Translating Genotype Information into a Qualitative Measure of Phenotype Clinical Pharmacology & Therapeutics, 2008, 83 (2), 235

16. Novalbos J, López-Rodríguez R, Román M, Gallego-Sandín S, Ochoa D, Abad-Santos F. Effects of CYP2D6 genotype on the pharmacokinetics, pharmacodynamics, and safety of risperidone in healthy volunteers. J Clin Psychopharmacol. 2010 Oct;30(5):504-11.

17. Chang, M. (2014). Adaptive Design Theory and Implementation using SAS and R - Second Edition (Chapter 9; p. 192). Boca Raton, FL; Taylor and Francis Group

15. PROGRAMMING CONSIDERATIONS

All tables, data listings, figures (TLFs), and statistical analyses will be generated using SAS® for Windows, Release 9.3 (SAS® Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output will adhere to the following specifications.

15.1 GENERAL CONSIDERATIONS

- A separate SAS program will be created for each output.
- Each output will be stored in a separate file.
- Output files will be delivered in Word format.
- Numbering of TFLs will follow ICH E3 guidance

15.2 TABLE, LISTING, AND FIGURE FORMAT

15.2.1 General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8
- The data displays for all TLFs will have a minimum 1-inch margin on all 4 sides. This area should be completely blank.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

15.2.2 Headers

- All output should have the following header at the top left of each page:

  < Laboratorios Farmacéuticos ROVI, S.A.> Protocol ROV-RISP-2016-01 (1004855)

  Draft/Final Run < date in DD-MMM-YYYY format>

- All output should have Page n of N at the top or bottom right corner of each page. TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.

15.2.3 Display Titles

- Each TLF should be identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended but sponsor preferences should be obtained prior to final determination. A decimal system (x.y and x.y.z) should be used to identify TLFs with related contents. The title is centered. The analysis set should be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
(ITT Analysis Set)

15.2.4 Column Headers

- Column headings should be displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.
- For numeric variables, include “unit” in column or row heading when appropriate.

- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of patients in the analysis set.
- The order of treatments in the tables and listings will be Placebo first in the case of placebo controlled studies and Active comparators first in the case of active comparator trials, followed by a total column (if applicable).

15.2.5 Body of the Data Display

15.2.5.1 General Conventions

Data in columns of a table or listing should be formatted as follows:

- alphanumeric values are left-justified;
- whole numbers (e.g., counts) are right-justified; and
- numbers containing fractional portions are decimal aligned.

15.2.5.2 Table Conventions

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

  Where percentages are presented in these tables, zero percentages will not be presented and so any counts of 0 will be presented as 0 and not as 0 (0%).
- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 patient represented in 1 or more groups should be included.
- An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more patients.
- Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more significant digit than the original values, and standard deviations should be printed

out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean (SD)	XXX.X (XXX.XX)
Median	XXX.X
Minimum	XXX
Maximum	XXX
95% CI	XXX.X, XXX.X

- P-values should be output in the format: "0.xxx", where xxx is the value rounded to 3 decimal places. Any p-value less than 0.001 will be presented as <0.001. If the p-value should be less than 0.0001 then present as <0.0001. If the p-value is returned as >0.999 then present as >0.999

- Percentage values should be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Pre-determine how to display values that round down to 0.0. A common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of patients in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% should be presented as 100%, without any decimal places.

- Tabular display of data for medical history, prior / concomitant medications, and all tabular displays of adverse event data should be presented by the body system, treatment class, or SOC in alphabetical order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC1 code), and adverse events (by preferred term) should be displayed in alphabetical order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated should be reported as "-".

- The percentage of patients is normally calculated as a proportion of the number of patients assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of patients exposed. Describe details of this in footnotes or programming notes.

- For categorical summaries (number and percentage of patients) where a patient can be included in more than one category, describe in a footnote or programming note if the patient should be included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The

overall summary statistics for the subheading should only be output on the first relevant page.

15.2.5.3 Listing Conventions

- Listings will be sorted for presentation in order of treatment groups as above, patient number, visit/collection day, and visit/collection time.
- Missing data should be represented on patient listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.
- Dates should be printed in SAS® DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates should be represented on patient listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the patient are output as "N/A", unless otherwise specified.
- All observed time values must be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available

15.2.5.4 Figure Conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

15.2.6 Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with "Note:" if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line where possible.
- Patient specific footnotes should be avoided, where possible.
- Footnotes will be used sparingly and must add value to the table, figure, or data listing. If more than six lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., 'Program : myprogram.sas Listing source: 16.x.y.z').

16. QUALITY CONTROL

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. Syneos Health SOPs Developing Statistical Programs (3907) and Quality Deliveries (SDTM, ADaM, TLF) (3908) describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

17. MOCK-UPS

Table, listing and figure mock ups will be presented in a separate document.