COVER PAGE

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 NUMBER: ROV-RISP-2016-01

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PROTOCOL VERSION 7.0

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Laboratorios Farmacéuticos ROVI, S.A.
C/ Julián Camarillo 35, 28037 Madrid, Spain

CLINICAL STUDY PROTOCOL

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

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EudraCT N°: 2016-002206-39

CLINICAL DEVELOPMENT PHASE

III

DOCUMENT DATE

22 March 2018

CONFIDENTIAL

Synopsis

Protocol Number: ROV-RISP-2016-01

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)

Active Study Drug: Risperidone ISM®

Study Sites: Multinational multicenter

Phase: III

Objectives:

Primary:

- To evaluate the efficacy of Risperidone ISM as compared with that of placebo in the treatment of patients with acute exacerbation of schizophrenia

Secondary:

- 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

Study Design:

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. The study design includes a screening period, a 12-week treatment period, a follow-up period, and a 12-month open-label extension period. Eligible patients will be randomly assigned, under double-blind conditions, to receive Risperidone ISM (75 or 100 mg) or placebo.

If indicated for an individual patient, prohibited medications may be washed out during the screening period. 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 intramuscular (IM) study drug is administered. Either of these circumstances may, at the investigators' discretion, involve admitting the patient to the inpatient unit during the screening period.

An ophthalmological examination, including slit-lamp biomicroscopy examination (eyelids, conjunctiva, iris, crystalline lens, sclera, and cornea), best corrected visual acuity, visual field, and intraocular pressure, should be done at any time during the screening period. The result of the ophthalmological examination must be available by study day -1. These tests need to be done again at visit 14 or at early termination visit.

Patients enrolled in the double-blind segment of the study will be admitted to the study site's inpatient unit sometime during the screening period (from 1 to 8 days before study day 1). It is generally

anticipated that patients may remain in the inpatient unit for at least 7 days after the first dose of study drug is administered, though inpatient duration for a given patient will be flexible.

The IM study drug (double-blind active Risperidone ISM or placebo) will be administered in a deltoid or gluteal muscle for a total of 3 times, once every 4 weeks, during the 12-week treatment period (i.e., at study days 1, 29, and 57).

Efficacy will be assessed by describing changes in scores on standard psychiatric assessment tools at each visit. Safety assessments will also be conducted at each visit.

Patients who complete planned double-blind study drug treatments and study evaluations may be eligible to participate in an optional long-term extension segment of the study, in which treatment with open-label Risperidone ISM 75 or 100 mg would begin immediately. For patients who do not participate in the extension segment, a safety follow-up phone contact will occur approximately 2 weeks after the end-of-treatment visit.

In addition to patients continuing from the double-blind segment of the study (rollover patients), clinically stable patients not previously enrolled in the study (de novo patients) may 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.

Number of Patients: Approximately 436 patients total randomized are planned (145 per arm) in the double-blind segment of the study. Approximately 100 de novo patients are planned to be enrolled in the extension segment of the study, in addition to rollover patients.

Interim Analysis: One unblinded interim analysis will be conducted when 196 (approximately 50%) randomized patients, for whom the blinding was not compromised, 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).

Treatment: The active study drug is Risperidone ISM, and the comparator study drug (inactive) is placebo. Eligible patients will be randomly assigned under double-blind conditions to receive the following study drug treatments in a 1:1:1 ratio during the double-blind treatment period: Risperidone ISM 75 mg, Risperidone ISM 100 mg, or placebo.

During the treatment period of the double-blind segment of the study, treatment assignment for each individual patient will remain blinded for patients, investigators, and all study site staff, with the exception of certain identified individuals at each study site who will be unblinded in order to prepare and administer IM study drug for each patient at that study site.

However, in the extension segment 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 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. 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 still be blinded at least up to locking the aforementioned database.

De novo patients participating in the extension segment of the study will receive either 75 or 100 mg Risperidone ISM depending on their previous oral risperidone dose. 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.

Duration of Patient Participation: Approximately 12 to 15 weeks in total is planned, including a screening period ranging from 1 day to 2 weeks (screening > 8 days requires medical monitor approval), a 12-week treatment period, and a 2-week follow-up period (not applicable for patients who enter into the long-term extension study). For rollover patients, the optional long-term extension segment of the study begins immediately upon completion of the end-of-treatment visit and continues for approximately 12 months. For de novo patients, a screening period of up to 8-day is planned, followed by a 12-month open-label treatment period. There is a 4-week follow-up period for all patients in the extension segment of the study.

Study Population: Selected main inclusion criteria for the double-blind segment of the study include the following:

- Current diagnosis of schizophrenia, according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria (DSM-5)
  - Currently experiencing an acute exacerbation or relapse with onset < 2 months before screening
  - If inpatient at screening, has been hospitalized for < 2 weeks for the current exacerbation
  - ≥ 2 years have elapsed since initial onset of active-phase schizophrenia symptoms
- Has been able to achieve outpatient status for > 4 months during the past year
- Has previously had a clinically significant beneficial response (improvement in schizophrenia symptoms), as determined by the investigator, to treatment with an antipsychotic medication other than clozapine
- Agrees to discontinue prohibited medications as applicable and as clinically indicated according to investigator instructions
- Dosages of all permitted medications are considered to have been stable (with the exception of medication to be used on an as-needed basis) for ≥ 2 weeks prior to the baseline visit and to remain stable during participation in this study
- Positive and Negative Syndrome Scale (PANSS) results at the screening and baseline visits meets the following criteria:
  - Total score between 80 and 120, inclusive
  - Score of ≥ 4 (moderate or greater) for ≥ 2 of the following Positive Scale items:
    - Item 1 (P1: delusions)
    - Item 2 (P2: conceptual disorganization)
    - Item 3 (P3: hallucinatory behavior)
    - Item 6 (P6: suspiciousness/persecution)
- Clinical Global Impression – Severity (CGI-S) score of ≥ 4 (moderately ill or worse)
- Age ≥ 18 and ≤ 65 years

- Resides in a stable living situation and is anticipated to return to that same stable living situation after discharge from the inpatient study unit, in the opinion of the investigator
- Has an identified reliable informant who is anticipated to remain the same after the patient is discharged from the inpatient study unit, in the opinion of the investigator

To be eligible for rollover into the extension segment of the study, a patient must meet inclusion criteria including the following:

- Has completed scheduled participation in the main part of the study, through to the end of the treatment period and including the end-of-treatment visit
- Continues to require long-term treatment with an antipsychotic medication, in the opinion of the investigator

Selected main inclusion criteria for clinically stable de novo patients in the extension segment of the study include the following:

- Subject is ≥ 18 and ≤ 65 years old, inclusive, at screening
- Subject is on a stable dose of oral risperidone from 4 to 6 mg daily as maintenance therapy for at least the last 4 weeks prior/before screening/baseline and would potentially benefit from conversion to an extended release injectable, in the opinion of the investigator
- Subject has a current diagnosis of schizophrenia, according to the DSM-5 criteria that is clinically stable as evidenced by:
  - No hospitalizations for acute exacerbations of schizophrenia and psychiatrically stable without significant symptom exacerbation over the last 3 months before screening based on the investigator's judgment
- PANSS total score < 70 at screening
- CGI-S score of ≤ 3 (mild) at screening
- Subject has previously had a clinically significant beneficial response (improvement in schizophrenia symptoms), as determined by the investigator, to treatment with an antipsychotic medication other than clozapine
- Subject with ≥ 2 years elapsed since initial onset of active-phase schizophrenia symptoms
- Subject resides in a stable living situation, in the opinion of the investigator
- Subject has an identified reliable informant, in the opinion of the investigator

The protocol includes a more extensive set of eligibility (inclusion and exclusion) criteria.

Variables:

Efficacy Variables

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

Primary Efficacy Variable

- PANSS total score mean change from baseline to endpoint

Secondary Efficacy Variables

Key Secondary Efficacy Variable

- CGI-S score mean change from baseline to endpoint

Other Secondary Efficacy Variables

- Clinician Global Impression – Improvement (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
    - 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
- 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

Health Economics and Outcomes Research Variables

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

- 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, 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 direct 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) total score mean change from baseline at each post-baseline assessment time point
- PSP domain score mean change from baseline at each post-baseline assessment time point
- 20-item Subjective Well-Being Under Neuroleptics Treatment Scale (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

Safety Variables

- 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 adverse events
- Occurrence, nature, time to onset, duration, seriousness criteria, relationship to study drug, and outcome of treatment-emergent serious adverse events
- Occurrence of extrapyramidal symptoms, as assessed using the Simpson-Angus Scale, Barnes Akathisia Rating Scale, and Abnormal Involuntary Movement Scale
- Columbia-Suicide Severity Rating Scale
- Physical examination, vital signs, weight, body mass index, clinical laboratory test results, and electrocardiogram findings
- Time to early termination

Pharmacokinetic Variables (Double-Blind segment only)

- Summary plasma concentrations of Risperidone, its active metabolite (9-OH-Risperidone), and the active moiety (i.e., 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 based on minimum concentration values by injection site (gluteal and deltoid) and by study drug dose level
- Exploratory associations of pharmacokinetic results with efficacy results

Genotype Sampling (Double-Blind segment only)

A blood sample will be collected for evaluation of genotypes for cytochrome P450 enzymes and/or genes that are potentially related to efficacy response and/or adverse effects.

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Abbreviations

AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
ANCOVA	Analysis of covariance
AUC_{tau}	Area under the concentration-time curve for a dosing interval
BARS	Barnes Akathisia Rating Scale
CGI-I	Clinician Global Impression – Improvement
CGI-S	Clinician Global Impression – Severity
C_{max}	Maximum concentration
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
C_{trough}	Trough concentration in plasma
CHW	Cui, Hung, Wang
DMC	Data Monitoring Committee
DMSO	Dimethyl sulfoxide
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	Electrocardiogram
eCRF	Electronic case report form
GCP	Good Clinical Practice
HRQL	Health-related quality of life
HRU	Healthcare resource utilization
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IM	Intramuscular
IOP	Intraocular pressure
IRB	Institutional Review Board
ISM	In situ microparticle
ITT	Intent-to-treat
mITT	modified Intent-to-treat
MMRM	Mixed effect model with repeated measurements
OLE	Open-label extension
PANSS	Positive and Negative Syndrome Scale
PLGA	Poly lactic-co-glycolic acid
PP	Per-protocol
mPP	modified Per-Protocol
PSP	Personal and Social Performance Scale
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
RO	Receptor occupancy
SAE	Serious adverse event
SAS	Simpson-Angus Scale
SWN-20	20-item Subjective Well-Being Under Neuroleptics Treatment Scale
THC	Tetrahydrocannabinol

T_{max}	Time to maximum concentration
VAS	Visual analog scale

1 Introduction

In the outpatient clinical setting, nonadherence with prescribed oral antipsychotic medication regimens is prevalent in patients with schizophrenia and has been associated with relapse and worsening of long-term functional and mental outcomes.[1,2] Long-acting formulations of antipsychotic medications, developed to promote treatment adherence, have helped to improve compliance and thus efficacy.[3] Initially developed long-acting formulations include typical antipsychotic agents, which are known to be associated with a number of safety and tolerability concerns that limit their acceptability in current clinical practice. Long-acting formulations also are available for certain atypical antipsychotics, including Risperidone (Risperdal Consta®) and paliperidone palmitate (Xeplion® and Invega Sustenna®). Risperdal Consta has been shown to be efficacious in achieving and maintaining remission status, and studies have shown an overall reduction in healthcare costs associated with frequent relapse and hospitalization.[4]

Clinical studies have shown that intramuscular (IM) paliperidone palmitate may be clinically useful in the treatment of patients with acute schizophrenia who were previously unsuccessfully treated with oral antipsychotics.[5,6] However, the number of currently available long-acting atypical antipsychotic medication options is limited, and thus there is a clinical need for additional long-acting atypical antipsychotic medication options.

Risperidone ISM® is an injectable IM in situ microparticle (ISM) long-acting formulation of risperidone currently in clinical development as a treatment for schizophrenia. Risperidone ISM is intended for IM administration once every 4 weeks, without any supplementation with oral risperidone. Previous studies of Risperidone ISM support its further clinical development.

Two single-dose clinical phase I studies have been conducted to characterize the pharmacokinetic characteristics and to evaluate the safety and tolerability of Risperidone ISM in healthy volunteers (n = 17) and in subjects with schizophrenia or schizoaffective disorder (n = 36), respectively.

In the phase I study in healthy volunteers (ROV-RISP-2009-01), single Risperidone ISM doses of 25 mg (n = 8) and 37.5 mg (n = 9) were evaluated, and all subjects completed the study. Risperidone, 9-OH-risperidone, and the active moiety (risperidone and 9-OH-risperidone combined) plasma concentration profiles showed that while plasma concentrations were higher for the 37.5 mg dose than for the 25 mg dose, maximum concentration (C_{max}) and area under the concentration-time curve values increases were not dose proportional. All subjects had at least 1 treatment-emergent adverse event (AE). The most frequently reported AEs were somnolence (10.1%) and injection site pain (8.1%), all of which were considered to be of mild or moderate intensity. Only 2 subjects, both in the second cohort (37.5 mg), had a serious AE (SAE). Each of these 2 subjects had 2 SAEs; the same 2 SAEs of tachycardia and oromandibular dystonia were reported by both subjects. All subjects were considered to have recovered by the end of the study.

In the phase I study in subjects with schizophrenia or schizoaffective disorder (ROV-RISP-2011-01 [PRISMA-1]), the pharmacokinetic characteristics of risperidone after single Risperidone ISM doses of 50 mg (n = 13), 75 mg (n = 12), and 100 mg (n = 11) were delineated. Risperidone, 9-OH-risperidone, and the active moiety (risperidone and 9-OH-risperidone combined) plasma concentration profiles over time (up to 75 days after administration of Risperidone ISM) showed the following active moiety mean

concentrations in the 50 mg, 75 mg, and 100 mg groups, respectively (for 3 selected time points after injection of Risperidone ISM): 21.4 ng/mL, 24.6 ng/mL, and 29.6 ng/mL at 24 hours; 22.8 ng/mL, 24.5 ng/mL, and 31.4 ng/mL at 48 hours; and 12.2 ng/mL, 17.3 ng/mL, and 20.0 ng/mL at 30 days). Estimated pharmacokinetic parameters of Risperidone ISM were in line with the results of the previous phase I study and with the literature on other marketed long-acting atypical antipsychotics, and overall, Risperidone ISM at all 3 tested dose strengths provided sustained release of risperidone and achieved therapeutic plasma levels within 1 day after injection. Overall, 34 subjects (94.4%) had at least 1 treatment-emergent AE during the study; the percentage of subjects reporting at least 1 treatment-emergent AE was similar across the 3 dose groups (92.3%, 100%, and 90.9% in the 50 mg, 75 mg, and 100 mg groups, respectively).

A phase II multiple-dose study has also been conducted (ROV-RISP-2011-02 [PRISMA-2]). Population pharmacokinetics modeling simulations were performed to guide the dose selection in this multicenter, open-label, 2-arm, parallel-design, repeat-dose clinical study to evaluate the pharmacokinetics, safety, and tolerability of 4 monthly IM injections of Risperidone ISM (75 mg) in subjects with schizophrenia. Risperidone ISM provided a sustained release of risperidone that achieved monthly therapeutic plasma levels within 1 day, without oral supplementation.

The preliminary safety data of Risperidone ISM from the clinical studies mentioned above are consistent with the well-known safety profile of other marketed risperidone products in subjects with schizophrenia or schizoaffective disorder and have shown Risperidone ISM to be well tolerated in the subjects evaluated.

Based on the pharmacokinetic results from the phase I study in healthy volunteers (ROV-RISP-2009-01), a population pharmacokinetic model was constructed to estimate plasma concentrations for therapeutic doses of Risperidone ISM. For the phase I clinical study (ROV-RISP-2011-01 [PRISMA-1]), both overall exposures and an active moiety C_{max} cutoff point of 80 ng/mL were considered in dose selection. A maximum dose of 100 mg was selected for use in the first part of the study, as the population pharmacokinetic model's worst-case estimate was that this dose would provide an active moiety median C_{max} value of approximately 80 ng/mL (i.e., assuming log-linear increases in bioavailability with ascending doses). Data from the phase I and phase II studies were used to further refine the population pharmacokinetic model to support dose selection for this and other phase III clinical studies.

Simulations and comparison of 5 multiple-dose regimens (37.5, 50, 75, 100, and 125 mg) showed that doses of 75 and 100 mg administered either in the gluteal or deltoid muscle resulted in predicted median C_{max} and trough concentration in plasma (C_{trough}) that stayed between thresholds of 7.5 and 80 ng/mL, thereby reducing the risk of extrapyramidal symptoms while maintaining plasma concentrations sufficiently high for efficacy.

Plasma concentration-time profiles and steady-state pharmacokinetic parameters of the active moiety after 4 doses (75 and 100 mg) Risperidone ISM were compared to commercially available Xeplion (paliperidone palmitate). Paliperidone is the active metabolite of risperidone (i.e., 9-OH-risperdione) and is administered as initial doses of 150 and 100 mg, given 1 week apart, followed by a maintenance dosing regimen of 75 or 100 mg, given every 4 weeks. There was a large overlap in pharmacokinetic profiles. In a number of patients, the predicted plasma concentrations of active moiety at the end of the 28-day treatment with 75 and 100 mg isperidone ISM were below the lower threshold of 7.5 ng/mL.[7] Steady-

state pharmacokinetic parameters varied between the 2 drugs with C_{max} being slightly higher and C_{trough} slightly lower after administration of Risperidone ISM.

Furthermore, the same 2 doses (75 and 100 mg) of Risperidone ISM were compared to oral risperidone given daily at doses of either 4 mg/day or 6 mg/day. Full adherence was assumed for oral risperidone. Compared to Risperidone ISM, 4 mg/day oral risperidone resulted in steady-state plasma concentrations of the active moiety above 7.5 ng/mL in almost all patients. In addition, all simulated profiles did not reach the upper threshold of 80 ng/mL, which is considered to be a surrogate for safety. For the higher dose of 6 mg/day, predicted plasma concentrations were higher than 80 ng/mL in a number of patients and over the entire dosing interval. The 75 mg dose of Risperidone ISM resulted in similar area under the concentration-time curve within a dosing interval and average plasma concentration as the oral 4 mg/day dose. However, it should be kept in mind that nonadherence to long-term oral medication is a well-known therapeutic issue in schizophrenia.[8,9] Hence, the simulated pharmacokinetic profiles after oral risperidone treatment are predicted to be higher than those that may be actually expected in patients with schizophrenia. As a consequence, C_{trough} values after oral treatment in patients with schizophrenia may well be in the same range or even lower than those predicted for Risperidone ISM.

In an exploratory evaluation of predicted D2 receptor occupancy (RO), it was shown that after IM administration of a 100 mg and 125 mg dose of Risperidone ISM, median D2 RO stayed within the 65% to 80% window over the entire 4-week dosing interval, only slightly exceeding the upper limit in the first week after administration. Comparison of Risperidone ISM with Xeplion showed that predicted median average RO values were comparable for both compounds after administration of a maintenance dose of 75 or 100 mg. However, predicted median C_{trough} RO values were slightly lower and predicted median peak RO slightly higher after administration of Risperidone ISM. When evaluating predicted D2 RO, it should be kept in mind that the correlation between D2 RO and clinical responses to an antipsychotic drug might be more complex and that patients might experience efficacy on much lower predicted D2 RO or might not experience any extrapyramidal symptoms at higher predicted D2 RO.[10]

These doses are expected to produce therapeutic levels of risperidone within 24 hours of the first injection; these therapeutic levels will be maintained for 28 days and will provide sustained levels of risperidone throughout the duration of the study. Thus, this study is designed to statistically demonstrate superior efficacy of Risperidone ISM to placebo.

2 Objectives

2.1 Primary Objective

The primary objective of this study is the following:

- To evaluate the efficacy of Risperidone ISM as compared with that of placebo in the treatment of patients with acute exacerbation of schizophrenia

2.2 Secondary Objectives

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 Investigational Plan

3.1 Overall Study Design and Plan

This is a multicenter, randomized, double-blind 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 baseline day (designated as study day 1), a treatment period (duration 12 weeks), a follow-up period (duration 2 weeks; not applicable for patients who enter into a long-term extension study), and an open-label extension period (duration 12 months).

The screening period for a given patient generally should be as brief as is clinically feasible (e.g., target of 3 days preferred) but may last up to 8 days (e.g., in order to safety washout any prohibited medications); an extension up 14 days maximum may be permitted with medical monitor approval. Eligible patients should be admitted to the inpatient study unit upon completion of screening assessments at the initial screening visit.

Patients will have a diagnosis of schizophrenia experiencing an acute exacerbation. 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.

The randomization scheme will ensure that an overall 1:1:1 ratio of assignments to each of these 3 study drug treatments is approximated.

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.

Patients enrolled in the double-blind segment of the study will be admitted to the study site's inpatient unit sometime during the screening period (from 1 to 8 days before study day 1). It is generally anticipated that patients may remain on the inpatient unit for at least 7 days after the first IM dose of long-acting study drug is administered. However, inpatient duration may vary for individual patients and potentially may range from 1 to 14 days. If the investigator determines that a given patient should remain inpatient beyond study day 15, the medical monitor should be contacted to discuss the extension.

Study drug will be administered as IM injections (see Section 5.1.2). 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, each 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).

Efficacy will be assessed by describing changes in scores on standard psychiatric assessment tools at each visit, and safety assessments will be conducted at each visit as well.

Patients who complete planned participation in this study through to the end of the treatment period may be eligible to enter into an optional long-term extension segment 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. 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 of the study will begin participation in the extension segment immediately upon completion of the end-of-treatment visit assessments and procedures. Patients who do not enter into the extension segment will have a final safety follow-up phone contact approximately 2 weeks after the end-of-treatment visit.

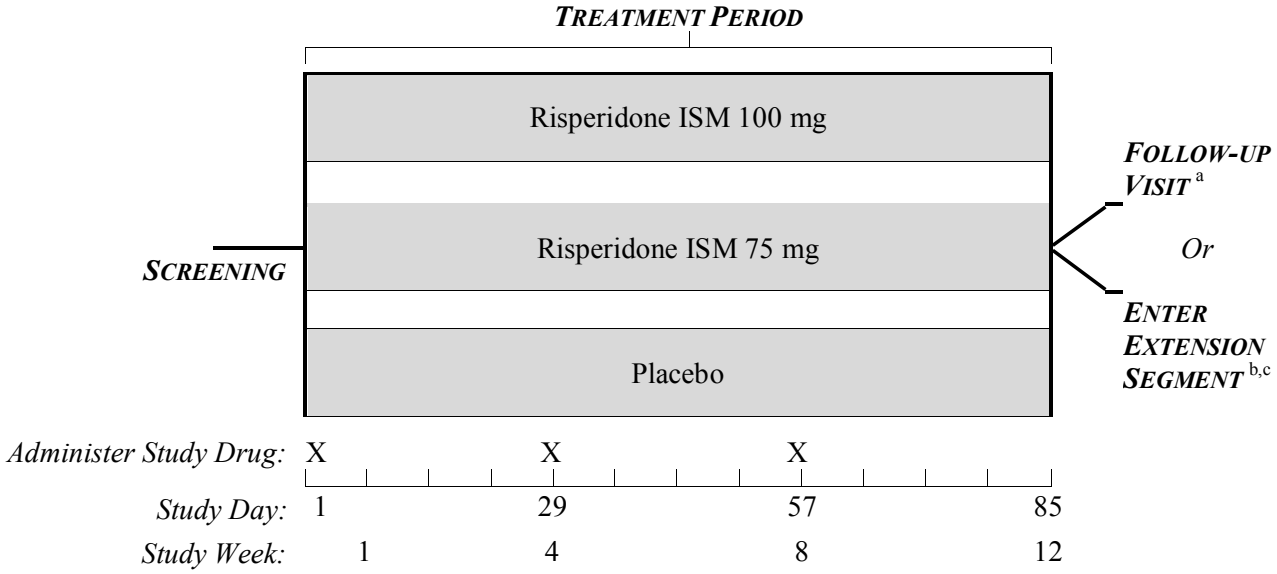
The planned total number of randomized patients in the double-blind segment of the study is approximately 436 patients total randomized planned (145 in each of the 3 treatment groups) (see Section 7.4). Note: due to a potential accidental unblinding quality issue, it was considered that 43 patients were potentially compromised and therefore the sample size has been increased to compensate them.

In addition to patients continuing from the double-blind segment of the study (rollover patients), patients not previously enrolled in the study (de novo patients) may 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.

Approximately 100 de novo patients are planned to be enrolled in the extension segment of the study, in addition to rollover patients.

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

	Screening	Baseline	Treatment Period (Double-Blind)												Follow-up
Study Visit Number:	1	2	3	4	5	6	7[1]	8	9	10	11	12	13	14[2]	15[3]
Study Day[4]:	-8 to -1[5]	1	3	4	8	15	22	29	31	43	57	59	71	85	99
Treatment Week:					1	2	3	4		6	8		10	12	
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]															
PSP (clinician administered)		X						X			X			X	
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				
Injection site pain VAS[18]		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	
Ophthalmological examination[19]	X													X	
Blood sample for:															
Hematology panel[20]	X	X			X	X		X			X			X	

	Screening	Baseline	Treatment Period (Double-Blind)												Follow-up
Study Visit Number:	1	2	3	4	5	6	7[1]	8	9	10	11	12	13	14[2]	15[3]
Study Day[4]:	-8 to -1[5]	1	3	4	8	15	22	29	31	43	57	59	71	85	99
Treatment Week:					1	2	3	4		6	8		10	12	
Overall Dosing Sequence:		*1*						*2*			*3*				
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; 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] 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 (i.e., 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 (i.e., the week 12 time point or earlier in the case of an early termination). This visit is not applicable for patients who enter into a long-term extension study.

[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 (i.e., 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 Section 4.1.1.1) have been met and that none of the exclusion criteria have been met (see 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 in the inpatient study unit for the remainder of the screening period (i.e., 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 Section 5.1.2). The IM study drug will contain either active Risperidone ISM (75 or 100 mg) or placebo (double blind).

[12] See 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 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 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 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 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 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 be sent to the laboratory for analysis (see 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 Segment for Rollover Patients

	Extension Baseline	Extension Segment Treatment Period (Open-Label)													Extension Follow-up
Extension Visit Number:	1[1]	2	3	4	5	6	7	8	9	10	11	12	13	14[2]	15[3]
Extension Study Day[4]:	1[5]	29	57	85	113	141	169	197	225	253	281	309	337	365	393
Extension Treatment Week:		4	8	12	16	20	24	28	32	36	40	44	48	52	56
Extension 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	X	X	X	X	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[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG[15]	X[8]	X		X		X		X			X			X	
Injection site evaluation[16]	X	X	X	X	X	X	X	X	X	X	X	X	X		
Injection site pain VAS[16]	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

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[1] The extension 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 extension segment, a patient must first complete all assessments and procedures scheduled for the end-of-treatment 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 extension segment.

[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 extension 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 extension 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 extension visits is ± 3 days (i.e., extension visits 2 through 15, inclusive).

[5] Extension day 1 (the extension 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 extension 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 extension segment of the study must be signed before any assessments or procedures for the extension segment 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 extension segment inclusion criteria (see Section 4.1.2.1) have been met and that none of the extension segment exclusion criteria have been met (see Section 4.1.2.2).

[8] In the extension segment 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 double-blind segment of the study will continue to receive 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. All Risperidone ISM doses will be administered by deep IM injection (deltoid muscle or gluteal muscle).

[9] For identified assessments at the extension baseline visit time point (on extension 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 extension baseline values and do not need to be repeated for the extension baseline visit time point if and only if the extension baseline visit occurs on the same day and date as the main study visit 14/week 12/end-of-treatment visit. If the extension baseline visit instead occurs on a day 1 to 3 days after the main study visit 14/week 12/end-of-treatment visit (see extension segment footnotes 2 and 3), all of the designated assessments must be performed separately on the day of the extension baseline visit, and the main study visit 14/week 12/end-of-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 extension segment will be reported at the extension 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 extension segment (i.e., extension segment visits 2 through 14, inclusive), the reference time point for the CGI-I scores will be that patient's overall status at the extension 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 extension segment 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 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 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 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 extension segment 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 Segment for De Novo Patients

	Screening	Baseline	Extension Segment Treatment Period (Open-Label)													Extension Follow-up
Extension Visit Number:	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14[1]**	**15**
Extension Study Day[2]:	**-8 to -1[3]**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**393**
Extension Treatment Week:			**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**
Extension 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[9]		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	
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)*	

	Screening	Baseline	Extension Segment Treatment Period (Open-Label)													Extension Follow-up
Extension Visit Number:	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14[1]**	**15**
Extension Study Day[2]:	**-8 to -1[3]**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**393**
Extension Treatment Week:			**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**
Extension Dosing Sequence:		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**		
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.

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[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 extension visits is ± 3 days (i.e., extension 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 extension segment of the study must be signed before any assessments or procedures for the extension segment 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 extension segment 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 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 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 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 extension segment 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 (X). 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.

3.2 Requirements and Restrictions

3.2.1 Contraception and Pregnancy

All patients must agree to use an acceptable method of contraception for the duration of the study and for ≥ 6 months after the last dose of IM study drug has been administered.

The following are considered acceptable methods:

- Condom (male or female) with or without a spermicidal agent
- Diaphragm or cervical cap with spermicide
- Intrauterine device
- Hormonal contraceptive (e.g., birth control pills or patches, vaginal ring, or contraceptive implant)

Female patients who have had a hysterectomy, bilateral tubal ligation, or bilateral salpingo-oophorectomy are considered surgically sterile and are thus are exempt from the requirement to use contraception. Men with an exclusive female partner meeting 1 of these surgically sterile criteria, as well as men who have themselves had a vasectomy, are also exempt from the requirement to use contraception.

Female patients who are postmenopausal are considered not of childbearing potential and thus exempt from the contraception requirement; for the purpose of this study, postmenopausal is defined as the permanent cessation of menstruation for at least 12 months prior to screening in women ≥ 45 years of age.

Patients who are abstinent from sexual intercourse are eligible for participation in this study if they agree to use an acceptable contraceptive method should they engage in such sexual activity while participating in this study.

If a female patient becomes pregnant while participating in the study, study drug must be discontinued immediately and early termination and safety follow-up visits should be scheduled. Any pregnancy must be reported to the sponsor (see Section 6.4.9).

3.2.2 Concomitant Therapy

All concomitant medications (including those used during ophthalmological examination, if any) and other therapies received during a patient's participation in this study (i.e., from the date of the informed consent form is signed through to the date of the final study visit) should be recorded.

The investigator may discontinue or adjust the dose of a concomitant medication to ensure patient safety; however, unnecessary changes in concomitant medications for reasons other than safety are generally discouraged to avoid confounding study evaluations.

The medical monitor should be consulted for any questions concerning concomitant medications.

3.2.2.1 Prohibited Therapy

3.2.2.1.1 Prohibited Medications

3.2.2.1.1.1 Cytochrome P450 3A4 Inducers and Inhibitors and 2D6 Inhibitors

Clinically significant inducers and inhibitors of cytochrome P450 3A4 and inhibitors of cytochrome P450 2D6 (whether prescription medications, over-the-counter medications, or dietary supplements) are prohibited during the course of the study and within 30 days before study day 1 (see Appendix B).

3.2.2.1.1.2 Antipsychotics

Antipsychotic medications, other than the study drugs administered according to this protocol, are not permitted during a patient's participation in the treatment period of this study. Existing antipsychotic medication must be discontinued during the screening period (for patients in the double-blind segment of the study, this will be while the patient is admitted to the inpatient study unit), if deemed clinically appropriate by investigator judgment. The same applies to de novo patents where all antipsychotic medication other than oral risperidone must be discontinued during the screening period. The last dose of oral risperidone should be administered on the day preceding baseline visit.

This restriction applies also for antipsychotics given as sleep aids.

The duration of the antipsychotic medication washout period (e.g., approximately 3 to 5 times the half-life of an oral antipsychotic, if appropriate and feasible) will be at the discretion of the investigator, in consultation with the medical monitor when deemed indicated.

If administration of an additional or different antipsychotic medication (other than protocol-defined study drug), or any other treatment for schizophrenia, is considered clinically indicated during a patient's participation in the study, the investigator should contact the medical monitor to discuss the circumstance and determine a course of action for the given patient.

3.2.2.1.1.3 Other Psychotropic Medications

Monoamine oxidase inhibitors (e.g., phenelzine, tranylcypromine, selegiline, moclobemide) are strictly prohibited during a patient's participation in this study and for ≥ 14 days before the screening visit. All other antidepressant medications are also not permitted during the treatment period. Patients taking antidepressants may be considered for washout of these medications during the screening period.

Lithium and mood stabilizers are not permitted during a patient's participation in the treatment period of this study.

Nicotine replacement therapy, including nicotine replacement patch and oral nicotine gum, is permitted. However, varenicline (Chantix®) is not permitted.

Otherwise, in general, use of psychotropic medications other than study drug is discouraged during a patient's participation in the study, with the exception of medications specifically identified in this protocol as permissible.

The medical monitor should be consulted for any questions about use of any psychotropic medications during a patient's participation in this study.

3.2.2.1.1.4 Drugs of Abuse

Prohibited substances include amphetamines, barbiturates, cocaine, methadone, opioids, and phencyclidine. If it is determined that a patient has been using any of these substances during participation in this study, the investigator should contact the medical monitor to discuss the course of action.

Tobacco and/or caffeine use is allowable if use is anticipated to remain relatively stable throughout a patient's participation in the study.

While it is preferable that patients do not use any alcohol or tetrahydrocannabinol (THC)-containing substances (e.g., marijuana), in certain cases patients with occasional and stable use of small amounts

these substances may not be exclusionary if exclusion criterion 9 is not met, and only if the medical monitor provides approval (also see Section 6.4.5.4.3).

3.2.2.1.2 Prohibited Nonmedication Therapy

Psychotherapy should not be started or changed during a patient's participation in the study. It is acceptable for a patient already receiving psychotherapy to participate in the study.

While on the inpatient study unit during participation in the study, initiation of new augmenting psychotherapies (i.e., group therapy) is discouraged, though standard milieu-related activities are acceptable.

Partial hospitalization after discharge from the inpatient study unit is discouraged, though the level of care after discharge from the inpatient study unit ultimately should be made based on investigator judgment.

Psychiatric hospitalization during the treatment period after the patient has been discharged from the inpatient study unit could result in early withdrawal of that patient from the study (see Section 4.2).

3.2.2.2 Permitted Therapy

3.2.2.2.1 Rescue Medication

Permitted rescue medications for this study include the following:

- Benzodiazepines
  - Indications: agitation, anxiety, insomnia, and/or restlessness
  - Maximum dosage: 6 mg/day lorazepam or equivalent for other benzodiazepines
  - Notes:
    - Short half-life benzodiazepines are preferable to longer half-life benzodiazepines due to the potential for lingering effects on daytime functioning and study assessments
    - For treatment of agitation and/or anxiety, the dose benzodiazepines should be kept as stable as possible throughout the patient's participation in study in order to avoid interference with daytime functioning and study assessments
- Anticholinergics
  - Indication: extrapyramidal symptoms
  - Maximum dosage: 4 mg/day benztropine or equivalent for other anticholinergics
- Propranolol
  - Indications: akathisia or tremor
  - Maximum dosage: 20 mg 3 times daily (60 mg/day total)

4 Patients

4.1 Eligibility

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.

4.1.1 Eligibility Criteria for Enrollment into the Double-Blind Segment of the Study

4.1.1.1 Inclusion Criteria

To be eligible for enrollment into the double-blind segment of the study, each patient must meet all of the following criteria at screening:

1. Capable of providing informed consent
   a. A signed informed consent form must be provided before any study assessments are performed
   b. Patients must be fluent in the language that is spoken by the investigator and the study site staff (including raters) and must be able to read and understand the words in which the informed consent is written
2. Age ≥ 18 and ≤ 65 years
3. Body mass index 18.5 to 40.0 kg/m^2 (inclusive)
4. Current diagnosis of schizophrenia, according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria
   a. Currently experiencing an acute exacerbation or relapse with onset < 2 months before screening
   b. If inpatient at screening, has been hospitalized for < 2 weeks for the current exacerbation
   c. ≥ 2 years have elapsed since initial onset of active-phase schizophrenia symptoms
5. Has been able to achieve outpatient status for > 4 months during the past year
6. Has previously had a clinically significant beneficial response (improvement in schizophrenia symptoms), as determined by the investigator, to treatment with an antipsychotic medication other than clozapine
7. Agrees to discontinue prohibited medications as applicable and as clinically indicated according to investigator instructions
8. Dosages of all permitted medications are considered to have been stable (with the exception of medication to be used on an as-needed basis) for ≥ 2 weeks prior to the baseline visit and to remain stable during participation in this study
9. Positive and Negative Syndrome Scale (PANSS) results at the screening and baseline visits meets the following criteria:
   a. Total score between 80 and 120, inclusive
   b. Score of ≥ 4 (moderate or greater) for ≥ 2 of the following Positive Scale items:
      i. Item 1 (P1: delusions)
      ii. Item 2 (P2: conceptual disorganization)
      iii. Item 3 (P3: hallucinatory behavior)
      iv. Item 6 (P6: suspiciousness/persecution)
10. Clinical Global Impression – Severity (CGI-S) score of ≥ 4 (moderately ill or worse)
11. Resides in a stable living situation and is anticipated to return to that same stable living situation after discharge from the inpatient study unit, in the opinion of the investigator
12. Has an identified reliable informant who is anticipated to remain the same after the patient is discharged from the inpatient study unit, in the opinion of the investigator
13. Meets the following criteria:
   a. If a sexually active, is using a medically accepted contraceptive method, and will continue to use such throughout participation in this study (and for ≥ 6 months after the last dose of IM study drug has been administered); acceptable methods include the following:
      i. Condoms (male or female) with or without a spermicidal agent
      ii. Diaphragm or cervical cap with spermicide
      iii. Intrauterine device
      iv. Hormonal contraceptive
   b. If not currently sexually active, then meets the following criteria:

i. Agrees that if sexual activity resumes while participating in this study, a medically accepted contraception method will be used

14. Willing and able to be confined to an inpatient study unit for up to 2 weeks (or longer if clinically indicated), as applicable and as clinically indicated according to investigator instructions
15. Agrees not to post any personal medical data related to the study or information related to the study on any website or social media site (e.g., Facebook, Twitter, and others) during the study duration

4.1.1.2 Exclusion Criteria

An individual who meets any of the following criteria at screening will not be permitted to enroll in the study:

1. History of proven inadequate clinical response to treatment with therapeutic doses (with good compliance) of risperidone or paliperidone
2. History of treatment resistance, defined as failure to respond to 2 discrete adequate trials (≥ 4 weeks with an adequate dose) of 2 different antipsychotic medications; history of clozapine use (exception: use was not because of treatment resistance or refractory psychotic symptoms)
3. Improvement in PANSS total score 20% or greater between the initial screening visit and first injection
4. Known or suspected intolerance of or allergy or hypersensitivity to risperidone, paliperidone, or any of the excipients in the IM formulations of these
5. History of neuroleptic malignant syndrome, clinically significant tardive dyskinesia, or tardive dystonia
6. History of any other medical condition that is considered to pose any unjustifiable risk or interfere with study assessments
7. Clinically significant extrapyramidal symptoms at screening or baseline
8. Answer of "yes" on item 4 or on item 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) (ideation) with the most recent episode occurring within the past 2 months, or answer "yes" to any of the 5 items (behavior) with an episode occurring within the last year
9. Current diagnosis or a history of substance use disorder according to DSM-5 criteria within 6 months prior to the screening visit (with the exception of tobacco, mild cannabis, or mild alcohol use disorder) or a positive drug screen test (with the exception of cannabis) verified by repeat testing
10. Lifetime history of diagnosis of schizoaffective disorder or bipolar disorder
11. Clinically significant comorbid neuropsychiatric disorders including any of the following:
    a. Current untreated or unstable major depressive disorder
    b. Clinically significant cognitive difficulties including dementia, delirium, or amnesic syndrome, within the past 2 years and would interfere with participation in the study
    c. Any other psychiatric condition that would, in the judgment of the investigator, interfere with participation in the study
12. Clinically significant or unstable medical illness/condition/disorder that would be anticipated, in the investigator's opinion, to potentially compromise patient safety or adversely affect the evaluation of efficacy, including (but not necessarily limited to) the following:
    a. Clinically significant hypotension or hypertension not stabilized by medical therapy (diastolic blood pressure > 105 mmHg)
    b. Unstable thyroid dysfunction in the past 6 months
    c. Malignant tumor within the last 5 years
    d. Neurologic conditions including the following:

i. History of seizure disorder or condition associated with seizures
ii. History of brain tumor, subdural hematoma, or other clinically significant neurological condition within the past 12 months
iii. Head trauma with loss of consciousness within 12 months before screening
iv. Active acute or chronic central nervous system infection
v. Stroke within 6 months before screening

e. Cardiac conditions including the following:
i. Clinically significant cardiac arrhythmia, cardiomyopathy, or cardiac conduction defect
ii. History of myocardial infarction or unstable angina within the last 3 months before screening, or clinically significant abnormality on screening or baseline electrocardiogram (ECG) including but not limited to the following: QT interval corrected for heart rate using Fridericia's formula (QTcF) > 465 msec if male or > 485 msec if female

13. Laboratory abnormality that, in the opinion of the investigator, would compromise the well-being of the patient, or any of the following laboratory abnormalities at screening or baseline:
a. Aspartate aminotransferase or alanine aminotransferase value ≥ 2 times the upper limit of the laboratory normal reference range
b. Hemoglobin A1c > 9%
c. Absolute neutrophil count ≤ 1.5×10^3 µL
d. Platelet count ≤ 75×10^3 µL
e. Creatinine clearance < 60 mL/min
f. Positive test result for human immunodeficiency virus, hepatitis B surface antigen, or antihepatitis C virus antibody
g. Positive pregnancy test result
h. Urine drug screen at screening or baseline shows a positive result for any of the tested substances (potential exceptions: results positive for benzodiazepine may not be exclusionary if the investigator confirms that such medication was medically indicated and consults the medical monitor before enrolling a patient with such a finding; results positive for THC may not be exclusionary in certain cases only if exclusion criterion 9 is not met and only if the medical monitor provides approval)
14. Pregnant, lactating, or breastfeeding
15. Inadequate gluteal or deltoid musculature or excessive fat, as determined by the investigator, that would interfere with IM study drug injections
16. Any contraindication for IM injections
17. Receipt of any long-acting antipsychotic medication by IM injection within 60 days before screening
18. Current involuntary hospitalization or incarceration
19. Hospitalized for more than 30 days during the 90 days before screening
20. Participation in another clinical study in which the patient received an experimental or investigational drug or agent within 6 months before screening
21. Participation in a clinical study with Risperidone ISM within 12 months before screening
22. Study site personnel and/or persons employed by the investigator or study site or is an immediate family member of such persons
23. Patients taking any prohibited concomitant medication (see Section 3.2.2.1.1) at the time of randomization visit
24. Clinically significant ocular disease or visual impairment interfering with the planned ophthalmological examinations or that in the investigator's opinion could potentially compromise patients' ocular safety

25. Patients with planned or anticipated need for ocular surgery during the treatment period of the trial

4.1.2 Eligibility Criteria for Entry into Optional Extension Segment of the Study (Rollover Patients)

Participation in the open-label extension segment of the study is optional, and patients who complete participation in the main segment 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 extension segment.

4.1.2.1 Inclusion Criteria for Extension Segment

To be eligible for entry into the extension segment of the study, a patient must meet all of the following criteria at the extension baseline time point (immediately upon completion of the end-of-treatment visit assessments and procedures for the main part of the study):

1. Has completed scheduled participation in the main part of the study, through to the end of the treatment period and including the end-of-treatment visit
2. Continues to require long-term treatment with an antipsychotic medication, in the opinion of the investigator
3. Continues to meet contraceptive requirements of the study (see Section 3.2.1)
4. Is willing to participate in the extension segment of the study and remains capable of providing informed consent
    a. A signed informed consent form must be provided before any study assessments are performed for the extension segment
5. Continues to reside in a stable living situation, in the opinion of the investigator
6. Continues to have an identified reliable informant, in the opinion of the investigator

4.1.2.2 Exclusion Criteria for Extension Segment

An individual who meets any of the following criteria at the extension baseline time point (immediately upon completion of the end-of-treatment visit assessments and procedures for the main part of the study) will not be permitted to enter into the extension segment of the study:

1. Missed more than 1 scheduled study visit during participation in the main part of the study
2. Had an abnormal clinical laboratory value, vital sign, or ECG finding during participation in the main part of the study that, in the opinion of the investigator, was clinically relevant, related to study drug, and would compromise the well-being of the patient in the extension segment
3. Had a clinically significant or unstable medical illness/condition/disorder during the main part of the study that would be anticipated, in the investigator's opinion, to potentially compromise patient safety in the extension segment
4. Is taking or is anticipated to require any prohibited concomitant medication (see Section 3.2.2.1.1)
5. Pregnant, lactating, or breastfeeding
6. Any contraindication for continued IM injections (e.g., treatment with anticoagulant)
7. Inadequate gluteal or deltoid musculature or excessive fat, as determined by the investigator, that would interfere with IM study drug injections
8. Study site personnel and/or persons employed by the investigator or study site or is an immediate family member of such persons

4.1.3 Eligibility Criteria for Entry into Optional Extension Segment of the Study (De Novo Patients)

4.1.3.1 Inclusion Criteria: de novo patients

To be eligible for entry into the extension segment of the study, a de novo patient must meet all of the following criteria at the extension segment screening visit:

1. Capable of providing informed consent
   a. A signed informed consent form must be provided before any study assessments are performed
   b. Patients must be fluent in the language that is spoken by the investigator and the study site staff (including raters) and must be able to read and understand the words in which the informed consent is written
2. Age ≥ 18 and ≤ 65 years old, inclusive, at screening
3. On a stable dose of oral risperidone from 4 to 6 mg daily as maintenance therapy for at least the last 4 weeks prior/before screening/baseline and would potentially benefit from conversion to an extended release injectable, in the opinion of the investigator
4. Current diagnosis of schizophrenia, according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria that is clinically stable as evidenced by:
   - No hospitalizations for acute exacerbations of schizophrenia and psychiatrically stable without significant symptom exacerbation over the last 3 months before screening based on the investigator's judgment
   - PANSS total score < 70 at screening
   - CGI-S score of ≤ 3 (mild) at screening
5. Has previously had a clinically significant beneficial response (improvement in schizophrenia symptoms), as determined by the investigator, to treatment with an antipsychotic medication other than clozapine
6. At least 2 years elapsed since initial onset of active-phase schizophrenia symptoms
7. Subject is outpatient; not hospitalized for worsening of schizophrenia within the last 3 months (hospitalization for social management within this time period is acceptable)
8. Medically stable over the last month prior to screening based on the investigator's judgment
9. BMI of 18.5 to 40.0 kg/m^2 (inclusive) at screening
10. Agrees to discontinue prohibited medications as applicable and as clinically indicated according to investigator instructions
11. Dosages of all permitted medications are considered to have been stable (with the exception of medication to be used on an as-needed basis) for ≥ 2 weeks prior to the baseline visit and to remain stable during participation in this study
12. Resides in a stable living situation, in the opinion of the investigator
13. Has an identified reliable informant, in the opinion of the investigator
14. Meets the following contraceptive criteria:
    a. If sexually active, is using a medically accepted contraceptive method, and will continue to use such throughout participation in this study (and for ≥ 6 months after the last dose of IM study drug has been administered); acceptable methods include the following:
       i. Condoms (male or female) with or without a spermicidal agent
       ii. Diaphragm or cervical cap with spermicide
       iii. Intrauterine device
       iv. Hormonal contraceptive
    b. If not currently sexually active, then meets the following criteria:

i. Agrees that if sexual activity resumes while participating in this study, a medically accepted contraception method will be used

15. Agrees not to post any personal medical data related to the study or information related to the study on any website or social media site (e.g., Facebook, Twitter, and others) during the study duration

4.1.3.2 Exclusion criteria: de novo patients

An individual who meets any of the following criteria at screening will not be permitted to enroll in the study:

1. History of proven inadequate clinical response to treatment with therapeutic doses (with good compliance) of risperidone or paliperidone
2. History of treatment resistance, defined as failure to respond to 2 discrete adequate trials (≥ 4 weeks with an adequate dose) of 2 different antipsychotic medications; history of clozapine use (exception: use was not because of treatment resistance or refractory psychotic symptoms)
3. Known or suspected intolerance of or allergy or hypersensitivity to risperidone, paliperidone, or any of the excipients in the IM formulations of these
4. History of neuroleptic malignant syndrome, clinically significant tardive dyskinesia or tardive dystonia
5. History of any other medical condition that is considered to pose any unjustifiable risk or interfere with study assessments
6. Clinically significant extrapyramidal symptoms at screening or baseline
7. At significant risk of suicidal, homicidal or violent ideation or behavior, by history or as clinically assessed by the investigator at screening visit
8. Answer of "yes" on item 4 or on item 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) (ideation) with the most recent episode occurring within the past 2 months, or answer "yes" to any of the 5 items (behavior) with an episode occurring within the last year
9. Current diagnosis or a history of substance use disorder according to DSM-5 criteria within 6 months prior to the screening visit (with the exception of tobacco, mild cannabis, or mild alcohol use disorder) or a positive drug screen test (with the exception of cannabis) verified by repeat testing
10. Lifetime history of diagnosis of schizoaffective disorder or bipolar disorder
11. Clinically significant comorbid neuropsychiatric disorders including any of the following:
    a. Current untreated or unstable major depressive disorder
    b. Clinically significant cognitive difficulties including dementia, delirium, or amnesic syndrome, within the past 2 years and would interfere with participation in the study
    c. Any other psychiatric condition that would, in the judgment of the investigator, interfere with participation in the study
12. Clinically significant or unstable medical illness/condition/disorder that would be anticipated, in the investigator's opinion, to potentially compromise patient safety or adversely affect the evaluation of efficacy, including (but not necessarily limited to) the following:
    a. Clinically significant hypotension or hypertension not stabilized by medical therapy (diastolic blood pressure > 105 mmHg)
    b. Unstable thyroid dysfunction in the past 6 months
    c. Malignant tumor within the last 5 years
    d. Neurologic conditions including the following:
        i. History of seizure disorder or condition associated with seizures

ii. History of brain tumor, subdural hematoma, or other clinically significant neurological condition within the past 12 months
iii. Head trauma with loss of consciousness within 12 months before screening
iv. Active acute or chronic central nervous system infection
v. Stroke within 6 months before screening

e. Cardiac conditions including the following:
i. Clinically significant cardiac arrhythmia, cardiomyopathy, or cardiac conduction defect
ii. History of myocardial infarction or unstable angina within the last 3 months before screening, or clinically significant abnormality on screening or baseline electrocardiogram (ECG) including but not limited to the following: QT interval corrected for heart rate using Fridericia's formula (QTcF) > 465 msec if male or > 485 msec if female

13. Laboratory abnormality that, in the opinion of the investigator, would compromise the well-being of the patient, or any of the following laboratory abnormalities at screening or baseline:
a. Aspartate aminotransferase or alanine aminotransferase value ≥ 2 times the upper limit of the laboratory normal reference range
b. Hemoglobin A1c > 9%
c. Absolute neutrophil count ≤ 1.5×10^3 µL
d. Platelet count ≤ 75×10^3 µL
e. Creatinine clearance < 60 mL/min
f. Positive test result for human immunodeficiency virus, hepatitis B surface antigen, or antihepatitis C virus antibody
g. Positive pregnancy test result
h. Urine drug screen at screening or baseline shows a positive result for any of the tested substances (potential exceptions: results positive for benzodiazepine may not be exclusionary if the investigator confirms that such medication was medically indicated and consults the medical monitor before enrolling a patient with such a finding; results positive for THC may not be exclusionary in certain cases only if exclusion criterion 9 is not met and only if the medical monitor provides approval)
14. Pregnant, lactating, or breastfeeding
15. Inadequate gluteal or deltoid musculature or excessive fat, as determined by the investigator, that would interfere with IM study drug injections
16. Any contraindication for IM injections
17. Receipt of any long-acting antipsychotic medication by IM injection within 60 days before screening
18. Current involuntary hospitalization or incarceration
19. Hospitalized for more than 30 days during the 90 days before screening
20. Participation in another clinical study in which the patient received an experimental or investigational drug or agent within 6 months before screening
21. Participation in a clinical study with Risperidone ISM within 12 months before screening
22. Study site personnel and/or persons employed by the investigator or study site or is an immediate family member of such persons
23. Patients taking or anticipated to require any prohibited concomitant medication (see Section 3.2.2.1.1)

4.2 Patient Withdrawal

A patient may be withdrawn from the study at any time if the patient, investigator, or sponsor determines that it is not in the best interest of the patient to continue.

Reasons for patient withdrawal may include, but are not limited to, noncompliance, safety, development of a medical condition that requires treatment with a prohibited medication, a positive result on a pregnancy or urine drug screen test, or patient withdrawal of consent. In addition, if a patient's condition changes during the course of the study so that he or she no longer satisfies the inclusion and exclusion criteria, he or she may be withdrawn.

If psychiatric hospitalization for worsening, relapse, or exacerbation of schizophrenia symptoms occurs during the treatment period at a time point after the patient has been discharged from the inpatient study unit, the medical monitor should be contacted to discuss whether early withdrawal of that patient from the study may be indicated.

All efforts should be made to perform an early termination visit for any patient who withdraws or is withdrawn from the study, except for patients who withdraw consent.

If a patient is withdrawn because of an AE or other medical reason, the patient should be followed until the AE resolves or is deemed stable by the investigator or until the patient is deemed by the investigator to be lost to follow-up.

If, in the opinion of the investigator, it is clinically indicated to monitor a patient beyond the early termination visit, subsequent clinical contacts (in addition to protocol-designated study visits) may be extended on an as-needed basis. In such instances, the medical monitor should be contacted so that the sponsor or designee and the investigator can agree to an acceptable clinical follow-up schedule.

In the event that a patient chooses to withdraw from the study, the investigator should make a reasonable effort to ascertain the reason for withdrawal while fully respecting the patient's rights to withdraw.

The investigator will determine the most appropriate post-study treatment for each withdrawn patient, which may include conferring with the patient's treating psychiatrist.

The investigator must maintain a record of all patients who withdraw from the study and the reasons for discontinuation. The reason for discontinuation will be documented. If a patient is lost to follow-up, a reasonable attempt to contact the patient must be made and documented.

5 Study Treatment

The following 3 study drug treatments will be used in the study:

- Risperidone ISM 75 mg (Double-Blind and Open-label Segment)
- Risperidone ISM 100 mg (Double-Blind and Open-label Segment)
- Placebo (Double-Blind Segment only)

In the double-blind segment of the study, the treatment assignment for each 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 IM study drug for each patient at that study site. In the extension segment 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 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 be still blinded at least up to locking the aforementioned database.

5.1 Study Drugs

5.1.1 Study Drugs

Risperidone ISM is the active study drug being evaluated in this study.

Risperidone ISM is a long-acting formulation of risperidone that uses ISM technology. Laboratorios Farmacéuticos ROVI, S.A. is the manufacturer of Risperidone ISM. The World Health Organization Anatomical Therapeutic Chemical class of risperidone is N05AX08 (other antipsychotics).

The active moiety of Risperidone ISM is risperidone.

The following excipients are contained in both, Risperidone ISM and placebo: poly lactic-co-glycolic acid (PLGA; copolymer of lactic and glycolic acids) and dimethyl sulfoxide (DMSO). Risperidone ISM and placebo are formulated as a suspension and dissolution for injection, respectively.

The manner in which Risperidone ISM and placebo study drugs are provided to study sites requires a reconstitution procedure to be performed at the study site for each dose to be administered.

Risperidone ISM/placebo kits will be provided to study sites, and they will be stored refrigerated at a temperature between 2ºC and 8ºC. Each kit includes 2 syringes, 1 of which contains the Risperidone ISM study drug (except for placebo) plus PLGA in the form of a solid powder, and the other of which contains DMSO solvent.

Each kit will also contain 2 needles: a 2-inch 20 gauge safety needle and a 1-inch 21 gauge safety needle.

Risperidone ISM study drug kits will be provided for the dose levels of 75 and 100 mg. Corresponding placebo study drug will also be provided. Risperidone ISM and corresponding placebo kits will be labelled appropriately.

5.1.1.1 Justification of Selected Doses

Results from previously conducted phase I and phase II studies as well as pharmacokinetic modeling are considered to support the doses selected for this study (see Section 1).

5.1.1.2 Oral Test Doses for Risperidone-Naïve Patients

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 hypersensitivity reactions before the first dose of IM study drug is administered.

A trial of oral risperidone is not required or indicated for patients who have previously taken any formulation of risperidone.

Risperidone tablets will be provided by study sponsor to all participating sites for risperidone-naïve patients testing.

5.1.2 Preparation and Administration of Study Drug

At each study site, during the double-blind treatment period (and until the Data Base lock of the Double-blind segment), each dose of study drug for each patient will be prepared individually by 1 or more identified members of the study site personnel; such designated individuals will be unblinded to the study drug identities and assignments to patients. An unblinded individual will also administer the IM injections of study drug to each patient in a manner that maintains the blind. The designated unblinded individuals must be considered appropriately experienced, trained, and qualified to perform these critical functions.

The study days on which administration of double-blind study drug injections are scheduled are study day 1, study day 29 (treatment week 4), and study day 57 (treatment week 8).

An unblinded study staff member will reconstitute the appropriate dosage of the study drug according to the instructions provided by the sponsor and will administer the study drug immediately after reconstitution.

For a given patient, each of the IM injections of study drug should be administered at approximately the same time of day, if possible. Generally, at a given study visit, the IM injection of study drug should be administered after efficacy evaluations have been performed and after any required blood samples (e.g., pharmacokinetic sample), if applicable at the given study visit, have been collected.

For each injection, the study drug should be injected slowly, deep into the muscle. Care should be taken to avoid inadvertent injection into a blood vessel. Each individual dose is to be administered in a single injection; divided injections are not permitted.

Generally, serial gluteal injections should be alternated between the 2 gluteal muscles, and serial deltoid injections should be alternated between the 2 deltoid muscles. However, the investigator may determine which injection site is most appropriate for a given patient.

The recommended needle size for administration of study drug into the gluteal muscle for most patients is the 2-inch 20 gauge needle. The injection should be administered into the upper-outer quadrant of the gluteal muscle.

The recommended needle size for administration of study drug into the deltoid muscle is 1-inch 21 gauge needle.

Risperidone ISM doses are summarized for each double-blind treatment group by study day in Table 4.

Table 4 Risperidone ISM Doses by Study Day

Study Drug Treatment Group	Study Day 1		Study Day 29		Study Day 57
Risperidone 75 mg	75 mg	→	75 mg	→	75 mg
Risperidone 100 mg	100 mg	→	100 mg	→	100 mg
Placebo	0 mg	→	0 mg	→	0 mg

ISM = in situ microparticle.
Note: During the conduct of the study, assignments of double-blind study drug treatments to patients will be under double-blind conditions and will not be revealed to investigators, study staff (except for specifically identified unblinded individuals only), or patients.

5.2 Study Site Inpatient Unit

A patient who, after completion of all scheduled assessments on the screening visit day, is considered provisionally eligible for participation in the double-blind segment of this study will be admitted directly to the inpatient study unit that day. Patients subsequently will remain on the inpatient study unit for the remainder of the screening period (i.e., through study day -1, inclusive).

All confirmed eligible patients will remain inpatient on study day 1. No patient should be discharged from the inpatient unit 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 to discuss the extension.

De novo patients entering the extension segment of the study are not planned to be admitted to the inpatient study unit.

5.3 Treatment Assignment and Blinding

5.3.1 Treatment Assignment

Upon confirmation of eligibility for a given patient to participate in the double-blind segment of the study, a unique randomization number for that patient will be assigned via an interactive voice or web response system 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) that 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 study completion and subsequent locking of the study database.

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 patient's randomization number must not be reused for any other patient).

5.3.1.1 Extension Segment of the Study

In the extension segment 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 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. 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.

De novo patients participating in the extension segment 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 an interactive voice or web response system that is to be accessed by study site personnel immediately after confirmation of patient eligibility has been recorded.

5.3.2 Blinding

During the double-blind segment 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 during the whole study in order to keep the blinding. The placebo and Risperidone ISM doses are practically indistinguishable before or after reconstitution. Reconstitution follows 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 an interactive voice or web response system based on the above described criteria (see Section 5.3.1.1) so that both investigator and patient can know the treatment administered, consistent with the open-label definition of this segment of the study.

Nevertheless, the management of the study drug will be performed by different study personnel (see Section 5.4). Only designated unblinded individuals at sites 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, if applicable for a given patient, will be administered under open-label conditions.

5.3.2.1 Breaking the Blind

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 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 interactive voice or web response system 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.

5.3.2.2 Extension Segment of the Study

All patients who participate in the optional extension segment of the study will receive active Risperidone ISM (i.e., 75 or 100 mg; see Section 5.3.1.1) 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 be still blinded at least up to locking the aforementioned database. For de novo patients, the corresponding IMP kit will be assigned via interactive voice or web response system based on the above described criteria (=4 mg or >4 to 6 mg oral risperidonesee Section 5.3.1.1) so that both investigator and patient can know the treatment administered, consistent with the open-label definition of this segment of the study.

5.4 Study Drug Accountability, Adherence, Handling, and Disposal

The clinical site is required to maintain current drug dispensation and accountability logs throughout the study for study drug.

The study drug injections will be reconstituted and administered directly by appropriately qualified and trained unblinded study site personnel until the Data Base lock of the Double-blind segment. The date and time of each study drug administration will be recorded for each patient and as such will serve to document adherence.

Unused supplies will be checked against study drug records periodically throughout the study.

After completion and verification of accountability logs by the study monitor, all remaining study drug must be destroyed. Packages may be destroyed on site according to Good Clinical Practice (GCP) and site practice; alternatively, the sponsor may arrange for destruction with a third-party vendor operating in accordance with GCP.

The same procedure applies to risperidone tablets provided for risperidone-naïve patients testing, as applicable.

6 Procedures

The overall schedules of assessments and procedures by visit are displayed in Table 1, Table 2, and Table 3.

A by-visit list of assessments and procedures is provided in Appendix A.

6.1 General

6.1.1 Informed Consent

During the screening visit, the nature of the study and anticipated risks and benefits of participation will be explained to the patient by the investigator or designated study personnel. Each patient will receive an informed consent form that summarizes pertinent study information and will be given ample time to read it and to ask questions about the study. If a patient chooses to participate, the patient must sign the informed consent form before any study-specific procedures are conducted (see Section 10.3).

Screen Failure patients (applicable for patients entering the double-blind segment and de novo patients entering the extension segment) can be considered to be allowed for Re-Screening purposes as long as they have previously been discussed between the Principal Investigator and the Medical Monitor. More than 14 days, from the initial ICF signature, should be elapsed and all the procedures required (except the Ophthalmological examination, if this is not the reason of the re-screening), including the signature of a new ICF, should be repeated within the established screening period. In these specific cases a new ID number will be assigned.

6.1.2 Demographics, Medical History, and Psychiatric History

To determine eligibility during screening, the patient's demographic data, medical history, and psychiatric history will be reviewed and documented. At later visits, each patient's medical and psychiatric history since the prior visit will be reviewed and any significant change will be recorded in the source documents and electronic case report form (eCRF) as an AE as appropriate.

6.1.3 Concomitant Medication Review

At screening, patients will be asked about all medications they have taken in the last 30 days, including prescription and nonprescription medications, vitamins, and supplements.

Patients will also be asked about any long-acting injectable antipsychotic medications taken in the last 60 days (see inclusion criterion 6 in Section 4.1.1.1, exclusion criterion 17 in Section 4.1.1.2, inclusion criterion 5 in Section 4.1.3.1, and exclusion criterion 17 in Section 4.1.3.2) as well as any past use of risperidone (see exclusion criteria 1 and 4 in Section 4.1.1.2, and exclusion criteria 1 and 3 in Section 4.1.3.2). Patients will also be asked about any history of failure to respond to adequate trials of antipsychotic medications, as well as about any history of clozapine use (see exclusion criterion 2 in Section 4.1.1.2 and Section 4.1.3.2). The investigator will record in the eCRF the use of all medications taken in a period of 30 days prior to the trial, and the use of any long-acting injectable antipsychotic medications taken in the period of 60 days prior to the trial.

At each subsequent visit, enrolled patients will be asked about use of concomitant medications since the previous visit. Any new medications or changes in previously recorded medications will be documented. The investigator will record the following data on all medications used by the patient: medication name, dose, regimen, route of administration, start and stop dates, and the indication for use.

6.1.4 MINI International Neuropsychiatric Interview for Schizophrenia and Psychotic Disorders Studies

The MINI International Neuropsychiatric Interview for Schizophrenia and Psychotic Disorders studies, version 7.0.2 (see Appendix C) will be completed at the screening visit to verify schizophrenia and any other psychiatric diagnoses according to the DSM-5 (see inclusion criterion 4 and exclusion criterion 9 in Section 4.1.1 and Section 4.1.3).

6.2 Efficacy Assessments

6.2.1 Positive and Negative Syndrome Scale and Clinician Global Impression

Efficacy assessments will include the PANSS, CGI-S, and Clinical Global Impression – Improvement (CGI-I). The PANSS, CGI-S, and CGI-I are performed at scheduled time points throughout the treatment period as indicated in Table 1, Table 2 and Table 3.

The investigator or qualified designee will complete these scale ratings.

The PANSS total score is defined as the sum of scores on the PANSS positive, negative, and general psychopathology subscales. The PANSS results will be used for the primary efficacy variable (Section 6.7.1.1) as well as secondary variables (Section 6.7.1.2).

6.3 Health Economics and Outcomes Research Assessments

6.3.1 Healthcare Resource Utilization

Healthcare resource utilization data will be collected in 2 ways: site-based reporting and patient-based (or informant-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 in following categories is collected: medication, emergency visits, inpatient services, outpatient services (specialist consultations and other outpatient hospital care contacts), and therapy. During the double-blind phase, clinician-reported data will be recorded once at 3 months (see Table 1). During the open-label extension, data will be recorded every 6 months for a total of 2 measurement points (see Table 2 and Table 3).

Study site staff will administer a survey to patients (or their informant) to report any HRU that occurred outside the clinical trial center. The patient survey will be administered at the clinical trial center by designated study site staff (paper and pencil). The information will subsequently be recorded into the applicable forms of the eCRF. Detailed resource use in the following categories is collected: medication, emergency visits, inpatient services, outpatient services, therapy, community-based day services, primary and community care contacts, criminal justice services, and days absent from work due to illness. During the double-blind phase, patient- (or informant)-reported data will be administered every month for a total of 3 measurement points (see Table 1). During the open-label extension, the survey will be administered every month for a total of 12 measurement points (see Table 2 and Table 3).

Clinician-reported and patient- (or informant)-reported HRU will be combined for analysis. For each item, total quantity of resources used will be calculated as the sum of resources both within and outside the participating center during the double-blind and open-label extension phases, respectively. This will define the secondary HRU variables (Section 6.7.2).

6.3.2 Health-Related Quality of Life

Health-related Quality of Life will be assessed by the patient-completed 20-item Subjective Well-Being Under Neuroleptics Treatment Scale (SWN-20). The SWN is a 38-item instrument developed to measure subjective effects of neuroleptic medications in patients with schizophrenia and consists of 20 positive statements and 18 negative statements.[11] The short form of the SWN, the 20-item SWN-20, was developed in order to allow for quick assessment of subjective side effects in a clinical setting.[12] Like in the original SWN, with 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 subscales: mental functioning, self-control, emotional regulation, physical functioning, and social integration. Each subscale 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, Table 2 and Table 3. The baseline administration of the SWN-20 should occur prior to the administration of the medication dose on study day 1 (double blind segment) or extension study day 1 (de novo patients in the extension segment).

6.3.3 Social Functioning

Social functioning will be assessed by the clinician-administered Personal and Social Performance Scale (PSP). The PSP is a 100-point single-item rating scale that is based on 4 areas: family and social functioning, self-care, work and socially useful activities, and disturbing and aggressive behaviors.[13] Higher scores indicate better social functioning. The PSP will be administered by a trained clinician, either the study investigator or a qualified designee. The PSP will be performed at scheduled time points throughout the treatment period as indicated in Table 1, Table 2 and Table 3. The baseline administration of the PSP should occur prior to the administration of the medication dose on study day 1 (double blind segment) or extension study day 1 (de novo patients in the extension segment).

6.4 Safety Assessments

Safety assessments will include AEs, vital signs (blood pressure, pulse rate, respiratory rate, and body temperature), weight, body mass index, laboratory tests (i.e., hematology, chemistry [including prolactin], urinalysis, urine drug screen), ECGs, physical examinations, injection site reactions, and selected safety scales. Safety scales will include the C-SSRS and the following 3 scales to assess extrapyramidal symptoms: the Abnormal Involuntary Movement Scale (AIMS), the Barnes Akathisia Rating Scale (BARS), and the Simpson-Angus Scale (SAS).

6.4.1 Physical Examination, Body Height, Weight

A physical examination will be performed at time points identified in Table 1, Table 2 and Table 3. The physical examination will include assessment of the following: general appearance, skin, lymphatic, eyes, ears, nose, throat, neck, respiratory, cardiovascular, gastrointestinal, musculoskeletal, and neurological.

Body height (cm) will be measured at screening only. Body weight (kg) will be measured at time points identified in Table 1, Table 2 and Table 3.

The body mass index value at each of these time points will be calculated; the body mass index value must be within the range of 18.5 to 40.0 kg/m^2, inclusive, at screening.

6.4.2 Ophthalmological Examination

The Risperidone ISM formulation is composed of risperidone and 2 excipients: PLGA and DMSO. Although DMSO is widely used in the pharmaceutical product formulations for topical, subcutaneous, and intravenous dosage forms and during pharmaceutical manufacturing processes, there have been published reports of toxicity to the eyes in animals treated with DMSO, including crystalline lens opacity. Therefore, an ophthalmological examination of study patients is required. All efforts should be made to have both examinations performed by the same ophthalmologist in order to get consistent data.

An ophthalmological examination will be performed at any time during the screening period of the double-blind segment of the study, and the result must be available by study day -1. This examination needs to be done again at visit 14 or at an early termination visit during the Double-blind period.

Ophthalmological examination includes best corrected visual acuity, visual field, intraocular pressure (IOP) measurements, and slit-lamp biomicroscopy examination of the eyelids, conjunctiva, iris, crystalline lens, sclera, and cornea.

Slit-lamp examination must be performed prior to IOP measurements or instillation of the fluorescein agent.

6.4.2.1 Best Corrected Visual Acuity Testing

A standard procedure is to be used to obtain best corrected visual acuity measurements. This activity may be performed by an optometrist, ophthalmologist, or certified ophthalmic technician.

6.4.2.2. Slit-Lamp Examination (Biomicroscopy)

A slit-lamp examination of the eyelids, conjunctiva, iris, crystalline lens, sclera, and cornea will be performed without pupil dilation (unless needed). Any abnormalities will be graded as mild, moderate, or severe. Any abnormality found during the slit-lamp examination should be noted.

Presence of cataract (absent, mild, moderate, severe), aphakia, or intraocular lens (anterior chamber intraocular lens, posterior chamber intraocular lens, or iris clip) and status of the posterior lens capsule (intact, open, or absent) should be specified. Slit-lamp examination should precede IOP measurement.

6.4.2.3. Intraocular Pressure

The IOP will be measured by a routinely used applanation tonometer. Study sites should calibrate the applanation tonometer according to the manufacturer's instructions. The IOP in both eyes will be measured, with the right eye preceding the left eye. If it is a routine practice at the site, a non-contact air-puff tonometry can also be used.

6.4.2.4. Visual Fields

The visual field will be examined using a standard procedure at the site. The recommended visual fields examination is automated perimetry including Humphrey (24-2 full threshold, 24-2 SITA standard, 30-2 central threshold, [Note: 24-2 SITA fast not allowed]) and Octopus (GI dynamic strategy, GI normal strategy, 24-2 dynamic strategy, 24-2 normal strategy) perimetry.

If this procedure was performed within the past 90 days and documented in the patient's medical record, this procedure need not be repeated (unless the investigator suspects a change). This may be performed by a trained certified ophthalmic assistant, certified ophthalmic technician, nurse, or research coordinator.

6.4.3 Vital Signs

Vital signs will include blood pressure, pulse rate, respiratory rate, and body temperature.

Vital signs will be measured at time points identified in Table 1, Table 2 and Table 3.

At each of these time points, 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 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.

Efforts should be made to take all blood pressure and pulse rate measurements from the same arm (preferably the patient's dominant arm) throughout the study. The same blood pressure cuff should be used to measure blood pressure each time. Automated measurement is preferred, but if measurements are performed manually, pulse rate will be measured in the brachial artery for at least 30 seconds.

6.4.4 Electrocardiogram

A 12-lead ECG will be performed at the study visits identified in Table 1, Table 2 and Table 3.

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 post-dose.

All scheduled ECGs must be performed after the patient has rested quietly for at least 5 minutes in the supine position.

Absolute values for QT intervals should be automatically corrected for heart rate by the ECG machine using both Bazett's fomula (QTcB) and Fridericia's formula (QTcF).

The ECGs will be evaluated by a central reader. Additional details regarding recording and evaluation of ECGs will be described in a manual provided to the study site.

6.4.5 Laboratory Assessments

Blood and urine samples for laboratory assessments will be collected at screening and at time points identified in in Table 1, Table 2 and Table 3.

Samples will be collected in accordance with the study site's usual procedures and analyzed by a central laboratory.

In the event of abnormal laboratory test values, follow-up samples may be obtained for repeat testing if deemed clinically indicated by the investigator.

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.

Additional details regarding laboratory sample collection and processing will be described in a manual provided to the study site.

6.4.5.1 Hematology

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

6.4.5.2 Chemistry

The chemistry panel includes the following tests:

- 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, alanine aminotransferase, aspartate aminotransferase, lactic dehydrogenase, gamma-glutamyl transferase, alkaline phosphatase, and creatine phosphokinase
- Prolactin (see Section 6.4.9.3)
- Hemoglobin A1c
- Thyroid-stimulating hormone
- Lipid panel: low-density lipoprotein, high-density lipoprotein, total cholesterol, and triglycerides

6.4.5.3 Urinalysis

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

6.4.5.4 Other Laboratory Tests

6.4.5.4.1 Serology

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.

6.4.5.4.2 Pregnancy Testing

A serum pregnancy test will be performed for all women at screening. Results must be negative for initial study eligibility. Urine pregnancy test (dipstick) will be performed on site for all women at baseline and subsequently at time points identified in Table 1, Table 2 and Table 3. Results at baseline must be negative for initial study eligibility.

Results must be negative for continued participation. On each IM study drug dosing day, the urine pregnancy test must be performed and a negative result confirmed before the scheduled dose of study drug for that day is administered.

A serum pregnancy test is not required during the open-label extension stage but may be performed. The investigator may order a serum pregnancy test at any time according to her or his judgment.

6.4.5.4.3 Drug Screening

A urine drug screen for prohibited substances will be performed at time points identified in Table 1 and Table 3 (mandatory at screening and baseline) and on as-needed basis as indicated in Table 1, Table 2 and Table 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 THC, alcohol, and benzodiazepines.

Urine drug screen will be performed at each scheduled timepoint and the collected sample will be sent to the central laboratory for analysis. In addition, onsite dipstick urine drug screen testing may be optionally performed on the sample collected.

Results at screening or baseline indicating the presence of a prohibited substance will exclude a patient from further participation in the study (see Section 3.2.2.1.1.4 and exclusion criterion 13.h in Section 4.1.1.2 and Section 4.1.3.2).

If a patient has a positive result for benzodiazepines, the investigator should determine if benzodiazepine use was medically indicated; a positive benzodiazepine result may not be exclusionary if the investigator determines that the benzodiazepine use is clinically appropriate and is not indicative of abuse (see Section 4.1.1.2 and Section 4.1.3.2).

A positive result for THC and/or alcohol generally is to be considered exclusionary; however, such a finding may not necessarily be exclusionary in certain cases only if exclusion criterion 9 is not met and only if the medical monitor provides approval.

6.4.6 Injection Site Reactions

Approximately 1 hour after an injection, the investigator will inspect the injection site where the study drug has been administered for redness, swelling, and induration. The investigator will also observe all injection sites where IM study drug has been injected on previous visits. At the same time (approximately 1 hour after injection), the study patient will perform and record self-assessment of pain at the injection site using a visual analog ccale (VAS; see Appendix D). If clinically significant, the injection site reaction will be recorded as an AE and the nature, duration, intensity, and relationship to the study drug will be recorded.

Any injection site reaction that occurs outside the schedule established in Table 1, Table 2 and Table 3 will be recorded as AE.

6.4.7 Extrapyramidal Symptoms Rating Scales

Extrapyramidal symptoms rating scales will include the AIMS, BARS, and SAS. The investigator or designee will complete the set of abnormal movement rating scales at time points identified in Table 1, Table 2 and Table 3. Clinically significant changes from baseline in extrapyramidal symptoms are to be recorded as AEs.

6.4.8 Columbia-Suicide Severity Rating Scale

The investigator or designee will complete the C-SSRS at time points identified in Table 1, Table 2 and Table 3.

At screening, the baseline version will be administered. At subsequent visits, the since-last-visit version will be administered.

The C-SSRS results for each patient should be reviewed by the investigator at each applicable visit. If at any time the C-SSRS results for a given patient reveal potential suicidality, the investigator should assess the clinical significance of such results. If a clinically significant risk of suicidality is identified for a patient, the investigator should consider further clinical evaluation of that patient and implementation of appropriate clinical measures as deemed indicated to help ensure patient safety.

Clinically significant changes from baseline in the level of suicidality are to be recorded as AEs.

6.4.9 Adverse Events

An AE is any symptom, physical sign, syndrome, or disease that either emerges during the study (from the informed consent form signature) or, if present at screening, worsens during the study,

regardless of the suspected cause of the event. All medical and psychiatric conditions (except those related to the indication under study) that are present at screening will be documented on the appropriate page of the eCRF. Changes in these conditions and new symptoms, physical signs, syndromes, or diseases are to be noted on the source documents and the AE page of the eCRF during the rest of the study. Clinically significant laboratory abnormalities are also to be recorded as AEs.

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.

Adverse events may be volunteered spontaneously by the patient, discovered as a result of general questioning by the study staff, or determined by physical examination. At each study visit, the patient will be asked the open-ended question, "Have you experienced any health problems since your last visit?" All AEs will be recorded on the source documents and the eCRF. For all AEs, the investigator must pursue and obtain information that is adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification. If the AE persists, follow-up even after the date of therapy discontinuation is required until the event resolves or stabilizes at a level acceptable to the investigator. Patients will be instructed to contact the investigator at any time after randomization if any symptoms develop.

In order to avoid vague, ambiguous, or colloquial expressions, all AEs should be recorded in standard medical terminology rather than in the patient's own words. Each AE will also be described in terms of duration, frequency, intensity, association with the study drug, assessment of possible causes, actions taken, and outcome, using choices given on the eCRF. Specific guidelines for classifying AEs by intensity and by relationship to study drug are given below:

Classification of Adverse Events by Intensity
The severity (or intensity) of an AE refers to the extent to which it affects the patient's daily activities and will be classified as mild, moderate, or severe using the following criteria:

- Mild: An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities

When changes in the intensity of an AE occur within a day, the maximum intensity for that day should be noted. If the intensity category changes over a number of days, those changes should be recorded separately (with distinct onset dates).

Classification of Adverse Events by Relationship to Study Drug
The investigator's assessment of an AE's relationship to study drug is part of the documentation process but is not a factor in determining what is or is not reported in the study.

The investigator will assess causality (i.e., whether there is a reasonable possibility that the study drug caused the event) for all AEs and SAEs. The relationship will be characterized using the following classification:

- Suspected: The temporal relationship of the AE with the investigational medicinal product makes causality possible, and the AE cannot be due to another cause such as other drugs, a surgical intervention, or an underlying disease
- Not suspected: The temporal relationship of the AE with the investigational medicinal product makes causality improbable, and the AE may be due to another cause such as other drugs, surgical intervention, or underlying disease

6.4.9.1 Serious Adverse Events

An SAE is defined as any AE that meets 1 or more of the following criteria:

- The event is fatal or life threatening
- The event is permanently disabling (incapacitating or interfering with the ability to resume usual life patterns)
- The event results in unplanned inpatient hospitalization or prolongation of existing hospitalization
- The event is a congenital anomaly
- The event requires medical intervention of any kind in order to prevent any of the aforementioned outcomes

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An AE is considered "life threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

An SAE is not necessarily severe; for example, an overnight hospitalization for a diagnostic procedure must be reported as an SAE even though the occurrence is not medically serious. By the same token, a severe AE is not necessarily serious: nausea of several hours' duration may be rated as severe but may not be considered serious.

Protocol-allowed psychiatric inpatient stays (e.g., during the screening period and for up to 2 weeks during the first part [administration] of the treatment period or longer if needed) will not be reported as AEs. Subsequent hospitalizations will be recorded and tracked as SAEs.

6.4.9.2 Reporting Adverse Events

The investigator is responsible for recording all AEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance. If there is any doubt as to whether a clinical observation is an AE, the event should be recorded.

All AEs, regardless of causality and severity, occurring during the conduct of the clinical trial whether observed by the investigator or spontaneously reported by the patient or in response to an open-ended question about any medical problems since the last visit, must be recorded in the source document and in the relevant section of the eCRF. Adverse events will be recorded from informed consent signature until completion of the final follow-up visit.

Any SAE due to any cause, whether or not related to the study drug, must be reported within 24 hours of occurrence or when the investigator becomes aware of the event. The investigator must send a preliminary report of the SAE to the ROVI Pharmacovigilance Department by fax/email within 24 hours (see Appendix F), using an SAE Report Form.

ROVI Pharmacovigilance Department
Phone: +34 917617561/+34 911863678
Fax: +34 912444421
Email: farmacovigilancia@rovi.es

The event must also be recorded on the standard AE eCRF page. Preliminary reports of SAEs must be followed by detailed descriptions, including legible photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable. The SAE reports must be made whether or not the investigator considers the event to be related to the study drug.

Appropriate remedial measures should be taken to treat the SAE, and the response should be recorded. Patients must be closely followed until sufficient information is obtained to indicate a return to normal status or until the event stabilizes at a level acceptable to the investigator.

Clinical, laboratory, and diagnostic measures should be employed as needed in order to determine the etiology of the event. For this purpose, additional blood samples (as needed) will be collected and analyzed whenever an SAE is identified until the event stabilizes at a level acceptable to the investigator. The results must be reported promptly to the sponsor.

During the double-blind part of the study and until Data Base lock (of the double-blind part), this process must be conducted in a manner that maintains blinding of study drug assignment.

As information is available, a pregnancy diagnosed during a patient's active participation in the study (and any voluntarily provided notice of a pregnancy that is received within 6 months after a patient's last dose of study drug) as patients staff that is will be reported immediately to the sponsor or designee, including pregnancy in female partners of male patients. The pregnancy may be followed to term and/or outcome, and this outcome may be reported to the sponsor. Pregnancy, in and of itself, is not regarded as an AE or SAE unless the birth results in a congenital anomaly/birth defect or there is suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication or method.

6.4.9.3 Other Significant Adverse Events

To ensure patient safety, the investigator should also notify the safety coordinator or medical monitor should any AE occur that is considered significant but does not meet the criteria for an SAE or that is considered unexpected. An unexpected AE is an AE that is not identified in nature, intensity, or frequency in the reference safety information of the investigator brochure. In addition, any field monitor who notes a significant AE or medical condition while reviewing eCRFs or source documents at the study site must immediately convey this information to the medical monitor.

An increase in prolactin plasma levels should be considered an AE when any of the following criteria are present:

- Values above 1000 mIU/L for 3 consecutive determinations after randomization, although no clinical symptoms are present

- Values above 530 mIU/L if clinical symptoms of hyperprolactinemia are present (e.g., headache, decreased libido, oligo-amenorrhea)

However, where patients have prolactin concentrations above the upper limit of normal at screening, the following criteria could be used by the investigator as a guideline:

- For patients at screening with prolactin blood levels above the normal limit, an increase of prolactin from baseline (day 1, pre-dose) values is recommended to be considered as an AE when the patient presents 3 consecutive determinations with a prolactin value above 1000 mIU/L, if the increase is > 20% even though no other clinical symptoms are associated
- For patients at screening with prolactin blood levels above 1000 mIU/L, it is recommended to consider it as an AE when there is an increase > 20% of the baseline (day 1, pre-dose) level in 3 consecutive determinations even though no other clinical symptoms are associated

As a general rule, it should be considered that the "hyperprolactinemia" event has finished the day when a prolactin value lower to 1000 mIU/L is obtained, or when levels return to the basal value for patients with prolactin concentrations above the upper normal limit at screening.

- The day and time of the determination should be recorded in the eCRF. It has to be noted that same date could be registered as the end of hyperprolactinemia for 1 event (AE #1) and the start of another hyperprolactinemia for another event (AE #2). As an example: if the day when 4 prolactin determinations are made matches that in the first determination the hyperprolactinemia has finished (AE #1) but after the injection of Risperidone ISM, a new event of hyperprolactinemia (AE #2) is considered as started (as per protocol), and that date should be registered as the date of the end of AE #1 and start date of AE #2. The times of finalization and starting of both events should be recorded.

To this end, the date of the third abnormal determination will be considered as the start date of the AE.

Those patients with values out of range that are considered an AE will be monitored either until the values do not fulfill the aforementioned AE criteria or stabilize at a level acceptable to the investigator.

6.5 Pharmacokinetic Sample Collection

During the double-blind segment of the study, pharmacokinetic samples will be collected from all patients participating in the study in a manner that maintains the double-blind with respect to patient treatment assignment. All patients will have pharmacokinetic samples collected on days 1, 3, 29, 31, 57, 59, and 85 (visits 2, 3, 8, 9, 11, 12, and 14, respectively). Additionally, 75 patients irrespective of randomized treatment will be selected to have additional sampling on days 8, 15, and 22 (visits 5, 6, and 7, respectively). In addition, pharmacokinetic samples will be collected at the time of an SAE.

In order to maintain study drug blinding, at the selected study sites, pharmacokinetic samples will be collected from all enrolled patients (regardless of treatment assignment); however, only samples from patients receiving active Risperidone ISM will be analyzed.

A blood sample (approximately 4 mL each) for measurement of concentration in plasma of risperidone and its active metabolite (9-OH-risperidone) will be obtained at time points shown in Table 1.

These pharmacokinetic samples will be obtained before administration of study drug as applicable (i.e., on study days when pharmacokinetic samples and study drug administration both occur). Pharmacokinetic blood samples will be processed at the study site (e.g., centrifugation, separation of plasma, and freezing) according to instructions that will be provided to the study site in a manual. Contact information and sample handling and shipment instructions will be described in the manual.

Pharmacokinetic samples from patients receiving active Risperidone ISM will be analyzed by a central laboratory; however, the samples from patients receiving placebo will not be analyzed (they are collected nevertheless in order to maintain the double-blind). The process for this selective pharmacokinetic analysis will be performed in a manner than maintains the double-blind with respect to patient treatment assignment.

6.6 Genotype Sample Collection

Genotype samples will be collected from all patients who will sign the appropriate consent in the double-blind segment of the study.

A separate informed consent form for participation genotype sample collection must be signed before any blood samples for genotype assessment sample are collected for a given patient.

A single blood sample will be collected from each patient for evaluation of genotypes for cytochrome P450 enzymes and/or genes considered potentially related to response. The blood sample for genotype testing may be collected at any time point after randomization during the Double-blind period.

6.7 Outcome Variables

6.7.1 Efficacy Variables

Efficacy variables are listed within this section. In this context, endpoint is defined as study day 85 or the last post-baseline double-blind assessment.

6.7.1.1 Primary Efficacy Variable

The primary efficacy variable is the following:

- PANSS total score mean change from baseline to endpoint

6.7.1.2 Secondary Efficacy Variables

6.7.1.2.1 Key Secondary Efficacy Variable

The key secondary efficacy variable is the following:

- CGI-S score mean change from baseline to endpoint

6.7.1.2.2 Other Secondary Efficacy Variables

Other secondary efficacy variables include the following:

- 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

        - 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

6.7.2 Health Economics and Outcomes Research Variables

Health economics and outcomes research variables are listed within this section. In this context, endpoint is defined as study day 85 or the last post-baseline double-blind assessment.

- 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, 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 direct medical costs at endpoint and average cost per 3 months will be calculated.
    - Indirect costs (days absent from work due to illness) at endpoint
- PSP total score mean change from baseline at each post-baseline assessment time point
- PSP domain score mean change from baseline at each post-baseline assessment time point
- 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

6.7.3 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 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, BARS, and AIMS
- C-SSRS

- Physical examination, vital signs, weight, body mass index, clinical laboratory test results, and ECG findings
- Time to early termination

6.7.4 Pharmacokinetic Variables

The pharmacokinetic variables are the following:

- Summary plasma concentrations of risperidone, its active metabolite (9-OH-Risperidone), and the active moiety (i.e., 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
- Exploratory associations of pharmacokinetic results with efficacy results

6.7.5 Genotype Sampling

For all study patients who consent to collecting genotype sample and sign a separate consent form, a blood sample will be collected for evaluation of genotypes for cytochrome P450 enzymes and/or genes that are potentially related to efficacy response and/or adverse effects. The sample may be obtained at any point after randomization occurs during the Double-blind period. The samples will be tested for all patients for correlation with pharmacokinetic and/or efficacy results.

7 Statistics

7.1 General Considerations

The statistical analysis methods are described below and refer to the main (double-blind) part of the study. Additional details will be provided in a separate Statistical Analysis Plan document, which will be finalized before database lock and unblinding of the study. Analysis for the extension segment of the study will be descriptive only.

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. Source data for the summary tables and statistical analyses will be presented as patient data listings.

Baseline in the main (double-blind) part of the study will be defined as last non-missing observation before first dose of study drug. Baseline in the extension segment of the study will be defined as last non-missing observation before first dose of Risperidone of the extension segment of the study.

7.2 Analysis Populations

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.

The safety population will include all patients who receive at least 1 dose of study drug. Analyses performed on the safety population will be as treated.

The modified safety population will consist of all patients in the safety population for whom blinding was not potentially compromised. Analyses performed on the modified safety population will be as treated. This population will be used for selected safety analyses.

The intent-to-treat (ITT) population will consist of all randomized patients who received 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, including health economics and outcomes research endpoints.

The modified intent-to-treat (mITT) population will consist of all patients in the ITT population for whom blinding was not potentially compromised. Analyses performed on the mITT population will be as randomized. The mITT population will be used for analyses of efficacy endpoints.

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 treatment period and have no major protocol deviations that may impact the primary efficacy variable. Patients will be analyzed according to assigned treatment. The PP population will be used for supporting analyses of efficacy endpoints.

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

The pharmacokinetic 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 affect plasma concentration data, 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 confirmed with sponsor. An intense pharmacokinetic subset of patients with additional samples measured after dose 1 will be used to evaluate non-compartmental pharmacokinetic parameters during dosing interval after dose 1.

Explanations for pharmacokinetic parameters that could not be estimated will be provided in the clinical study report as applicable.

Genotyping data will be listed and summarized for all patients in safety population if available.

A blinded data review meeting will be held before database lock and unblinding of the double-blind phase to clarify any open questions or doubts and agree upon the PP and pharmacokinetic populations. Attendees will include appropriate individuals from the sponsor and Contract Research Organization (CRO). All decisions will be documented. Details regarding the data to be reviewed at the meeting will be documented in the Statistical Analysis Plan, and a separate blinded data review meeting plan. Prior consideration will be given to ensure that no data will be reviewed which has potential to present blinding issues (e.g., pharmacokinetic concentration data). Reasons for excluding patients from the PP or pharmacokinetic population will be determined and documented before database lock. All patients satisfying the ITT and mITT population definition will be included in the respective efficacy analyses.

The open-label population will consist of all patients who received at least 1 dose of study drug in the extension segment of the study. Analyses performed on the open-label population will be as treated, and by double-blind segment treatment arm and de novo entry at the time of OLE phase.

7.3 Planned Analyses

7.3.1 Patient Disposition

The number of patients who enter and complete the main (double-blind) part of the study will be tabulated. Patients who fail to complete the main (double-blind) part of the study will be summarized and categorized by reason for termination. Similarly, the description of the patients' dispositions in the extension segment of the study (including whether the patient was a rollover or de novo patient) will be performed.

In addition, the numbers of patients randomly assigned to each study drug treatment and the number of patients included in each analysis population (e.g., safety, modified safety, ITT, mITT, PP, mPP, open label, and pharmacokinetic) will be summarized by treatment group, along with reasons for exclusion as applicable.

7.3.2 Demographics and Baseline Data

Demographics and baseline characteristics will be summarized by treatment group for safety, ITT, mITT, PP, mPP, open-label, and pharmacokinetic populations using descriptive statistics as described in Section 7.1.

Cytochrome P450 2D6 inferred metabolic status will be summarized and details of the genotype will be listed and summarized by treatment group for safety modified safety, ITT, mITT, PP, mPP, open-label, and pharmacokinetic populations using descriptive statistics. Predicted phenotypes will be determined following the activity score system published by Gaedigk et al (2008).[14] Patients with an activity score > 2 will be considered as ultra-rapid metabolizers, a value of 1.5 to 2 as extensive metabolizers, 0.5 to 1 as intermediate metabolizers, and a value of 0 as poor metabolizers.

Medical and psychiatric history will be summarized by treatment group for the safety and open-label populations.

7.3.3 Study Drug Administration

Study drug administration data will be summarized for all randomized patients by treatment group. Study drug administration data from the extension segment of the study will be similarly summarized for the open-label population.

7.3.4 Efficacy

Results for efficacy variables will be summarized by treatment group for the mITT, ITT and PP populations using descriptive statistics (see Section 7.1) for data obtained during the main (double-blind) part of the study. 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, the mITT will be used as the primary population to describe efficacy results in the CSR. For the primary and key secondary variables, results will also be summarized separately for stage 1 and stage 2 of the study (see Section 7.5).

Efficacy variables (PANSS, CGI-S, CGI-I) from the extension segment of the study will be summarized similarly for the open-label population, as applicable, for descriptive purposes.

To account for patients for whom the post-baseline endpoint (i.e., at the time when the last post-baseline double-blind assessment was performed) occurs at a time point before study day 85, a mixed effect model with repeated measurements (MMRM) using an unstructured covariance matrix approach will be used as the primary method. It is assumed that the majority of the missing values will be one of 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[17] and are already usual.[16]

If a patient has a PANSS assessment recorded, but any of the 30 items are missing, the last non-missing score for the respective item from previous assessments will be carried forward.[22] 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.

7.3.4.1 Primary Efficacy Variable Analyses

The primary efficacy analysis is designed to show superiority of active treatment versus placebo in the primary efficacy variable (Section 6.7.1.1).

Two hypotheses will be tested:

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

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

An MMRM approach 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. 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 will be presented.

In order to maintain the type 1 error rate for the primary analysis, each hypothesis will be tested using a weighted test statistic in accordance with Cui, Hung, Wang[18] (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).

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

To account for multiplicity of testing and to keep the type 1 error rate at 5%, the Hommel's closed-testing correction procedure[19] as implemented in SAS software (PROC MULTTEST) will be used to provide adjusted p-values to assess for superiority of either dose.

The primary efficacy analysis will be supported with sensitivity analyses. All sensitivity analyses will use the CHW and Hommel adjustment to present p-values. The MMRM (as above) and analysis of covariance (ANCOVA) models using both observed endpoint values and multiply imputed[20] study day 85 values will be performed for the mITT population. The ANCOVA models will include country where enrolled and treatment as fixed effects and baseline PANSS total score as a covariate.

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 using weights of sqrt(0.55) and sqrt(0.45) for stage 1 and 2 respectively.

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 a treatment by country or baseline PANSS total score (< 95 v ≥ 95) interaction as a fixed effect in order to explore the treatment differences within each country and baseline PANSS total score (< 95 v ≥ 95).

The unadjusted 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).

The effect of CYP2D6 phenotype on the primary efficacy variable will be assessed using subgroup analyses. Summaries will be repeated by CYP2D6 phenotype groupings (using combined data across stages). The MMRM applied to all data combined will be repeated with additional fixed effects for CYP2D6 phenotype and treatment-by-CYP2D6 phenotype interaction.

7.3.4.2 Secondary Efficacy Variables Analyses

7.3.4.2.1 Key Secondary Efficacy Variable Analyses

The key secondary variable will be analyzed at endpoint for the mITT and ITT population in a hierarchical order, taking multiplicity into account.

If, and only if, the primary efficacy analysis shows the superiority of the Risperidone ISM treatment versus the IM placebo treatment for both doses will the confirmatory testing be performed sequentially on the mITT and ITT population with regard to the key secondary efficacy variable (Section 6.7.1.2.1). Otherwise, all analyses for the key secondary efficacy variable will be deemed supportive/exploratory evidence.

The CGI-S mean change will be analyzed using identical methods as described for the primary, sensitivity and subgroup analyses of the primary efficacy variable (Section 7.3.4.1). The only exception to this will be that the baseline CGI-S will be used as a covariate in the MMRM/ANCOVA models instead of the baseline PANSS score.

7.3.4.2.2 Other Secondary Efficacy Variables Analyses

The other secondary efficacy variables (see Section 6.7.1.2.2) will be displayed as described in Section 7.1, in each treatment group and at each applicable visit on the mITT, ITT and PP populations. The analysis will be performed using only observed cases with both stages of the study combined.

The mean scores and their changes from baseline will be displayed for PANSS, PANSS subscales, CGI-S and CGI-I at each applicable post-baseline visit and endpoint. Treatments will be compared at each time point using a MMRM with country where enrolled, visit, treatment, and treatment-by-visit interaction as fixed effects and the respective baseline (PANSS will be used for CGI-I model) as a covariate. Each dose level of Risperidone ISM will be compared to placebo at each study day. Unadjusted p-values and 95% confidence intervals will be presented. For PANSS and CGI-S, the models applied as part of the primary and key secondary variable sensitivity analyses (on all data patient data combined) will be used for these comparisons.

Overall and PANSS response rates will be shown with exact (Clopper-Pearson) 95% confidence intervals at each respective time point and endpoint. 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 time to reach the overall or the PANSS response will be displayed graphically using Kaplan-Meier estimates. Pairwise comparisons of each dose level of Risperidone ISM to placebo will be conducted using a log-rank test stratified by country where enrolled and baseline PANSS total score (≥ 95 or < 95).

7.3.4.2.3 Efficacy Variables Analyses in the Extension Segment of the Study

The following efficacy parameters will be summarized in the extension segment of the study for the open-label population by treatment group and overall. There will be no formal statistical testing.

Durability of effect evaluations:

- PANSS total score
- Positive, negative, and general psychopathology subscale scores
- CGI-I score
- CGI-S score
- Overall response (as defined in 6.7.1.2.2)
- PANSS response (as defined in 6.7.1.2.2)
- 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
- Time to discontinuation

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

7.3.4.3 Health Economics and Outcomes Research Variables Analyses

Clinician-reported and patient-reported (or informant reported) HRU will be combined for analysis. When all data are missing for a time point, no imputation will take place. Analyses will be performed by study phase (double-blind vs. open-label). For analysis of each resource item and at each time point, non-zero missing data will be imputed using the Fully Conditional Specification procedure. Results for each HRU variable will be summarized by treatment group (placebo, two Risperidone ISM® arms, and all Risperidone ISM® combined) for the ITT and open-label populations using descriptive statistics, including 95% confidence limits. For each HRU variable, an average rate of use per 3 months will be calculated by treatment group, and potential differences between treatment groups will be tested. For analyses of the open-label population, de novo patients form a separate treatment group, and the rollover patients will be analyzed by their originally randomized treatment group in the double-blind segment.

Country-specific unit costs will be assigned to each resource use item and costs across all items will be summed to yield a total direct medical cost. Direct medical cost will be analyzed per individual

country for each resource use category and for all resource use categories combined for the ITT and open-label populations. The average cost per 3 months by treatment group will be calculated, and differences between treatment groups will be tested. Indirect costs (days absent from work due to illness) will also be analyzed per individual country. Parametric and nonparametric methods for cost analyses will be assessed. This may include bootstrapping technique to calculate 95% confidence intervals.

Details of HRU and cost analyses will be specified in the Statistical Analysis Plan.

The PSP and SWN-20 scores will be summarized by treatment group for the ITT and PP populations using descriptive statistics (see Section 7.1) for data obtained during the main double-blind segment of the study. The PSP and SWN-20 scores from the extension segment of the study will be similarly summarized for the open-label population, as applicable, for descriptive purposes.

Analyses of PSP and SWN-20 data will be according to instrument-specific guidance, as specified in the Statistical Analysis Plan.

7.3.5 Safety

All safety variables will be displayed as described in Section 7.1 for the safety (and modified safety for selected endpoints) population in the main (double-blind) part of the study and the open-label population in the extension segment 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.

Descriptive statistics will be used to summarize the changes from baseline in vital signs, body weight, body mass index, and safety scales (e.g., C-SSRS, SAS, AIMS, and BARS) for each treatment group at each visit as described in Section 7.1.

7.3.5.1 Adverse Events

Events that occur after a patient provides informed consent but before the time of the first dose of study drug will be considered pretreatment AEs. Treatment-emergent AEs are defined as events that are newly occurring or worsening from the time of the first dose of IM study drug. All AEs will be listed by patient but only treatment-emergent AEs will be included in summary tables. Reported AE terms will be coded using Medical Dictionary for Regulatory Activities preferred terms and system organ classes.

The incidence of treatment-emergent AEs will be summarized by treatment group and overall, by severity, and by relationship to study drug (for both safety and modified safety populations separately).

The summary tables will include the number and percentage of patients with treatment-emergent AEs together with the number of the respective treatment-emergent AE overall, by system organ class, and by preferred terms within each system organ class (for both safety and modified safety populations separately). Treatment-emergent AEs resulting in treatment discontinuation or modification will be identified and summarized by treatment group (for both safety and modified safety populations separately).

7.3.5.2 Vital Signs and Physical Examinations

Vital sign measurements (systolic and diastolic blood pressure [mmHg], pulse rate [beats/minute], respiration rate [breaths/minute], and body temperature [°C]) will be summarized by treatment group at each time point for the absolute value and for changes from baseline as described in Section 7.1. Orthostatic measurement data will also be summarized.

7.3.5.3 Weight and Body Mass Index

Weight (kg) and body mass index (kg/m^2) measurements will be summarized by treatment group at each time point for the absolute value and for changes from baseline.

7.3.5.4 Clinical Laboratory Tests

Laboratory test results, including prolactin results, will be summarized by treatment group at each time point for the absolute value itself and for changes from baseline. Tables showing the shift of clinically relevant abnormalities from baseline to endpoint will also be presented.

7.3.5.5 Electrocardiograms

QT, QTcB, and QTcF intervals will be calculated at each ECG assessment. Interval data will be summarized by treatment group at each time point for the absolute value and for changes from baseline. Additionally, QTcF values will be categorized and summarized, using the following QTcF value categories: increase from baseline > 30 msec, increase from baseline > 60 msec, as well as absolute values > 450 msec for males or > 470 msec for females.

Other ECG variables that are collected will be listed.

7.3.5.6 Extrapyramidal Symptoms Rating Scales

For the SAS, AIMS, and BARS, total scores and subcategory scores, as applicable, will be summarized by treatment group at each time point for the absolute value and for changes from baseline.

7.3.5.7 Columbia-Suicide Severity Rating Scale

Individual items of the C-SSRS will be summarized by treatment group at each time point by the number and percentage of patients responding to that item. Data will be summarized by treatment group.

7.3.5.8 Concomitant Medications

Concomitant medications will be categorized and presented using the World Health Organization Anatomical Therapeutic Chemical drug classification system. The number and percentage of patients using concomitant medications will be summarized by treatment group.

7.3.5.9 Injection Site Reactions

Injection site reaction data will be summarized by treatment group. The number and percentage of patients having reactions at each assessment time point will be presented.

7.3.5.10 Time to Early Termination

Time to early termination will be summarized by treatment group as described in Section 7.1. Additionally, Kaplan-Meier estimates will be displayed graphically.

7.3.5.11 Ophthalmological Examination

Data will be summarized by treatment group. The number and percentage of patients having changes from baseline will be presented.

7.3.6 Pharmacokinetics

Descriptive statistics will be used to summarize plasma concentrations of risperidone, its active metabolite (9-OH-risperidone), and the active moiety (risperidone plus 9-OH-risperidone), whenever possible, at each sampling time point by injection site (gluteal and deltoid) and by study drug dose.

Concentration values for all patients in the pharmacokinetic population will be listed.

Pharmacokinetic parameters, including C_{trough}, and accumulation index will be derived if possible, and results will be summarized as applicable. Plasma concentrations will be presented graphically.

A set of non-compartmental parameters will be estimated for a subset of patients after dose 1 (e.g., maximum concentration [C_{max}], time to C_{max} [T_{max}], area under the concentration-time curve for a dosing interval [AUC_{tau}], and others).

Association of SAEs with the measured pharmacokinetic concentration either planned or outside the regular schedule will be evaluated.

Comparisons of pharmacokinetic parameters between the gluteal and deltoid muscle injections will be performed.

Effects of the CYP2D6 phenotype on pharmacokinetic parameters in the complete pharmacokinetic population and in a subset with intense pharmacokinetic sampling will be evaluated.

A population pharmacokinetic analysis will be performed according to a separate pharmacokinetic analysis plan document.

7.4 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 Double-blind period.

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

The difference between the active treatments and placebo in the PANSS total score mean change from baseline to endpoint (primary efficacy variable; see Section 6.7.1.1) will be assumed as a 9-point decrease.

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 for a Risperidone ISM group 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 Section 1) and use of a less conservative multiplicity adjustment than Bonferroni (i.e., Hommel – see Section 7.3.4.1).

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, 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 7.5).

Taking into account the 43 patients for whom blinding was potentially compromised, 436 randomized patients in total will be required.

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

7.5 Sample Size Re-estimation/Interim Analysis

One unblinded interim analysis will be conducted when 196 (approximately 50%) randomized patients, for whom the blinding was not compromised, 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. The unblinded interim statistical analysis will be conducted by an independent statistical center.

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 7.3.4.1) 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 (M_2) as suggested by Cui et al. (1999)[18] as follows:

M_2 = 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[21] at interim <10%.

8 Data and Documentation

8.1 Data Handling and Record Keeping

8.1.1 Data Handling

The data obtained during the study should be transcribed faithfully from the source documents to the forms of the eCRF, as these data are considered valid information for further evaluation of the efficacy and safety of the treatment under investigation.

The sponsor or designee will provide the site with eCRFs. The investigator is to provide patient data according to the sponsor's instructions, in the designated data collection form, compliant with GCP practices. All data collection forms and the databases from the study are the exclusive property of the sponsor.

The investigator must maintain records and data during the study in compliance with all applicable legal and regulatory requirements. Records of the patient's participation in this study will be held confidential except as disclosure is required by law or as described in the informed consent document. If the results of this study are published or presented at meetings, the patients will never ever be identified. Each data point must be supported by a source document at the study site. Any records or documents used as the source of information (called the "patient source data") are to be retained for review by authorized representatives of the sponsor or a regulatory agency. In this study, eCRFs will be used. Further details may be provided in monitoring guidelines, as applicable.

The investigator will ensure that there are sufficient time, staff, and facilities available for the duration of the study to conduct and record the study as described in this protocol and according to all applicable guidances, laws, and regulations.

All data collection forms, such as eCRFs, should be completed as soon as possible after the evaluation has occurred. All dates appearing on the sponsor's patient data collection forms for laboratory tests, cultures, and other data collected must be the dates on which the specimens were obtained or the procedures performed.

Within 1 week (or other agreed timeframe) of study completion by each patient, the investigator should agree to have the patient's eCRF available for inspection by the field monitor.

8.1.2 Data Recording

This study will use eCRFs for recording data. All entries, corrections, and alterations will be made by the investigator or other authorized study personnel, and all data entries will be verified for accuracy and correctness. The electronic data capture system will maintain an audit trail.

Source documents will remain at the study site.

8.1.3 Inspection of Records

The sponsor or its representative will be allowed to conduct site visits to the investigational facilities for the purpose of monitoring any aspect of the study. The investigator must agree to allow the unblinded or blinded monitor as applicable to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and source documents, and other records relative to study conduct.

8.1.4 Retention of Records

Retention and storage of essential clinical study documents (e.g., worksheets, drug accountability forms, and other administrative documentation) will be according to the clinical study agreement as applicable.

Sponsor-specific essential documents should be retained until at least 25 years after the last approval of a marketing application in an International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or if needed by the sponsor.

Medical files should be retained in accordance with the applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution, or private practice.

8.1.5 Use of Information and Publication Policy

Data generated in this study are proprietary information that is the sole property of the sponsor. Results of the study are to be held in confidence by both the investigators and the sponsor.

The clinical study report will be issued at 2 time points: the first will have the data from the double-blind phase of the trial, and the second will be issued after the open-label extension phase of the study is completed and will contain all study data (both double blind and open label).

Please refer to the clinical study agreement for details on the procedures for publishing and presenting data.

8.2 Source Materials Access

8.2.1 Study Monitoring

Monitoring of the study site (including, but not limited to, reviewing eCRFs for accuracy and completeness) will be performed by a study monitor.

Blinded and unblinded monitors may be involved in the study site monitoring process, and each will interact with blinded and unblinded study site staff in a manner that maintains the blind for all blinded individuals until the Data Base lock of the Double-blind period.

8.2.2 Institutional Review Board

The investigator must obtain Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approval for the investigation. Initial IRB/IEC approval as well as all materials approved by the IRB/IEC for this study, including the patient informed consent form and recruitment materials, must be maintained by the investigator and made available for inspection.

8.2.3 Audits and Inspections

Authorized representatives of the sponsor, a regulatory authority, and/or an IRB/IEC may visit the site to perform audits or inspections, including the drug storage area, study drug stocks, drug accountability records, patient charts and source documents, and other records relative to study conduct. The purpose of a sponsor audit or inspection is to systematically and independently examine study-related activities and documents (e.g., laboratory reports, radiographs, workbooks, patients' medical records) to determine if these activities were conducted and if data were recorded, analyzed, and accurately reported according to the protocol, ICH GCP guidelines, and any applicable regulatory requirements.

The investigator should contact the sponsor and/or CRO immediately if contacted by a regulatory agency regarding an inspection.

9 Quality Control and Assurance

This study will be conducted under GCP and applicable regulatory requirements. To ensure compliance, the sponsor may conduct a quality assurance audit.

9.1 Data Collection

The eCRFs will be completed by study site staff before review by the study monitor. All eCRFs will be reviewed by the investigator, as noted by his or her electronic signature, after review by the sponsor monitor or designated representative. The sponsor monitor or designated representative will review all source records onsite and compare them with the data collected on the eCRF.

As specified in Section 6.2.2, study site staff will retrospectively record any HRU that occurred within the clinical trial center into the applicable forms of the eCRF. Study site staff will administer a paper survey to patients (or their informant) to report any HRU that occurred outside the clinical trial center. The information will subsequently be recorded into the applicable forms of the eCRF.

Results of the clinician-administered PSP will be collected on the eCRF. Patients will complete the SWN-20 on paper, and the data will be entered into the eCRF by study site staff.

9.2 Confidentiality

The investigator must maintain in confidence information provided to him or her by the sponsor and will divulge such information to his or her respective IRB/IEC under an appropriate understanding of confidentiality with that body.

All data are considered the sole property of the sponsor.

10 Ethical Considerations

10.1 Ethics Review

The clinical site's IRB/IEC must meet all relevant regulatory requirements. The study protocol and informed consent form will be reviewed by the IRB/IEC before enrolling patients into the study; written approval from the committee must be received by the sponsor before study drug will be released to the investigator. The protocol must be re-approved by the IRB/IEC upon receipt of amendments and annually, as local regulatory requirements require.

The investigator is responsible for submitting all protocol changes and SAE reports to the IRB/IEC according to local procedures. At a minimum, all SAEs requiring an investigational new drug safety report must be immediately reported. All relevant correspondence from the IRB/IEC will be forwarded by the study site to the sponsor in a timely manner.

10.2 Ethical Conduct of the Study

This study must be conducted in accordance with this protocol, GCP (ICH GCP Guidelines E6), and applicable regulatory requirements. The sponsor is committed to complying with GCP standards to protect the rights, safety, and well-being of study patients, consistent with principles having their origin in the Declaration of Helsinki.

10.3 Informed Consent

The investigator (or authorized designee) at each study site will ensure that each patient is given full and adequate oral and written information about the nature, purpose, and possible risk and benefit of the study. Each patient will receive an informed consent form that summarizes the pertinent study information and will be given ample time to read and ask questions about the study. Patients must also be informed of their right to withdraw consent without prejudice at any time during the study. If the patient chooses to participate, he or she must sign the informed consent form before any study-specific procedures are conducted.

All patients will be informed of their rights to privacy and will be made aware that the study data will be submitted to the sponsor and to regulatory authorities for review and evaluation for the duration of the study and until the project has been approved for marketing or is withdrawn from investigation. They will also be informed that the study monitor may inspect their medical records to verify the accuracy and completeness of the study records and results.

Each consent form should contain an authorization allowing the Principal Investigator(s) and Laboratorios Farmacéuticos ROVI, S.A. to use and disclose private health information (i.e., patient-identifiable health information) in compliance with local laws.

Significant changes to the protocol or product safety information may cause a revision of the informed consent form, which must be reviewed and signed by all applicable study participants. The investigator must maintain the original, signed, and dated informed consent form. A copy of the signed and dated informed consent form, or a second original of a signed and dated informed consent form, must be given to the patient.

10.4 Patient Data Protection

The study patients should be informed by the investigator that complete confidentiality will be maintained concerning their identity. On eCRFs, patients will be identified only by the assigned trial number.

Prior to any testing under this protocol, including screening tests and assessments, candidates must also provide all authorizations required by local law (e.g., private health information authorization in North America).

A signed written informed consent signifies the explicit acceptance by the individual that data from the study and clinical notes will be available to the investigator and his/her staff, the representatives of the sponsor and, if required, by the IRB/IEC and regulatory authorities. However, all data contained

in the patients' clinical notes will be considered as confidential. Laboratorios Farmacéuticos ROVI, S.A. will also treat data according to European Union Data Privacy Directive 95/46/EC.

11 Indemnification

The sponsor will contract a clinical study insurance policy in compliance with all applicable laws, rules, and regulations.

12 Further Requirements and General Information

12.1 External Service Organizations

12.1.1 Interactive Voice Response System

An external vendor will be selected to provide interactive voice or web response system support for this study. Each site will be provided with appropriate training and a user manual before patients are screened or enrolled.

12.1.2 Contract Research Organization

A CRO will be responsible for all administrative aspects of the study including, but not limited to, regulatory submissions, study initiation, monitoring, data management and submissions of AE/SAE reporting. Prior to enrollment of the first patient at each site, the CRO will review study responsibilities with the investigators and other site personnel, as appropriate. The roles and responsibilities of all parties involved (CRO), third-party vendors, and the sponsor will be described in the Study Project Management Plan.

12.1.3 Central Laboratories for Laboratory Assessments

A central laboratory will be selected to analyze all hematology, blood chemistry, and urinalysis samples collected for this study. Pharmacokinetic determinations will be done by another laboratory selected by Laboratorios Farmacéuticos ROVI, S.A. Detailed procedures and instructions are included in the Laboratory Reference Guide.

12.1.4 Central Facility for Other Assessments

12.1.4.1Electrocardiogram Reading Center

An external vendor will be selected to evaluate all ECGs collected for this study. Detailed procedures and instructions are included in an ECG Study Reference Guide.

12.1.4.2Central Training

An external vendor will be selected to train the study raters before they perform any study assessments to ensure they understand and use the study scales consistency. All raters will be required to pass an assessment on the use of the PANSS before to perform any efficacy assessments. Patients should be rated as much as possible by the same rater across the study.

12.2 Study Committees

12.2.1 Data Monitoring Committee

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), and alert and/or make recommendations to the sponsor about any existing or potential problems. The DMC will be composed of a minimum of 3 voting members; they will not

be allowed to participate as investigators in this study and will not be affiliated in any way with Laboratorios Farmacéuticos ROVI, S.A. Findings and conclusions will be reported to the Laboratorios Farmacéuticos ROVI, S.A. Medical Director. Investigational sites will be notified of any relevant safety findings that may jeopardize patient safety. The DMC will meet approximately twice a year. A charter will be established between Laboratorios Farmacéuticos ROVI, S.A. and the DMC to outline the DMC's responsibilities and procedures. In one of their regular meetings, the DMC will receive from the unblinded statistician the results of outcome of the interim analysis for sample size re-estimation (blinded outcome only) performed as described in Section 7.5. The DMC will communicate to the sponsor the blinded outcome from the interim analysis together with the conclusions from any other data review performed.

12.3 Changes to Final Study Protocol

All protocol amendments must be submitted to the IRB/IEC. Protocol modifications that affect patient safety, the scope of the investigation, or the scientific quality of the study must be approved by the IRB/IEC before implementation of such modifications to the conduct of the study. If required by local law, such modifications must also be approved by the appropriate regulatory agency prior to implementation. However, Laboratorios Farmacéuticos ROVI, S.A., at any time, can amend this protocol to eliminate an apparent immediate hazard to a patient. In this case, the appropriate regulatory authorities will be notified subsequent to the modification. In the event of a protocol modification, the patient consent form may require similar modifications (see Sections 10.1 and 10.3).

12.4 Ethics Committee Notification of Study Completion or Termination

The Health Authority and the IRB/IEC in each country must be notified within 90 days of the completion of the study or within 15 days if the study is terminated early, unless any more restrictive period of time is specified by local applicable laws and regulations.

12.5 Retention of Study Data

The Principal Investigator(s) must maintain all essential documents (as listed in the ICH GCP Guidelines E6) until notified by Laboratorios Farmacéuticos ROVI, S.A. and in accordance with all local laws regarding retention of records.

12.6 Study Report Signatory

Laboratorios Farmacéuticos ROVI, S.A. will designate 1 of the participating study investigators as a signatory for the study report. This determination will be made by several factors, including, but not limited to, the investigator's experience and reputation in the studied indication; the investigator's contribution to the study in terms of design, management, and/or patient enrollment; or other factors determined to be relevant by Laboratorios Farmacéuticos ROVI, S.A.

References

1. Keith SJ, Kane JM. Partial compliance and patient consequences in schizophrenia: our patients can do better. J Clin Psychiatry. 2003;64(11):1308-15.
2. Ascher-Svanum H, Faries DE, Zhu B, Ernst FR, Swartz MS, Swanson JW. Medication adherence and long-term functional outcomes in the treatment of schizophrenia in usual care. J Clin Psychiatry. 2006;67(3):453-60.
3. Kane JM. Strategies for improving compliance in treatment of schizophrenia by using a long-acting formulation of an antipsychotic: clinical studies. J Clin Psychiatry. 2003;64(Suppl 16):34-40.
4. Keith S. Use of long-acting risperidone in psychiatric disorders: focus on efficacy, safety and cost-effectiveness. Expert Rev Neurother. 2009;9(1):9-31.
5. Hargarter L, Cherubin P, Bergmans P, Keim S, Rancans E, Bez Y, Parellada E, Carpiniello B, Vidailhet P, Schreiner A. Intramuscular long-acting paliperidone palmitate in acute patients with schizophrenia unsuccessfully treated with oral antipsychotics. Prog Neuropsychopharmacol Biol Psychiatry. 2015;58:1-7.
6. Lauriello J, Lambert T, Andersen S, Lin D, Taylor CC, McDonnell D. An 8-week, double-blind, randomized, placebo-controlled study of olanzapine long-acting injection in acutely ill patients with schizophrenia. J Clin Psychiatry. 2008;69(5):790-9.
7. Samtani MN, Gopal S, Gassmann-Mayer C, Alphs L, Palumbo JM. Dosing and switching strategies for paliperidone palmitate: based on population pharmacokinetic modelling and clinical trial data. CNS Drugs. 2011;25(10):829-45.
8. Seeman P. Atypical antipsychotics: mechanism of action. Can J Psychiatry. 2002;47(1):27-38.
9. Nakajima S, Uchida H, Bies RR, Caravaggio F, Suzuki T, Plitman E, Mar W, Gerretsen P, Pollock BG, Mulsant BH, Mamo DC, Graff-Guerrero A. Dopamine D2/3 receptor occupancy following dose reduction is predictable with minimal plasma antipsychotic concentrations: an open-label clinical trial. Schizophr Bull. 2016;42(1):212-9.
10. Catafau AM, Penengo MM, Nucci G, Bullich S, Corripio I, Parellada E, García-Ribera C, Gomeni R, Merlo-Pich E; Barcelona Clinical Imaging in Psychiatry Group. Pharmacokinetics and time-course of D(2) receptor occupancy induced by atypical antipsychotics in stabilized schizophrenic patients. J Psychopharmacol. 2008;22(8):882-94.
11. Naber D. A self-rating to measure subjective effects of neuroleptic drugs, relationships to objective psychopathology, quality of life, compliance and other clinical variables. Int Clin Psychopharmacol. 1995;10(Suppl 3):133-8.
12. Naber D, Moritz S, Lambert M, Pajonk FG, Holzbach R, Mass R, Andresen B. Improvement of schizophrenic patients' subjective well-being under atypical antipsychotic drugs. Schizophr Res. 2001;50(1-2):79-88.
13. Morosini PL, Magliano L, Brambilla L, Ugolini S, Pioli R. Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Scale (SOFAS) to assess routine social functioning. Acta Psychiatr Scand. 2000;101(4):323-9.
14. Gaedigk A, Simon SD, Pearce RE, Bradford LD, Kennedy MJ, and Leeder JS. The CYP2D6 Activity Score: Translating Genotype Information into a Qualitative Measure of Phenotype. Clinical Pharmacology and Therapeutics. 2008; 83(2):234-42.
15. Nasser AF, Henderson DC, 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. J Clin Psychopharmacol. 2016;36(2):130-40.

16. Kane JM, Peters-Strickland T, Baker RA, Hertel P, Eramo A, Jin N, Perry 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;75(11):1254-60.
17. European Medicines Agency (EMA); Committee for Medicinal Products for Human Use (CHMP). Guideline on missing data in confirmatory clinical trials. EMA/CPMP/EWP/1776/99 Rev. 1. 2 July 2010. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/09/WC500096793.pdf. Accessed 12 May 2016
18. Cui L, Hung HMJ, Wang SJ. Modification of sample-size in group sequential trials. Biometrics. 1999;55:853-7.
19. Hommel G. A stagewise rejective multiple test procedure based on a modified Bonferroni test. Biometrika. 1988;75(2):383-6.
20. Ratitch B, O'Kelly M. Implementation of pattern-mixture models using standard SAS/STAT procedures. SUGI 2011.
21. Chang M. Adaptive Design Theory and Implementation Using SAS and R. 2008: p144.
22. NDA/Serial Number 200603 / S 000 Drug Name: Lurasidone Hydrochloride Indication: Schizophrenia https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/200603Orig1s000StatR.pdf. Accessed 2 January 2018

Appendix A: Study Assessments and Procedures by Study Visit

The by-visit descriptive list of study assessments and procedures in this appendix reflects information in in the main body text of the protocol (Section 3.1) for the main (double-blind) part of the study, the optional open-label extension segment and the extension segment for de novo patients (Table 1, Table 2 and Table 3, respectively).

In order to ensure consistency and minimize inter-rater variability, all efforts should be made to have efficacy and safety scales assessments at all visits performed by the same investigator/rater.

Double-Blind Study

Allowable study visit time windows for treatment period study visits occurring after study visit 3 (study day 4) are as follows:

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

The follow-up telephone visitis to occur 14 (± 3) days after the end-of-treatment visit (i.e., the week 12 time point or earlier in the case of an early termination). This visit is not applicable for patients who enter into a long-term extension study.

Study Visit 1: Screening Visit

Study Day -8 to -1

Obtain informed consent from the patient.

- Informed consent form must be signed and dated by the patient before any study-related procedures are performed (see protocol Section 6.1.1)

Obtain the following information (see protocol Section 6.1.2):

- Demographic data
- Medical and psychiatric history data

Diagnostic interview will be performed, including the following:

- MINI International Neuropsychiatric Interview for Schizophrenia and Psychotic Disorders studies will be completed (see protocol Section 6.1.4)

Complete the following efficacy scales:

- PANSS (see protocol Section 6.2.1)
- CGI-S (see protocol Section 6.2.1.)

Complete the following safety assessments:

- Physical examination (see protocol Section 6.4.1)
- Ophthalmological examination (see protocol Section 6.4.2)
- Height
- Weight and body mass index
- Vital signs (see protocol Section 6.4.3 for details)
- ECG (see protocol Section 6.4.4)
- Assess for AEs (see protocol Section 6.4.9)
- Review concomitant medications (see protocol Section 6.1.3)

Complete the following safety scales:

- AIMS, BARS, SAS (see protocol Section 6.4.7)
- C-SSRS (see protocol Section 6.4.8)

Blood samples for the following will be obtained:

- Hematology panel (see protocol Section 6.4.5.1)
- Chemistry panel (see protocol Section 6.4.5.2)
- Prolactin (see protocol Section 6.4.5.2)
- Serology panel (see protocol Section 6.4.5.4.1)
- Pregnancy test, serum (see protocol Section 6.4.5.4.2)

Urine samples for the following will be obtained:

- Urinalysis (see protocol Section 6.4.5.3)
- Urine drug screen (see protocol Section 6.4.5.4.3)

Inclusion/exclusion criteria will be reviewed for patient eligibility.

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 (i.e., through study day -1, inclusive).

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.

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.

Study Visit 2: Baseline Evaluations and Administration of First Dose of Study Drug

Study Day 1

Patients must be already admitted to the inpatient study unit for study day 1; confirmed eligible patients will remain inpatient on study day 1 to complete the study day 1 assessments and procedures and to receive the first injection of IM study drug.

The following baseline evaluations are to be completed before randomization occurs (and before the first dose of study drug is administered), with the exception of vital signs and ECG that should be checked within one hour before study drug administration:

- PANSS
- CGI-S

Complete the following health economics and outcome research evaluations:

- Socio-demographic information
- PSP
- SWN-20

Complete the following safety assessments:

- Weight and body mass index
- Vital signs
- ECG
- Assess for AEs
- Review concomitant medications

Complete the following safety scales:

- AIMS, BARS, SAS
- C-SSRS

Blood samples for the following will be obtained:

- Hematology panel
- Chemistry panel
- Prolactin
- Pharmacokinetic sample

Urine samples for the following will be obtained:

- Urinalysis
- Pregnancy test, urine
- Urine drug screen

Inclusion/exclusion criteria will be reviewed for patient eligibility.

- Confirmation patient eligibility for continued participation in the study

Randomization will be performed (for patients confirmed to be eligible) after all of the above baseline evaluations have been performed.

- Obtain assigned unique randomization number via interactive voice or web response system

The following will be performed after randomization:

- First dose of IM study drug (i.e., double-blind Risperidone ISM 75 mg, Risperidone ISM 100 mg, or placebo) will be administered by IM injection
  - A designated unblinded individual at the study site will prepare and administer IM study drug in a manner that maintains the blind for investigators, other study site personnel, and the patient

A blood sample for genotype sample may be collected at any point after randomization during a patient's participation in the study (for patients who have given specific informed consent for genotyping).

The following will be performed after administration of IM study drug

- Complete the following safety assessments:
  - Vital signs
  - ECG
  - Injection site evaluation by investigator approximately 1 hour after injection
  - Injection site pain VAS by study patient approximately 1 hour after injection

All patients will remain on the inpatient study unit through the entire day of study day 1 and into study day 2.

Study Visit 3, Study Visit 9 and Study Visit 12

Treatment Week 1, Treatment Week 4, and Treatment Week 8 (Study Day 3, Study Day 31 and Study Day 59)

Complete the following safety assessments:

- Vital signs
- ECG
- Assess for AEs
- Review concomitant medications

Blood sample for the following will be obtained:

- Pharmacokinetic testing

Study Visit 4

Study Day 4

Complete the following efficacy scales:

- PANSS
- CGI-S and CGI-I

Complete the following safety assessments:

- Vital signs
- ECG
- Assess for AEs
- Review concomitant medications

Complete the following safety scales:

- AIMS, BARS, SAS

No patient should be discharged from the inpatient study unit 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.

Study Visit 5 and Study Visit 6

Treatment Week 1 (Study Day 8) and Treatment Week 2 (Study Day 15)

Complete the following efficacy scales:

- PANSS
- CGI-S and CGI-I

Complete the following safety assessments:

- Physical examination
- Weight and body mass index
- Vital signs
- ECG
- Assess for AEs
- Review concomitant medications

Complete the following safety scales:

- AIMS, BARS, SAS
- C-SSRS

Blood samples for the following will be obtained:

- Hematology panel
- Chemistry panel
- Prolactin (visit 5 [study day 8] only)
- Pharmacokinetic sample (a subgroup of 75 study participants only)

Urine samples for the following will be obtained:

- Urinalysis
- Optional: urine drug screen

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.

Study Visit 7 (a subgroup of 75 study participants only)

Treatment Week 3 (Study Day 22)

Complete the following safety assessments:

- Vital signs
- ECG
- Assess for AEs
- Review concomitant medications

Blood samples for the following will be obtained:

- Pharmacokinetic sample

- **Study Visit 8 and Study Visit 11: Study Drug Administration Visits**

Treatment Week 4 and Treatment Week 8 (Study Day 29 and Study Day 57)

Complete the following efficacy scales:

- PANSS
- CGI-S and CGI-I

Complete the following health economics and outcome research evaluations:

- Socio-demographic information
- HRU data collection – patient (or informant)
- PSP
- SWN-20

Complete the following safety assessments:

- Weight and body mass index
- Vital signs
- ECG
- Assess for AEs
- Review concomitant medications

Complete the following safety scales:

- AIMS, BARS, SAS
- C-SSRS

Blood samples for the following will be obtained:

- Hematology panel
- Chemistry panel
- Prolactin
- Pharmacokinetic sample

Urine samples for the following will be obtained:

- Pregnancy test, urine
- Urinalysis
- Optional: urine drug screen

Study drug (i.e., double-blind Risperidone ISM or placebo) will be administered by IM injection

- Study drug doses 3 and 4 at study visit 8 and study visit 11, respectively

The following will be performed after administration of IM study drug:

- Complete the following safety assessments:
  - Vital signs
  - ECG
  - Injection site evaluation by investigator approximately one hour after injection
  - Injection site pain VAS by study patient approximately 1 hour after injection

Study Visit 10 and Study Visit 13

Treatment Week 6 and Treatment Week 10 (Study Day 43 and Study Day 71)

Complete the following efficacy scales:

- CGI-I

Complete the following safety scales:

- AIMS, BARS, SAS

Complete the following safety assessments:

- Vital signs
- ECG
- Assess for AEs
- Review concomitant medications

Urine samples for the following will be obtained:

- Optional: urine drug screen

Study Visit 14: End-of-Treatment Visit

Treatment Week 12 (Study Day 85)

Complete the following efficacy scales:

- PANSS
- CGI-S and CGI-I

Complete the following health economics and outcomes research evaluations:

- Socio-demographic information
- HRU data collection - center
- HRU data collection - patient (or informant)
- PSP
- SWN-20

Complete the following safety assessments:

- Physical examination
- Ophthalmological examination
- Weight and body mass index
- Vital signs
- ECG
- Assess for AEs
- Review concomitant medications

Complete the following safety scales:

- AIMS, BARS, SAS
- C-SSRS

Blood samples for the following will be obtained:

- Hematology panel
- Chemistry panel
- Prolactin
- Pharmacokinetic sample

Urine samples for the following will be obtained:

- Pregnancy test, urine
- Urinalysis
- Optional: urine drug screen

Study Visit 15: Safety Follow-up Contact (Via Telephone)

Study Day 99

Complete the following safety assessments:

- Assess for AEs
- Review concomitant medications

Optional Open-Label Extension Segment of the Study

The allowable study visit time window for each of the extension 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 extension 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 extension visits is ± 3 days (i.e., extension visits 2 through 15, inclusive).

The follow-up telephone visit is to occur 28 (± 3) days after the end-of-extension visit (i.e. the week 52 time point, or earlier in the case of an early termination).

Extension Visit 0: Screening Visit (de novo patients only)

Study Day -8 to -1

Obtain informed consent from the patient.

- Informed consent form must be signed and dated by the patient before any study-related procedures are performed (see protocol Section 6.1.1)

Obtain the following information (see protocol Section 6.1.2):

- Demographic data
- Medical and psychiatric history data

Diagnostic interview will be performed, including the following:

- MINI International Neuropsychiatric Interview for Schizophrenia and Psychotic Disorders studies will be completed (see protocol Section 6.1.4)

Complete the following efficacy scales:

- PANSS (see protocol Section 6.2.1)
- CGI-S (see protocol Section 6.2.1)

Complete the following safety assessments:

- Physical examination (see protocol Section 6.4.1)
- Height
- Weight and body mass index
- Vital signs (see protocol Section 6.4.3 for details)
- ECG (see protocol Section 6.4.4)
- Assess for AEs (see protocol Section 6.4.9)
- Review concomitant medications (see protocol Section 6.1.3)

Complete the following safety scales:

- AIMS, BARS, SAS (see protocol Section 6.4.7)
- C-SSRS (see protocol Section 6.4.8)

Blood samples for the following will be obtained:

- Hematology panel (see protocol Section 6.4.5.1)
- Chemistry panel (see protocol Section 6.4.5.2)
- Prolactin (see protocol Section 6.4.5.2)
- Serology panel (see protocol Section 6.4.5.4.1)
- Pregnancy test, serum (see protocol Section 6.4.5.4.2)

Urine samples for the following will be obtained:

- Urinalysis (see protocol Section 6.4.5.3)
- Urine drug screen (see protocol Section 6.4.5.4.3)

Inclusion/exclusion criteria will be reviewed for patient eligibility.

Patients who, after completion of all scheduled assessments on the screening visit day, are considered provisionally eligible will be admitted directly to the study that day.

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.

Extension Visit 1: Baseline

Extension Study Day 1

Obtain informed consent from the prospective patient (rollover patients only)

- A separate informed consent form for participation in the optional extension segment of the study must be signed before any assessments or procedures for the extension segment are performed for a given patient, and before any dose of open-label Risperidone ISM is administered to that patient.

Inclusion/exclusion criteria for extension segment will be reviewed for patient eligibility.

Treatment arm assignment (de novo patients only)

- 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.

ECG and vital signs assessments will be performed within one hour before study drug administration.

A dose of IM study drug (Risperidone ISM 75 mg or Risperidone ISM 100 mg) will be administered by IM injection. 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 of Risperidone ISM during the extension segment"

The following will be performed after administration of IM study drug

Complete the following safety assessments:

- Vital signs
- ECG
- Injection site evaluation by investigator approximately 1 hour after injection
- Injection site pain VAS by study patient approximately 1 hour after injection

Collect socio-demographic information. Complete the following health economics and outcome research evaluations (de novo patients only):

- HRU data collection – center
- HRU data collection – patient
- SWN-20 - patient reported
- PSP - clinician-administered

For rollover patients, for assessments listed below results obtained as part of the main study visit 14 may be used as the extension baseline values and do not need to be repeated for the extension baseline visit time point if and only if the extension baseline visit occurs on the same day and date as the main study visit 14/week 12/end-of-treatment visit (rollover patients only).

If the extension baseline visit instead occurs on a day 1 to 3 days after the main study visit 14/study week 12/study day 85/end-of-treatment visit, and for all de novo patients, all of the following assessments must be performed on the day of the extension baseline visit:

Complete the following efficacy scales:

- PANSS
- CGI-S

Complete the following safety assessments:

- Physical examination
- Weight and body mass index
- Vital signs
- ECG
- Assess for AEs
- Review concomitant medications

Complete the following safety scales:

- AIMS, BARS, SAS
- C-SSRS

Blood samples for the following will be obtained:

- Hematology panel
- Chemistry panel
- Prolactin
- Pregnancy test, serum - optional

Urine samples for the following will be obtained:

- Pregnancy testing
- Urinalysis
- Urine drug screen – optional for rollover patients, mandatory for de novo patients

Extension Visit 2, Extension Visit 6, and Extension Visit 11
Extension Week 4, Extension Week 20, and Extension Week 40

(Extension Day 29, Extension Day 141, and Extension Day 281)

Complete the following efficacy scales:

- PANSS
- CGI-S
- CGI-I

Complete the following health economics and outcome research evaluation:

- HRU data collection – patient

Complete the following safety assessments:

- Physical examination
- Vital signs
- ECG
- Assess for AEs
- Review concomitant medications

Complete the following safety scales:

- AIMS, BARS, SAS
- C-SSRS

Blood samples for the following will be obtained:

- Pregnancy test, serum - optional

Urine samples for the following will be obtained:

- Pregnancy testing
- Urine drug screen - optional

A dose of IM study drug (Risperidone ISM 75 mg or Risperidone ISM 100 mg) will be administered by IM injection.

The following will be performed after administration of IM study drug

- Complete the following safety assessments:
  - Vital signs
  - ECG
  - Injection site evaluation
  - Injection site pain VAS

Extension Visit 3, Extension Visit 5, Extension Visit 8, Extension Visit 9, and Extension Visit 12

Extension Week 8, Extension Week 16, Extension week 28, Extension Week 32, and Extension Week 44

(Extension Day 57, Extension Day 113, Extension Day 197, Extension Day 225, and Extension Day 309)

Complete the following efficacy scales:

- PANSS
- CGI-S
- CGI-I

Complete the following health economics and outcome research evaluation:

- HRU data collection – patient

Complete the following safety assessments:

- Physical examination
- Vital signs
- ECG (at Extension Visit 8 only)
- Assess for AEs
- Review concomitant medications

Complete the following safety scales:

- AIMS, BARS, SAS
- C-SSRS

Blood samples for the following will be obtained:

- Pregnancy test, serum - optional

Urine samples for the following will be obtained:

- Pregnancy testing
- Urine drug screen - optional

A dose of IM study drug (Risperidone ISM 75 mg or Risperidone ISM 100 mg) will be administered by IM injection.

The following will be performed after administration of IM study drug

Complete the following safety assessments:

- Vital signs
- Injection site evaluation
- Injection site pain VAS
- ECG (**at Extension Visit 8/Extension Day 197 only**)

Extension Visit 4
Extension Week 12 (Extension Day 85)

Complete the following efficacy scales:

- PANSS
- CGI-S
- CGI-I

Collect socio-demographic information.

Complete the following health economics and outcome research evaluations:

- HRU data collection – patient
- SWN-20 - patient reported
- PSP - clinician-administered

Complete the following safety assessments:

- Physical examination
- Weight and body mass index
- Vital signs
- ECG
- Assess for AEs
- Review concomitant medications

Complete the following safety scales:

- AIMS, BARS, SAS
- C-SSRS

Blood samples for the following will be obtained:

- Hematology panel
- Chemistry panel
- Prolactin
- Pregnancy test, serum - optional

Urine samples for the following will be obtained:

- Pregnancy testing
- Urinalysis
- Urine drug screen - optional

A dose of IM study drug (Risperidone ISM 75 mg or Risperidone ISM 100 mg) will be administered by IM injection.

The following will be performed after administration of IM study drug

Complete the following safety assessments:

- Vital signs
- ECG
- Injection site evaluation
- Injection site pain VAS

Extension Visit 7

Extension Week 24 (Extension Day 169)

Complete the following efficacy scales:

- PANSS
- CGI-S
- CGI-I

Collect socio-demographic information.Complete the following health economics and outcome research evaluations:

- HRU data collection – center
- HRU data collection – patient
- SWN-20 - patient reported
- PSP - clinician-administered

Complete the following safety assessments:

- Physical examination
- Weight and body mass index
- Vital signs
- Assess for AEs
- Review concomitant medications

Complete the following safety scales:

- AIMS, BARS, SAS
- C-SSRS

Blood samples for the following will be obtained:

- Hematology panel
- Chemistry panel
- Prolactin
- Pregnancy test, serum - optional

Urine samples for the following will be obtained:

- Pregnancy testing
- Urinalysis
- Urine drug screen - optional

A dose of IM study drug (Risperidone ISM 75 mg or Risperidone ISM 100 mg) will be administered by IM injection.

The following will be performed after administration of IM study drug

Complete the following safety assessments:

- Vital signs
- Injection site evaluation
- Injection site pain VAS

Extension Visit 10

Extension Week 36 (Extension Day 253)

Complete the following efficacy scales:

- PANSS
- CGI-S
- CGI-I

Collect socio-demographic information.

Complete the following health economics and outcome research evaluations:

- HRU data collection – patient

Complete the following safety assessments:

- Physical examination
- Weight and body mass index
- Vital signs
- Assess for AEs
- Review concomitant medications

Complete the following safety scales:

- AIMS, BARS, SAS
- C-SSRS

Blood samples for the following will be obtained:

- Hematology panel
- Chemistry panel
- Prolactin
- Pregnancy test, serum - optional

Urine samples for the following will be obtained:

- Pregnancy testing
- Urinalysis
- Urine drug screen - optional

A dose of IM study drug (Risperidone ISM 75 mg or Risperidone ISM 100 mg) will be administered by IM injection.

The following will be performed after administration of IM study drug

Complete the following safety assessments:

- Vital signs
- Injection site evaluation
- Injection site pain VAS

Extension Visit 13
Extension Week 48 (Extension Day 337)

Complete the following efficacy scales:

- PANSS
- CGI-S
- CGI-I

Complete the following health economics and outcome research evaluation:

- Collect socio-demographic information.
- HRU data collection – center
- HRU data collection – patient

Complete the following safety assessments:

- Physical examination
- Vital signs
- Assess for AEs
- Review concomitant medications

Complete the following safety scales:

- AIMS, BARS, SAS
- C-SSRS

Blood samples for the following will be obtained:

- Pregnancy test, serum - optional

Urine samples for the following will be obtained:

- Pregnancy testing
- Urine drug screen - optional

A dose of IM study drug (Risperidone ISM 75 mg or Risperidone ISM 100 mg) will be administered by IM injection.

The following will be performed after administration of IM study drug

Complete the following safety assessments:

- Vital signs
- Injection site evaluation
- Injection site pain VAS

Extension Visit 14
Extension Week 52 (Extension Day 365)

Complete the following efficacy scales:

- PANSS
- CGI-S
- CGI-I

Complete the following health economics and outcome scales:

- SWN-20 - patient reported
- PSP - clinician-administered

Complete the following safety assessments:

- Physical examination
- Weight and body mass index
- Vital signs
- ECG
- Assess for AEs
- Review concomitant medications

Complete the following safety scales:

- AIMS, BARS, SAS
- C-SSRS

Blood samples for the following will be obtained:

- Hematology panel
- Chemistry panel
- Prolactin
- Pregnancy test, serum - optional

Urine samples for the following will be obtained:

- Pregnancy testing
- Urinalysis
- Urine drug screen - optional

Extension Visit 15: Extension Follow-up Visit (Conducted by Telephone)

Extension Week 56 (Extension Day 393)

Complete the following safety assessments:

- Assess for AEs
- Review concomitant medications

Appendix B: Prohibited Medications

Cytochrome P450 3A4 Inducers and Inhibitors and 2D6 Inhibitors

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf

Also see the following SAMPLE TABLE:

Prohibited Medications Affecting Cytochrome P450 3A4 (Inducers and Inhibitors) or 2D6 (Inhibitors)

3A4 Inducers	3A4 Inhibitors	2D6 Inhibitors
• Carbamazepine • Barbiturates (e.g., phenobarbital) • Phenytoin • Rifampin • Hyperforin (e.g., St. John's Wort) • Modafinil • Cyproterone (e.g., antiandrogen, progestin, Diane-35) • Non-nucleotide reverse transcriptase inhibitors (e.g., efavirenz, nevirapine, etravirine)	• Ketoconazole • Itraconazole • Fluconazole • Clarithromycin • Erythromycin • Telithromycin • Nefazodone • Fluvoxamine • Protease inhibitors (ritonavir, indinavir, nelfinavir) • Verapamil • Grapefruit juice • Bergamottin • Quercetin	• Quinidine • Selective serotonin reuptake inhibitors (e.g., fluoxetine, paroxetine, citalopram) • Duloxetine Bupropion MDMA (3,4-methylenedioxymeth-amphetamine; ecstasy) • Terbinafine • Goldenseal (Hydrastis canadensis)

Appendix C : Rating Scale and Interview Descriptions

MINI

The MINI International Neuropsychiatric Interview for Schizophrenia and Psychotic Disorders Studies is a short, structured diagnostic interview that was developed for DSM-V and ICD-10 psychiatric disorders that has been validated against the Structured Clinical Interview for DSM diagnoses (SCID). It will be used to assess for excluded psychiatric conditions outlined in the study entry criteria.

PANSS

The Positive and Negative Syndrome Scale (PANSS), is a 30-item clinician-rated instrument for assessing the symptoms of schizophrenia and will be used as the primary efficacy endpoint measure. The positive scale consists of 7 items which measure delusions, conceptual disorganization, hallucinations, grandiosity, and suspiciousness/persecution. The negative subscale consists of items which measure blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking. The general psychopathology scale consists of 16 items which measure somatic concern, anxiety, guilt feelings, tension, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation and active social avoidance. The change from baseline in the PANSS total score at 12 weeks is the primary efficacy endpoint.

CGI-S

The Clinical Global Impression Severity of Illness (CGI-S) is a 7-point clinician-rated scale for assessing the global severity of the illness. The change in CGI-S score from baseline to 12 weeks will be used as a secondary efficacy endpoint. Also the change in PANSS positive subscale response change from baseline to 12 weeks will be included as a secondary endpoint. The PANSS positive subscale assesses features such as delusions and hallucinations.

CGI-I

The CGI-I consists of a single 7-point rating score total improvement, regardless of whether or not the change it is due entirely to drug treatment. Raters select one response based on the following question, “Compared to your patient’s condition at the beginning of treatment, how much has your patient changed?” Scores are: 1, Very much improved; 2, Much improved; 3, Minimally improved; 4, No change; 5, Minimally worse; 6, Much worse; or 7, Very much worse. For the CGI-I Scale, the patient’s condition at the Day 1 (baseline) visit will be the criterion for judging improvement at subsequent visits.

AIMS

The Abnormal Involuntary Movement Scale (AIMS) will be used to document occurrences of dyskinesias in patients, specifically tardive dyskinesia. The scale incorporates observation and brief examination of the patient and consists of 12 items. Items 1-4 assess the severity of orofacial movements. Items 5-7 assess extremity and truncal dyskinesias. Items 8-10 rate global severity of

movements as indicated by the examiner's judgment of the severity of abnormal movements (item 8), the examiner's judgment of the patient's incapacitation due to the movements (item 9), and the patient's awareness of the movements and associated distress (item 10). Items 11 12 concern the patient's dental status

BARS

The Barnes Akathisia Rating Scale (BARS) will be administered to assess akathisia. The scale is designed to rate akathisia through observation of restless behavior and questioning of the patient to determine the degree of subjective restlessness and distress associated with restlessness. A global clinical rating completes the assessment. The first 3 items of the BARS (Objective, Subjective, and Distress related to restlessness) are rated on a 4 point scale (0-3). The fourth item, the global clinical assessment of akathisia, uses a 6 point scale (0-5). Only the global clinical assessment measure from this scale will be analyzed. Higher scores indicate increased severity. All ratings are anchored. The BARS takes approximately 10 minutes to administer

SAS

The Simpson Angus Scale (SARS) will be administered to assess parkinsonian symptoms and related extrapyramidal side effects through observation of the patient. The scale contains 10 items, including gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, glabellar tap, tremor, and salivation. The head rotation item (from the modified SAS) will be substituted for the original #7 item, head dropping. Seven of the 10 items measure parkinsonian rigidity. Each item is rated on an anchored 5-point scale, with 0 = the absence of the condition or normal and 4 = the most extreme form of the condition. A total score is obtained by adding all of the scores of the individual items. The SAS takes approximately 10 minutes to administer.

C-SSRS

The Columbia Suicide Severity Rating Scale (C-SSRS) is an interview-based rating scale to systematically assess suicidal ideation and suicidal behavior. Versions are available for screening /baseline and follow-up visits.

PSP

This operationalized, 100-point scale consists of 4 main areas: socially useful activities, personal and social relationships, self-care, and disturbing and aggressive behavior. Each of the 4 domains is rated in 6 degrees of severity (absent, mild, manifest, marked, severe, very severe). A difference of 8 points can be classified as a clinically highly relevant difference.

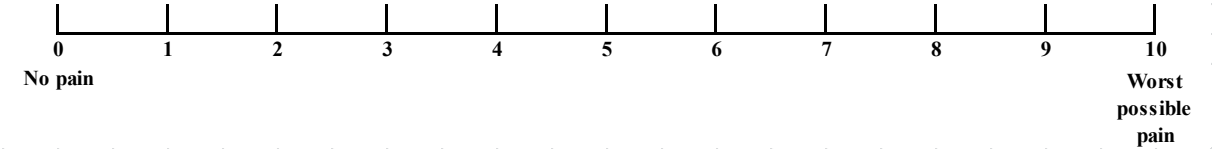
SWN-20

The Subjective Well-being Under Neuroleptic Treatment Scale (SWN) is used to assess well-being in patients with schizophrenia undergoing antipsychotic treatment. The 20-item version of the SWN scale consists of 20 items referring to the last 7 days. The total score ranges from a minimum of 20 (poor) to a maximum of 120 (excellent). 10 items are formulated positively and 10 items are formulated negatively, describing each complaint in a positive and negative phrase. The SWN-20 measures subjective experience in 5 subscales: emotional regulation, self-control, mental functioning, social integration and physical functioning.

Appendix D: Visual Analog Scale (VAS)

VISUAL ANALOG SCALE

On the scale of zero to ten, where zero means no pain and ten equals the worst possible pain, what is the level of the pain right now at the injection site? Please circle the number that corresponds to it.



Appendix E: Risperidone ISM Investigator Brochure

Due to the size of the document, the most updated version of the Investigator's Brochure for Risperidone ISM® is available as a separate document.

Appendix F: Contact Information

ROVI Pharmacovigilance Department
Phone: +34 917617561/+34 911863678
Fax: +34 912444421

Email: farmacovigilancia@rovi.es

Laboratorios Farmacéuticos ROVI S.A. (SAEs)

ROVI Pharmacovigilance Department
Fax number: +34 912444421
E-mail: farmacovigilancia@rovi.es
Phone number: +34 917617561/+34 911863678

INC Research – (SUSARs only)

Milan Matković MD, Senior Project Manager
Fax number: +381 11 240 25 70
E-mail: milan.matkovic@syneoshealth.com
Phone number: +381 11 715 8058

Enrique Comesaña MD, MBA
Executive Medical Director - Medical Affairs
E-mail: enrique.comesana@syneoshealth.com
Moble Phone number: +1 (512) 367 0592

Appendix G: Protocol Signatories

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 No.	ROV-RISP-2016-01
Protocol /Amendment Date:	22 March 2018
Protocol /Amendment No.:	4.0
Protocol Version:	7.0

SPONSOR: Laboratorios Farmacéuticos ROVI, S.A.
C/ Julián Camarillo, 35
28037 Madrid, Spain

Carolina Gómez de la Bárcena,
Pharmacovigilance Responsible,
Pharmacovigilance Department
Laboratorios Farmacéuticos ROVI, S.A.

23/ Mar/2018
Date

Javier Martínez-González, MD
Medical Director
Laboratorios Farmacéuticos ROVI, S.A.

23/MAR/2018
Date

Appendix H : Investigator Agreement

Laboratorios Farmacéuticos ROVI, S.A.

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 No. ROV-RISP-2016-01, Version No. 7.0

Date: 22 March 2018

Amendment No.: 4.0

PRINCIPAL INVESTIGATOR COMMITMENT:

I will provide copies of the protocol, any subsequent protocol amendments and access to all information provided by the Sponsor to the study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational drug and the study protocol.

I agree to conduct this clinical trial according to the attached protocol, except when mutually agreed to in writing. I also agree to conduct this study in compliance with all federal, state and local regulations, Good Clinical Practices (GCP), as well as with the requirements of the appropriate Institutional Review Board(s) (IRB)/Independent Ethics Committee(s) (IEC) and any other institutional requirements.

_____

Printed Name of Principal Investigator

_____

Signature of Principal Investigator

_____

Date

_____

Institution