COVER PAGE

Subject Information Sheet (SIS) and Informed Consent Form (ICF)

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

PROTOCOL NUMBER: ROV-RISP-2016-01

NCT NUMBER: NCT03870880

ICF VERSION 4.0

DOCUMENT DATE: 13 APRIL 2018

SUBJECT INFORMATION SHEET AND CONSENT FORM
- OPEN-LABEL EXTENSION SEGMENT OF THE STUDY -

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
EudraCT number: (applicable to EU countries only)

Sponsor Name: Laboratorios Farmacéuticos ROVI, S.A.
Address of Sponsor: C/ Julián Camarillo, 35. 28037 Madrid, Spain

Principal Investigator: Insert Name, affiliation, location
Telephone number
Daytime:
After Office Hours:

Introduction and Purpose of the Study

You are being asked to volunteer to take part in an extension segment of the study you were participating until now. You have completed the double-blind segment of this study and you are 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.

If you decide to participate in the long-term extension segment, you should sign this Subject Information Sheet and the Informed Consent Form. If you are not willing to participate in the extension segment, a safety follow-up phone contact will occur in approximately 2 weeks.
You can take as much time as you need to read and understand the information provided in this form and to ask questions. One of the research team members will go through the information sheet with you and answer any questions you have. Talk to others about the study if you wish.

Since the open label extension segment is optional, it is not known how many subjects will participate in the long-term extension segment.

Study Plan

The study design includes 13 additional visits (beside the day 1) – every 4 weeks, for a total of one year, and one additional follow up visit on week 56. At each visit (except final visit 14 at week 52) you will receive Risperidone ISM® injection (either 75 or 100 mg) and you may have laboratory tests done, ECG, vital signs assessments, physical examination, weight, injection site appearance and sensitivity examination and

questionnaires and scales completed the way you had during the double-blind segment of the trial ("double-blind" means that neither you nor your study doctor know what treatment you are receiving).

Your visits to study center may take several hours.

Eligibility

To be eligible for participation in the open-label extension segment of the study, you must meet all of the inclusion criteria and none of the exclusion criteria defined in the study protocol. These criteria will be checked by your study doctor.

You may be withdrawn from the study at any time if you, investigator or sponsor determines that it is not in your best interest to continue. Reasons for withdrawal may include, but are not limited to non-compliance, 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 your withdrawal of consent without penalty or loss of benefits to which you are otherwise entitled. In addition, if your condition changes during the course of the study so that you no longer satisfy the inclusion and exclusion criteria, you may be withdrawn.

Study Procedures

Extension Visit 1: Day 1

This visit may occur on the same day as visit 14 (+3 day window) of the double-blind segment, once all the assessments and procedures have been completed.

If you qualify for open-label extension segment, at Visit 1 (Day 1) you will be administered a dose of Risperidone ISM® 75 mg or 100 mg by intramuscular injection, with examination of the injection site appearance and sensitivity on the same day. If you have received active Risperidone ISM® in the double-blind segment of the study, you will continue to receive active Risperidone ISM® at the same dose (ie, 75 or 100 mg) in the extension segment; if you had been receiving placebo in the double-blind segment of the study, you will be randomly (the study drug assignment will be done by chance, like tossing a coin) assigned to receive either 75 or 100 mg of Risperidone ISM® during the extension segment. "Open-label" means that you and your study doctor will know what treatment you will be receiving (Risperidone ISM® and not placebo).

But, if you enter this extension segment of the study while some subjects are still in the double-blind stage, you will not know do you receive 75 or 100 mg of Risperidone ISM® until the completion of the double-blind stage of the study. At that time, you may ask your doctor to be informed on the treatment received.

At Day 1 the following tests and procedures will be done to determine if you are eligible for transition into the extension segment:

- A set of standard questions/scales/questionnaires that will assess your physical sensations and symptoms, your quality of life and how it is affected by your schizophrenia, as well as assessment scales to assess your movements (the way you move and whether you have movements you cannot control)
- Physical examination
- Weight and body mass index
- Vital signs (blood pressure, pulse rate, respiratory rate and body temperature)
- ECG (electrocardiogram, which records heart function)
- Review of your medications (including vitamins and herbal supplements)
- Blood samples (about 2 teaspoons, approximately 10 mL) for laboratory testing which will show the function of your blood and vital organs (eg liver, kidney)
- Blood sample (about 1/2 teaspoon, approximately 2.5 mL, will be taken from you for a pregnancy test if you are female able to have kids and if required by your study doctor
- Urine samples for laboratory analysis, pregnancy test for females, and drug screen (if applicable)

Results obtained at visit 14 for assessments performed for the end-of-treatment visit for the double-blind segment 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.

Blood testing (to the applicable visits)

Your samples will be coded before being shipped to a central laboratory and will be stored there awaiting analysis. The central laboratory is experienced in handling and testing samples from research studies. All samples will be destroyed once all tests are complete.

In case of a serious adverse event, an additional blood sample (about 4 mL) for pharmacokinetic testing will be taken. “Pharmacokinetic” testing is a procedure which is done to see what your body does to the drug and to show the levels of the drug in your blood. This sample will be processed in a same way as blood samples taken for visit related tests.

The samples will only be used for study related purposes, and no other analyses than study related analyses will be performed without you and the ethics committee’s approval.

Extension Study Visits 2-14 (every 4 weeks)

During each extension visit, you will receive Risperidone ISM® (75 or 100 mg) (except visit 14, week 52), your vital signs will be checked, a physical examination will be performed and questionnaires and assessment scales administered as it was done in double-blind segment of the study, to make sure it is safe for you to continue in the extension segment of the study. The injection site appearance and sensitivity will be examined. You will be asked if there have been any changes in your health and for any new medications you may have begun to take. A dipstick test will be done for pregnancy at each visit to applicable patients.

Additionally, at visits 4 (week 12), 7 (week 24), 10 (week 36) and 14 (week 52) the study staff will perform laboratory tests (including blood and urine tests) and body weight. ECG will be done at visits 2 (week 4), 4 (week 12), 6 (week 20), 8 (week 28), 11 (week 40) and 14 (week 52).

Extension Study Visit 15 (week 56)

This is a follow up visit where you will be asked if there have been any changes in your health and for any new medications you may have begun to take.

Subject's Responsibilities

While you are in this extension segment of the study, you will be required to:

- Come to the study clinic for all of your scheduled visits, complete all required study procedures, follow the instructions listed in this Subject Information Sheet and Informed Consent Form, and follow instructions given to you by the study staff.
- Notify the study doctor of any changes in your health and medications or if your availability to take part in this study changes. 'Medications' include prescriptions and non-prescription drugs as well as vitamins or supplements.
- Agree to continue to take your normal medications for your condition, as prescribed by your doctor, throughout this study. The study doctor will change your regular medication during this study only if it is necessary for your health.
- Agree to not donate blood for at least 30 days after you leave the study.
- For females able to have children, agree to use an acceptable form of birth control for the duration of the study and for ≥ 6 months after the last dose of IM study drug has been administered, such as intrauterine device (IUD), a condom (with or without spermicide), diaphragm or cervical cap with spermicide, oral contraceptive pills or other hormonal methods (patches, contraceptive implant or a vaginal ring). The study doctor or study staff will discuss this with you in more detail.
- All male subjects must agree to use an acceptable barrier method of birth control for the duration of the study, such as a condom with or without spermicide. Men

with an exclusive surgically sterile female partner, as well as men who have themselves had a vasectomy (surgical sterilization), are exempt from the requirement to use contraception. The study doctor or study staff will discuss this with you in more detail.

Avoid certain medicines, supplements, and beverages. Your study doctor will explain to you in detail which drugs/vitamins/supplements/herbal extracts/beverages you should not take. ***Please consult him/her prior to starting any new treatment.***

For your safety and the safety of others, it is important that you do not drink alcohol during the extension segment of the study, and especially you should not drink alcohol before or during any of the study visits. If you have any questions about any of these restrictions, medications or drugs, please ask the study doctor.

Benefits and Risks

In the outpatient clinical setting, non-compliance with prescribed oral antipsychotic medication regimens is frequently seen and has been associated with relapse and worsening of the disease. Long-acting formulations of antipsychotic medications, developed to promote treatment adherence, have helped to improve compliance and thus efficacy. Initially developed long-acting formulations of antipsychotic agents, which are known to be associated with a number of safety and tolerability concerns that limit their acceptability in current clinical practice.

Risperidone ISM® formulation is an alternative long-acting injectable form of the atypical antipsychotic, risperidone. As a once monthly intramuscular injection, Risperidone ISM® provides rapid achievement (within 24 hours) of therapeutic levels of risperidone with sustained therapeutic levels in the blood for a period of up to 4 weeks without the initial need for daily oral risperidone supplementation.

Your symptoms of schizophrenia may improve while participating in this extension segment of the study. Your participation will contribute to information about the study drug and may benefit other patients in the future.

However, please note that your symptoms of schizophrenia may not improve and could even worsen during the extension segment of the study.

<u>Possible Side Effects of Risperidone</u>

Risperidone ISM® injection has been previously tested in 3 clinical trials. Adverse events reported in adult subjects so far include:

- Endocrine disorders: hyperprolactinaemia - higher levels of prolactin in the blood. Prolactin is the hormone that controls the process of lactation

- Gastrointestinal disorders: dry mouth, odynophagia (is painful swallowing, in the mouth or gullet)
- General disorders and administration site conditions: injection site erythema (redness of the skin) and injection site pain
- Nervous system disorders: dizziness, headache, oromandibular dystonia (this is a condition involving slow or sustained involuntary contraction of the muscles of the mouth, tongue or jaw), sedation, and somnolence
- Psychiatric disorders: insomnia

These side effects observed in previous clinical studies occurred in more than 5% of study subjects; nevertheless it does not mean that all of them were the side effects of the study drug.

Frequency and severity of related side effects in previous studies:

The most frequently reported related side effect was hyperprolactinaemia (27.7%); in 4.0% it was moderate and in 96.0% it was mild. The second most frequently reported side effect was injection site pain (21.1%); in 3.9% was moderate and in 96.1% was mild. The third most frequently reported side effect was somnolence (6.3%); in 13.0% of cases it was moderate and in 87.0% it was mild.

Description of serious side effects in previous studies:

A total of 6 serious side effects related to Risperidone ISM® were observed in 4 subjects in previous studies. These serious side effects were 3 oromandibular dystonias (this is a condition involving slow or sustained involuntary contraction of the muscles of the mouth, tongue or jaw; 2 were severe and 1 was moderate), 2 tachycardias (is a heart rate that exceeds the normal resting rate; they were moderate) and 1 sedation which was moderate. In all of these cases the subjects recovered from the serious side effect.

<u>Possible Discomforts and Reactions Caused by Study Drug Injection</u>
Sometimes people have reactions at the spot where medications have been injected Reactions can include pain, tenderness, hardening of the area, swelling, redness, bruising, or itchiness. Very rarely a blood clot may form or an infection may occur. For your safety, call the study doctor right away if any of the following things happen at the injection site: intense pain, the area feels hard or has lumps, lots of swelling or blistering occurs, or if an open wound appears or a dark scab forms.

<u>Discomforts of Blood Tests and ECGs</u>
You may experience some discomfort, bruising, or slight bleeding on your arm where the blood samples are taken. Some people may feel faint or lightheaded for a few minutes after having blood taken.

The ECG may cause some discomfort or skin irritation where the adhesive (sticky) pads are applied to your body.

Unknown/Unforeseeable Risks

In addition to the risks or discomforts listed above, there may be other risks that are currently not known. Also, the risks or discomforts described may occur more often or be more severe than has been seen before.

Reproduction Risks

The effects of risperidone on a fetus are unknown. In animal studies, the risperidone has shown possible birth defects. Even with using an approved birth control method, a pregnancy can still occur. Also, pregnancy tests are not always accurate. There is always a possibility that a female is pregnant even if her pregnancy test results indicate that she is not pregnant.

Sexually active females able to have children and men who are sexually active must use a medically acceptable birth control method while in this study and up to six months after the last study drug administration. Your study doctor will discuss this with you in more detail. Subjects who are abstinent (not sexually active) must agree to use an acceptable method of birth control if they become sexually active.

Since the effects of the study drug on sperm are unknown, males are required to use a barrier birth control method, such as a condom with or without a spermicide, while being in this study.

If you are a female and become pregnant during the study, you will be withdrawn from the study. If you think you or your partner might be pregnant at any time during the study, please inform the study doctor right away. A member of the research team will follow up on you throughout the pregnancy in order to collect information on the outcome of the pregnancy and development of the child after birth. Female subjects should not breast-feed during or for two months after the last study drug administration.

New Findings

Your study doctor will tell you of any information learned during the course of the study that might cause you to change your mind about taking part in the study. You may contact the study doctor at any time after your participation ends to find out if any new information about this study has become available.

Possible Benefits

Your symptoms of schizophrenia may improve while participating in this study. Your participation in the study will contribute to information about the study drug and may benefit other patients in the future.

Costs

Being in this study will not cost you or your insurance company. Laboratorios Farmacéuticos ROVI, S.A. will pay for all charges for the study drugs. It will also pay for all study-related procedures, like lab tests and ECGs.

Alternative Treatments

You do not have to take part in this extension segment of the study to receive treatment for your condition. If you decide not to participate, there are other treatments for schizophrenia available to you. Your doctor will discuss alternative treatments with you and their benefits and risks.

Confidentiality and Data Protection

This section provides information about how your medical records and health information (together, your "records") will be used and disclosed in the clinical study referenced above. Your records may include information about your blood samples, physical examinations, medical history, and any other data collected or reviewed during the course of the study as described in the consent form for the study. By signing this form, you authorize the study doctor identified in the consent form and the study staff to use your records to carry out the study described in the consent form. If you do not sign this form, you cannot participate in the study.

Personal Data which will include the following general categories: name, contact details, date of birth, age, marital status; and the following sensitive categories: initials, gender, race, ethnic origin, health, sex life will be collected from you during the study and recorded in your medical notes by the Principal Investigator and/or the hospital/clinic staff.

For most purposes, your personal data will be coded and Study records will identify you only by number, not by name. This coded personal data will be processed electronically by INC Research on behalf of the Study Sponsor. INC Research is a contract research organization specialized in organization and management of clinical studies which has been contracted by the Sponsor to conduct this project. The Investigator is responsible for keeping the code list which makes it possible to link your assigned unique number to your name. This will be kept in a safe place to ensure that in case of an emergency you can be identified and contacted. The code list may be retained until 15 years after the end of the research or 2 years after the treatment has received its last authorisation for sale or development has discontinued or as required by applicable law, whichever is

longer. The information in your medical records, and the information you give to us, will be kept confidential (private) to the extent allowed by law. If any information from this study is published, your identity will not be disclosed, nor will your name be used in any way. Only coding or initials will appear on any records used.

In addition, qualified representatives of (i) the Study Sponsor and its worldwide affiliates; and/or (ii) INC Research and its worldwide affiliates; and/or (iii) the Food and Drug Administration (FDA); and/or (iv) independent auditors; and/or (v) national and foreign regulatory authorities (including the European Medicines Agency and the Ethics Committee) may look at your medical notes (including uncoded personal data) if necessary for data analysis. If your personal data is transferred outside the country the Sponsor of the Study is responsible for taking appropriate steps to protect your personal data and keep it secure.

With respect to data stored or processed in the United States by INC Research, INC Research will process personal data originating from Europe according to the relevant Safe Harbor Principles. INC Research subscribes to the "Safe Harbor Principles" issued by the U.S. Commerce Department on July 21, 2000. You can view INC Research's certification of compliance with the Safe Harbor Principles at https://safeharbor.export.gov/list.aspx.

By signing this form, you are consenting that the Principal Investigator and hospital/clinic staff can use your personal data for purposes of carrying out the Study, and can transfer and disclose your personal data to other members of the research team, as listed above.

With your permission your general practitioner will also be informed of your participation in this Study.

You have the right to access and correct the information collected about you during the Study and submit any queries or concerns about the collection or processing of your personal data by contacting the Principal Investigator at the address listed on page one of this document or INC Research's Global Privacy Officer at data.privacy@incresearch.com.

If you have personal insurance (eg, life insurance) your participation in this study may affect your policy. If necessary, before agreeing to take part in this study, you need to check this to ensure that your taking part does not affect your medical insurance or other personal insurance.

If you decide that you no longer wish to have your personal data shared:

- You must provide a written request to the Principal Investigator at the address listed on page one of this document and tell him or her that you no longer want to share your personal data.

- To ensure that the scientific integrity of the trial is not compromised, the research team may continue to process any of the personal data that they already have collected up until the date that you withdrew your consent. However, going forward, no additional personal data from you will be collected.
- You will no longer be able to take part in this Study.
- Your personal data may still be shared in accordance with applicable law if: (i) you have a bad reaction from the Study drug or device; and/or (ii) collection or further use of your personal is necessary to protect your vital interests; and/or it is legally required.

Your decision to withdraw your consent to participate will not involve any penalty or loss of access to treatment or other benefits to which you are entitled.

Your doctor, the sponsor company, or the regulatory authorities that have reviewed and approved the study has the right to stop your participation in the study at any time, with or without your consent, for any of the following reasons if:

- you have an adverse effect from the study drugs
- you need a treatment not allowed in this study

- your study doctor thinks that it is in your best interest not to take part any longer in the study
- you do not follow your study doctor's instructions, and you do not take the study drug as instructed
- you are a female and become pregnant
- or the study is canceled by the regulatory authorities or the sponsor company.

If this happens, the reason will be explained to you.

This authorization for use of your personal data will not expire until the end of the trial and the final results are obtained, but you may revoke your authorization at any time, by writing to the Principal Investigator.

Compensation

If you take part in this extension segment of the study, you will not be paid or rewarded in any way but your travelling expenses due to your participation in the study and after providing receipts for expenses encountered like travel, parking and meals, will be reimbursed with a maximum. Your study doctor can give you the details about how to get reimbursed. [If the volunteer is to be reimbursed, clearly state the total amount to be paid, conditions for the payment(s) and when the payment(s) will be made.]. You will not be charged for the [study drug/device] or for any of the procedures connected with your participation in this extension segment of the study.

If you become ill or are injured as a direct result of being in this extension segment of the study, necessary and associated professional medical care will be provided at no cost to you.

The sponsors of this extension segment of the *study* Laboratorios Farmacéuticos ROVI, S.A. *will pay (name of hospital department or research fund) for including you in this* extension segment of the *study. This payment represents a compensation for study-related tests and procedures completed, as required by the protocol.*

Contact Persons

If you have any questions about this study, or about what to do if you become ill while in the study, please call Dr. [name of principal investigator] at [phone number] or [name of sub-investigator, research nurse etc.] at [phone number].

If you have any questions about your rights as a study subject, please call [subject representative, ombudsman local EC etc.] at [phone number].

Insurance

In accordance with country regulation, the sponsor of the research has subscribed an insurance guaranteeing its civil liability, like that of the study doctors taking part in this research. A contract (enter policy number) was issued with the company
Name and address of the insurance company: .....
Policy number: .....

If you experience any unexpected symptoms or injury, and if emergency medical treatment is required, please report immediately to your study doctor.

Additional information

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov* as required by the U.S. Law and on https://www.clinicaltrialsregister.eu/ in agreement with the Declaration of Helsinki that recommends public registry of clinical trials [*add also any country specific public registry if applicable*.]. These web sites will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this web site at any time.

INFORMED CONSENT FORM TEMPLATE

- OPEN-LABEL EXTENSION SEGMENT OF THE STUDY -

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
EudraCT number: (applicable to EU countries only)

Sponsor name: Laboratorios Farmacéuticos ROVI, S.A.
Address of Sponsor: C/ Julián Camarillo, 35. 28037 Madrid, Spain

Principal Investigator: Insert Name, affiliation, location
Telephone number
Daytime:
After Office Hours:

	Please initial each box to indicate your agreement
1. I confirm that I have read and understand the information sheet for the above extension segment of the study. I confirm that the study has been explained to me and I have had the opportunity to ask questions and ample time to decide whether to participate. I know who to contact if I have any further questions.	
2. I confirm that I voluntarily agree to participate in this extension segment of the study, that I am aware of the conditions of participation and withdrawal and that I am free to leave the study at any time without giving a reason. I understand that I do not give up any of my legal rights by signing this Informed Consent Form.	
3. I understand that sections of my medical notes will be reviewed by representatives of INC Research, auditors and national and foreign regulatory authorities where it is relevant to my taking part in the study. I give permission for these individuals to have access to my medical records.	
4. I agree to the collection and transfer of my personal coded data including sensitive data initials, gender, race, ethnic origin, health, sex life, to Laboratorios Farmacéuticos ROVI, S.A. and to regulatory authorities both within and outside (insert country name), including to countries that may not have the same level of data protection as (insert country name),	
5. I agree that my personal coded data can be archived.	
6. I agree that my biological materials (blood, urine, etc) collected from me can be used for the purposes of this study.	

7. My consent does not discharge the sponsor and the study doctor for their responsibilities.	
8. I agree to take part in this study.	

Do you agree to have your general practitioner informed about your participation in the extension segment of this study? ☐ Yes ☐ No

An original or copy of the information sheet and signed consent form will be given to you to keep and an original will be placed in your subject's file at site.

Read and understood:

_____	_____	_____	_____
Patient's first and last Name	Signature	Date	Time

_____	_____	_____	_____
First and last Name of Investigator conducting consent	Signature	Date	Time