16 December 2021
EMA/CHMP/11233/2022 rev.1
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Okedi

International non-proprietary name: risperidone

Procedure No. EMEA/H/C/005406/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

Term	Definition
AFT	Antifungal therapy
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
AmB	Amphotericin B
AML	Acute myelogenous/myeloid leukaemia
ANC	Absolute neutrophil count
BAL8728	Inactive cleavage product of isavuconazonium sulfate
BMI	Body mass index
BMT	Bone marrow transplant
BRCP	Breast cancer resistance protein
CGI-S	Clinical global impression - severity of illness
CLSI	Clinical and Laboratory Standards Institute
CMH	Cochran-Mantel-Haenszel
COCs	Combined oral contraceptives
CT	Computed tomography
CV	Coefficient of variation
CYP	Cytochrome P
DB	Double-blind
DRC	Data review committee
ECG	Electrocardiogram
ECIL 3	3rd European Conference on Infections in Leukaemia
ESCMID/ECMM	European Society of Clinical Microbiology and Infectious Diseases/European Confederation of Medical Mycology
ECV	Epidemiological cut-off value
EORTC/MSG	European Organisation for the Research and Treatment of Cancer/Mycoses Study Group
EOT	End of treatment
ESRD	End-stage renal disease
EUCAST	European Committee on Antimicrobial Susceptibility Testing

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Laboratorios Farmacéuticos Rovi, S.A. submitted on 27 December 2019 an application for Marketing authorisation to the European Medicines Agency (EMA) for Okedi, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 July 2019. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of significant technical innovation.

The application concerns a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in a Member State on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

- *for the treatment of schizophrenia in adults.*
- *for the treatment of schizophrenia in adult patients with acute exacerbation where psychotic symptoms are moderate to severe.*
- *for the treatment of schizophrenia in adult patients previously stabilised with antipsychotics*

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data, a bioequivalence study with the reference medicinal product Risperdal, 4 mg, Coated tablet and appropriate non-clinical and clinical data.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Risperdal, 4 mg, Coated tablet
- Marketing authorisation holder: Janssen Cilag Ltd
- Date of authorisation: (06-12-1993)
- Marketing authorisation granted by:
  - Member State (EEA): United Kingdom
- Marketing authorisation number: PL00242/0189

Medicinal product authorised in the Union /Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Risperdal, 4 mg, Coated tablet
- Marketing authorisation holder: Janssen-Cilag GmBH
- Marketing authorisation granted by:

- Member State (EEA) Germany

- Marketing authorisation number: 28758.03.00

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Risperdal,4 mg, Coated tablet
- Marketing authorisation holder: Janssen Cilag GmbH
- Marketing authorisation granted by:
  - Member State (EEA): Germany
  - Marketing authorisation number(s): 28758.03.00
- Bioavailability study number(s): ROV-RISP-2020-01

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.4.2. Derogation(s) from market exclusivity

Not applicable

1.5. Applicant's request(s) for consideration

Not applicable

1.6. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
28 April 2016	EMEA/H/SA/3276/1/2016/III	*Carin Bergquist, Prof. Luca Pani*

The Scientific advice pertained to the following non-clinical, and clinical aspects:

- Justification of the choice of dose and site of injection for the proposed confirmatory Phase III study

based on a population PK model.

- Overall design of the proposed Phase III study and proposed PK sub-study
- Adequacy of proposed nonclinical and clinical data generated for the proposed product in conjunction with data referenced from the potential Reference Medical Products to support the registration a 'hybrid' Article 10(3) of Directive 2001/83/EC application.

In the scientific advice (EMA/CHMP/SAWP/ 270310/2016), the applicant's proposal to support the application with PK-data and only perform one clinical study in patients with acute exacerbations was not supported. "In conclusion, the CHMP consider that the differences in PK, the expected differences in TEAEs and the intention to show the new claim of treatment of acutely exacerbated schizophrenia patients the applicant should follow the CHMP guideline for medicinal products including depot preparations in the treatment of schizophrenia (EMA/CHMP/40072/2010 Rev. 1) and the different proposals of clinical development programme including comparator arm such as risperidone."

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: Ewa Balkowiec Iskra

The application was received by the EMA on	27 December 2019
The procedure started on	30 January 2020
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	20 April 2020
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	20 April 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	04 May 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	28 May 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	13 August 2020
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	22 September 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	01 October 2020
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	15 October 2020

The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	06 November 2021
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	01 December 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Okedi on	16 December 2021

2. Scientific discussion

2.1. Introduction

Schizophrenia is a severe mental illness characterised by psychosis, mood disorders, and cognitive disorders. The clinical signs and symptoms of schizophrenia are very complex and display different patterns which vary widely from patient to patient. The symptoms are commonly divided into several broad clusters.

- The positive symptoms represent an addition to normal behaviour that may involve hallucinations (perceptual experiences not shared by others), delusions (e.g., that others can interfere with one's thoughts), thought disorder, bizarre behaviour and disorganised speech, movement disorders (repetition of certain motions over and over), and catatonia (no movement or no response to others).
- The negative symptoms comprise elements that are absent from normal behaviour, including anhedonia (loss of the ability to experience pleasure), asociality (withdrawal from social contacts), lack of volition, lack of motivation, flat or blunted affect or emotion, and alogia (reduced quantity or content of speech).
- Patients with schizophrenia may also suffer from cognitive impairments such as diminished attention, memory, and executive function (e.g., the ability to plan, initiate, and regulate goal-directed behaviours).
- Behavioural and affective deficits including depression, lethargy, mood swings, and inappropriate and odd presentation are frequently associated with schizophrenia, causing avoidance on the part of others and thereby leading to social isolation.

The prevalence of schizophrenia (ie, the number of cases in a population at any one time point) approaches 1 percent internationally. The incidence (the number of new cases annually) is about 1.5 per 10,000 people.

As summarised in Meyer-Lindenberg (2002), while the pathophysiology of schizophrenia remains unclear, several neurotransmitter systems have been suggested to be implicated, including dopamine, serotonin, gamma-aminobutyric acid, glutamate, and acetylcholine. Of these, the dopamine system has received the most attention (Meyer-Lindenberg, Miletich et al. 2002). The importance of dopaminergic mechanisms in the pathophysiology of schizophrenia was inferred from the link between the antipsychotic efficacy of neuroleptic drugs and their affinity for the dopaminergic D_2 receptor. Frontal cortex dysfunction in this disorder has been postulated for even longer, since the modern conceptualisation of schizophrenia. Neuroimaging and basic research provide ample evidence for abnormalities in both of these domains in schizophrenia (Keks and Culhane 1999).

Antipsychotic drugs are commonly divided into typical (first generation) and atypical (second generation) categories. Seeman (2002) states that clinically effective doses of typical antipsychotic drugs generate a striatal dopamine D_2 receptor occupancy of about 60% to 80%, approaching a level that is associated with a high risk of extrapyramidal side effects (Seeman 2002). Typical antipsychotic drugs are mostly effective against positive symptoms, but have a more limited effect on and may even exacerbate negative and cognitive symptoms (Keks and Culhane 1999). In contrast, atypical antipsychotics have lower affinity for and occupancy of the dopaminergic receptors and a high degree of occupancy for the 5HT2A serotonin receptors. Compared to typical antipsychotics, atypicals induce fewer extrapyramidal side effects at clinically effective doses, and may have greater efficacy in reducing negative symptoms (Keks and Culhane 1999). According to Dazzan (2005) and Lieberman (2005), as a group atypicals also have a greater ability than typical antipsychotic drugs to treat mood symptoms in patients with either schizophrenia or affective disorders (Dazzan, Morgan et al. 2005, Lieberman, Stroup et al. 2005).

In 1984, based on the assumption that $5HT_{2A}$ antagonism might improve efficacy of D_2 blockers (particularly for negative symptoms) and reduce extrapyramidal side effects, Janssen Pharmaceutical developed the atypical antipsychotic risperidone, which combines potent $5HT_{2A}$ and D_2 blockades (Janssen, Niemegeers et al. 1988). Risperidone was launched in 1993 and rapidly incorporated into clinical practice, and is currently widely recommended as a first line option for treatment of psychosis (Keks and Culhane 1999).

Risperidone

Clinical experience has supported the efficacy and tolerability of both oral and long acting risperidone in several reviews (Grant and Fitton 1994, Rattehalli, Zhao et al. 2016, Sampson, Hosalli et al. 2016). The drug was first approved in Europe in 1993.

Risperidone is a benzisoxazole derivative and a second-generation antipsychotic agent which combines potent serotonin (5-hydroxytryptamine) 5-HT2 and dopamine D2 receptor antagonism (Grant and Fitton 1994). As with other oral antipsychotic drugs, a challenge associated with risperidone is that many patients with schizophrenia are poorly compliant with their medications. In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, 74% of patients were found to have discontinued their prescribed drug within 18 months, many due to either poor tolerability or lack of efficacy (Swartz, Stroup et al. 2008). Even among those who do not explicitly discontinue drug therapy, non-adherence to long-term oral medication regimes is one of the most significant therapeutic issues in the therapy of schizophrenia and related disorders. As a result, many patients do not experience the full benefit of antipsychotic drug therapy, and suffer frequent relapses or exacerbations, which require re-hospitalisation. Missing as few as 1 to 10 days of oral antipsychotic therapy nearly doubles the risk of hospitalisation (Keks and Culhane 1999, Byerly, Nakonezny et al. 2007). The use of depot antipsychotics as a maintenance treatment for individuals with a history of non-adherence with oral antipsychotics is well recognised.

The first depot second-generation antipsychotic drug on the market was Risperdal Consta, a long acting injection (LAI) risperidone formulation (Gaebel, Schreiner et al. 2010). Risperdal Consta is an IM risperidone microspheres formulation that is intended to deliver therapeutic levels of risperidone for 2 weeks. However, due to the inherent lag phase of most microsphere products, it takes approximately 3 weeks for sufficient amounts of risperidone to be released into systemic circulation; thus, patients must supplement the first 21 days post-injection with daily doses of oral risperidone.

Okedi is an LAI containing risperidone in situ microparticles (ISM) (Risperidone ISM). The application is a hybrid application where the reference product is oral risperidone. The proposed dosage is 75 mg or 100 mg monthly after titration with oral risperidone.

2.2. Quality aspects

Introduction

The finished product is presented as powder and solvent for prolonged-release suspension for injection containing 75 mg and 100 mg of risperidone as active substance. Other ingredients are poly(D,L-lactide-co-glycolide) (PLGA) as part of the powder and dimethyl sulfoxide (DMSO), the solvent.

The product is available as an integral Drug Device Combination product (DDC), as described in section 6.5 of the SmPC, containing:
Powder pre-filled syringe

Cyclic Olefin Polymer syringe with a nozzle cap and plunger stopper composed of chlorobutyl rubber covered with polytetrafluoroethylene.

Solvent pre-filled syringe

Cyclic Olefin Polymer syringe with a tip cap composed of chlorobutyl rubber, and a plunger stopper composed of bromobutyl rubber covered with ethylene-tetrafluoroethylene copolymer.

The doses are differentiated by the colour used in the finger flange of the solvent prefilled syringe, 100mg (blue) and 75 mg (red).

Each kit box of Okedi contains:

- An aluminium foil pouch with one pre-filled syringe containing powder and a silica gel desiccant sachet.
- An aluminium foil pouch with one pre-filled syringe containing the solvent and a silica gel desiccant sachet.
- One sterile needle for injection 2 inch (0.90 x 51mm [20G]) with safety shield used for gluteus administration.
- One sterile needle for injection 1 inch (0.80 x 25mm [21G]) with safety shield used for deltoid administration.

Active substance

General information

The chemical name of risperidone is 3-{2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-a]pyrimidin-4-one corresponding to the molecular formula $C_{23}H_{27}FN_4O_2$. It has a molecular mass of 410.68 g/mol and the following structure:

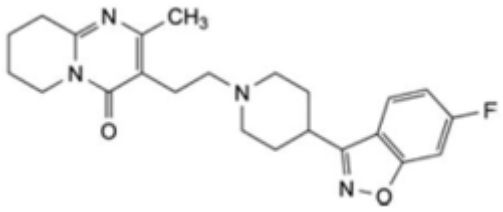


Figure 1: Active substance structure

The chemical structure of the active substance was elucidated by a combination of IR spectroscopy, ^{1}H NMR, ^{13}C NMR spectroscopy and mass spectrometry. The solid-state properties of the active substance were investigated by XRD.

The active substance is a white or almost white non-hygroscopic powder. It is practically insoluble in water, sparingly soluble in alcohol and freely soluble in dichloromethane, dissolves in dilute acid solutions.

Risperidone has a non-chiral molecular structure.

Polymorphism has been observed for risperidone. Literature describes the existence of three polymorphic forms: A, B and E. The selected polymorph was supplied and characterised by the sterile risperidone manufacturer. A study regarding polymorphism by X-ray diffraction on reference material and sterile risperidone from manufacturer (validation batches) was performed and indicates that the active substance manufacturer consistently manufactures the selected polymorph, which is controlled in the active substance release and shelf life specifications. It was also demonstrated that there is no polymorph change in the finished product at release or after storage under long term conditions for 36 months.

Manufacture, characterisation and process controls

As there is a monograph of risperidone in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for the active substance which has been provided within the current Marketing Authorisation Application. Sterile risperidone is manufactured from Ph. Eur. grade risperidone, with a Certificate of Suitability. The information relevant to risperidone has been assessed by the EDQM before issuing the Certificate of Suitability. Detailed information on the manufacturing process of the sterile active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

A single source of active substance has been used for manufacture of clinical batches and that manufacturer is the proposed commercial manufacturer.

Sterile risperidone is obtained by crystallisation, then sterilisation of crude risperidone.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate product and reagents have been presented. The process is carried out in a class A closed system to ensure sterility.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packaged in aluminium bins, which complies with the EU requirements.

Specification

Sterile risperidone is tested according to the Ph. Eur. monograph for risperidone with the addition of tests for residual solvents, sterility, bacterial endotoxins and particle size distribution. The active substance specification includes tests for: appearance, appearance of solution (Ph. Eur.), identity and polymorphism (IR, X-ray), assay (potentiometry per Ph. Eur.), related compounds (LC per Ph. Eur.), sulphated ash (Ph. Eur.), loss on drying (Ph. Eur.), residual solvents (GC), particle size distribution (laser diffraction), sterility (Ph. Eur.) and bacterial endotoxins (Ph. Eur.).

Neither class 1 nor class 2 solvent is used. The limit of residual amounts of organic solvents complies with the ICH Q3C.

Control for microbiological purity were introduced to ensure minimal microbiological contamination, taking into account the parenteral use and the sterile aspect.

The acceptance criteria for particle size distribution are based on functionality requirements and determined by the intended use.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on two commercial scale batches of the active substance as tested by the finished product manufacturer are provided. Further batch analysis data from the active substance manufacturer are provided as well. The results are within the specifications and consistent from batch to batch.

Stability

Stability data were provided on 12 commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 36 months under long term conditions (25 ºC / 60% RH), on 6 commercial scale batches for up to 12 months under intermediate conditions (30 ºC / 65% RH) and on 10 commercial scale batches for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines.

The following parameters were tested: appearance, polymorphism, assay, related compounds, loss on drying, particle size distribution (laser diffraction), sterility and bacterial endotoxins. The analytical methods used were the same as for release and are stability indicating.

All tested parameters were within their specification limits after 36 months under long term conditions, 12 months under intermediate and after 6 months under accelerated conditions.

Photostability testing following the ICH guideline Q1B was performed on one batch. The results show that the active substance is not sensitive to light.

One batch was exposed to stressed conditions: forced light, acid, alkaline, oxidant, and heating conditions were investigated. There is a slight degradation under dry heat and oxidative stress, but the active substance is stable under other stressed conditions.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months with no special storage conditions in the proposed container.

Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is presented as a powder and solvent for prolonged-release suspension for injection. Two strengths have been developed containing 75 mg or 100 mg risperidone respectively. The finished product is provided as a kit containing one powder pre-filled syringe with risperidone and the excipient PLGA, one solvent pre-filled syringe with DMSO and two sterile needles with safety shields included in a carton box.

The marketing authorisation for Okedi, powder and solvent for prolonged-release suspension for injection, 75 mg and 100 mg is applied for according to Directive 2001/83/EC Article 10(3), an abridged hybrid application.

The reference product is Risperdal 4 mg coated tablets (Janssen Cilag Ltd). Differences compared to the reference product are changes in therapeutic indication, pharmaceutical form, strength and route of administration.

The application submitted is partly based on data from the original reference medicine, and partly on data from the applicant's own non-clinical tests and clinical trials.

The finished product is a risperidone microparticle formulation which form *in situ*, developed as a prolonged-release formulation intended for intramuscular injection for treatment of schizophrenia by maintaining the effect for 1 month (28 days) after one single injection.

The formulation is administered after reconstitution as a risperidone suspension into the muscle tissue. When the formulation is exposed to body fluids or water, the solvent DMSO diffuses away from the polymer-drug mixture and water diffuses into the mixture. The polymer is hardened and thereby trapping or encapsulating the drug within the polymeric matrix which solidifies to form an implant.

The formulation consists of a controlled release system. The release of the active substance follows the general rules for diffusion or dissolution from the polymeric matrix.

The absorption process described by the pop PK model for the drug disposition in the PK section of this report comprises a complex absorption process that, in addition to the small fraction released immediately, describes and quantifies two first-order absorption processes, one combined zero-order and first order process, and a first-order elimination.

Pharmaceutical development of the finished product contains QbD elements.

Based on the clinical and pharmacokinetics characteristics of the known presentations of risperidone as well as the *in vitro* drug release and physiochemical characteristics of the reference product (Risperdal tablets) as well as the properties of the active substance, a QTPP was defined and justified.

Based on the QTPP and the controlled release mechanism, quality attributes were identified which ensure the performance of the finished product.

Since the finished product is packaged in two single use pre-filled syringes prior to reconstitution and administration, these components have been also evaluated to assess the quality attributes with potential impact on the finished product.

Critical material attributes of the active substance risperidone are polymorphism and particle size distribution.

DMSO is a well-known pharmaceutical ingredient and its quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation.

The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. No incompatibilities between sterile risperidone and the excipients have been observed in the stability studies performed both during the development of product and the formal and supporting studies.

Copolymer PLGA was selected as the excipient for the finished product formulation based on its properties and *in vivo* behaviour. Polymer degradation occurs via hydrolysis of the polymer within the body. This is a biocompatible and biodegradable polymer widely used for the development of sustained release formulations both for oral and systemic administration. As PLGA is critical to the release mechanism, its quality is controlled with specifications including tests such as appearance, identification (IR), bioburden (Ph. Eur.) and bacterial endotoxins (Ph. Eur.).

The formulation has been developed in several stages and the progress is extensively described. In clinical phase 1 and phase 2 studies, batches of risperidone with different particle size distributions and

with different sterilisation methods were used. Comparative *in vitro* drug release was demonstrated for all batches used in clinical studies including batches representative for marketing.

Drug release is a critical parameter for the reconstituted finished product and a dissolution test reflecting this property is included in the specification. A flow-through cell apparatus was selected for the development of a predictive and discriminatory dissolution method capable of detecting manufacturing differences and predicting the *in vivo* performance.

Apparatus 4 was chosen as it mimics the physiological flow of interstitial fluid after intramuscular administration across the *in situ* formed finished product depot. The development was based on the compendial flow through cell method described in the Ph. Eur. as well as in the USP.

A drug release test was developed with multiple time points to correlate with the three stages of the release mechanisms. The dissolution test is described and discriminatory power with regards to varying active substance particle size distribution has been demonstrated for the 28-day real time test method. An accelerated dissolution test was developed using a time scaling factor. Discriminatory power is also demonstrated for the accelerated release method with regards to meaningful variations for the most relevant critical material attributes. The formulation and manufacturing development have been evaluated through the use of risk assessment and design of experiments to identify the critical product quality attributes and critical process parameters. A risk analysis was performed using the failure mode effect analysis (FMEA) method in order to define critical process steps and process parameters that may have an influence on the finished product quality attributes. The risk identification was based on prior knowledge of products with similar formulations and manufacturing processes as well as on the experience from formulation development, process design and scale-up studies. The critical process parameters have been adequately identified.

Formulation Design Space is proposed with established acceptable ranges of the starting materials used in the manufacture of risperidone powder as well as the manufacturing process tolerances of the components of the formulation (risperidone, PLGA and DMSO). The ranges were investigated in multi-variate experiments and statistic methodology was applied to interpret the results and identify ranges where the formulation inputs will ensure the quality of the finished product.

The development of the reconstitution process is described. After removal of caps, the syringes can be joined together via a twist-locking mechanism in order to mix the contents. Data was provided demonstrating that mixing by 100 pushes of the syringe plunger provides a homogenous suspension. User errors have been evaluated by a comparability study demonstrating similar concentration and *in vitro* drug release using 50 pushes. The syringes are then disconnected by untwisting before attachment of a needle for intra-muscular administration. Clear instructions for healthcare professions, including diagrams, are given in the product information.

The powder pre-filled syringes are manufactured using aseptic processing since terminal sterilisation was not feasible. The sterilisation method is sufficiently justified according to EMA/CHMP/CVMP/QWP/850374/2015.

The pharmaceutical development of the solvent for reconstitution in pre-filled syringe is described with sufficient details. The solvent pre-filled syringes are manufactured by sterile filtration followed by aseptic filling. The sterilisation method has been discussed and due to the nature of the product presenting a low risk with regards to microbiological growth, the justification was considered sufficient.

The finished product for the pivotal clinical trial was manufactured by aseptic filling using a semiautomated procedure at the proposed commercial site, which is the same filling line and site where batches used for validation of manufacturing process and formal stability studies were produced. There are no significative differences between the manufacturing process used to produce the powder prefilled

syringes batches used in the pivotal clinical trial and the comparative bioavailability study and the manufacturing process proposed for commercialisation.

The primary packaging is cyclic olefin polymer syringe with a nozzle cap and plunger stopper composed of chlorobutyl rubber covered with polytetrafluoroethylene. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. Functional performance and compatibility aspects which determine the suitability of the DDC related to its intended use have been presented and found acceptable. Suitability of the DDC is also supported by full shelf life stability studies under ICH long term, intermediate and accelerated conditions.

Physical and chemical compatibility between the finished product and its container closure system has been demonstrated through interactions studies and during simulated transportation studies. The compatibility of the plastic material with the medicinal product has been demonstrated by performing extraction and interaction studies.

Manufacture of the product and process controls

The manufacturing process of risperidone powder in pre-filled syringes is carried out by semi-automatic aseptic filling of the two components the excipient PLGA and the active substance risperidone, under sterile conditions. The manufacturing process of 75 mg and 100 mg powder syringes is common for both presentations. The only difference consists in the filling weight of each component.

For the solvent for reconstitution in pre-filled syringe, the manufacturing process includes sterile filtration of DMSO and aseptic filling into syringes. The manufacturing process is adequately described and defined in the submission.

Process validation for the risperidone powder in pre-filled syringes has been performed on four commercial scale batches (two of each product strength), including measuring relevant attributes such as content uniformity. This approach was accepted due to similarity of the manufacturing process between different dosage strengths. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Process validation for the solvent for reconstitution in pre-filled syringe has been performed on four batches (two per strength). Both manufacturing process steps have been considered critical, i.e. sterile filtration of DMSO and aseptic filling into syringes. The holding time from beginning of compounding to beginning of filtration and the holding time from beginning to end of the aseptic filling of DMSO solvent syringe is proposed and accepted based on the data provided. The in-process controls presented are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The release specifications for syringes containing powder include appropriate tests for this kind of dosage form: appearance, identification (HPLC, UV), content uniformity (Ph. Eur.), assay (HPLC), impurities (HPLC), moisture content (KF), bacterial endotoxins (Ph. Eur.), sterility (Ph. Eur.) and closure system integrity (vacuum decay leak testing).

The release specifications for pre-filled syringes containing DMSO shown include appropriate tests: appearance, identification (IR, refractive index (both Ph. Eur.)), water (KF), related substances (USP), sub-visible particles (Ph. Eur.), extractable volume (in house), sterility (Ph. Eur.), bacterial endotoxins (Ph. Eur.).

Release and shelf-life specifications for the reconstituted finished product include tests such as appearance, drug release (Ph. Eur., UPLC), content uniformity (Ph. Eur.) and assay (HPLC) and injectability (in house).

Specifications for pre-filled syringes containing powder, for pre-filled syringes containing DMSO and for the reconstituted finished product have been set in line with ICH and Ph. Eur. Requirements, taking into account the CQAs of the product and clinical batches. The test parameters are relevant for the pharmaceutical form and administration and the acceptance criteria is sufficiently justified for all parameters.

For the pre-filled syringes containing powder specifications for impurities have been set in line with guideline ICH Q3B(R2) for potential degradation products identified during the forced degradation study are considered acceptable.

For the reconstituted finished product injectability determination test is included in line with ICH guideline. Both break force and glide force are appropriately controlled using the same limits at release and shelf-life.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. In addition, 3 batches of powder in syringes and 3 batches of DMSO in syringes covering both strengths were tested using a validated ICP-MS method and all elemental impurities were below 15% of their respective PDE. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed as requested by the CHMP in the form of Major Objection, considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for four commercial scale batches (two of each product strength) confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from four commercial scale batches of the powder pre-filled syringes (two batches of each product strength each made from two different batches of the active substance and excipient) stored for up to 24 months under long term conditions (25ºC / 60% RH), for up to 12 months under intermediate conditions (30ºC / 65% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Additional supportive data on clinical batches performed using the same formulation, manufacturing process and

container closure system as proposed for marketing the finished product were provided. These batches were stored at 25ºC ± 2ºC/ 60% RH ± 5% RH and 5ºC + 3ºC.

Samples of risperidone powder for prolonged-release suspension were tested for stability indicating parameters such as appearance, assay, impurities, bacterial endotoxins and sterility. Reconstituted finished product was tested for stability indicating parameters such as appearance, drug release, assay.

The analytical procedures used are stability indicating. Stability results of the powder prefilled syringes stored under long term conditions and intermediate conditions did not show changes, but the appearance of the product stored under accelerated conditions. No significant changes were observed for other parameters.

Stability data from four commercial scale batches of the pre-filled syringes containing solvent (two batches of each product strength) stored for up to 24 months under long term (25ºC / 60% RH), for up to12 months under intermediate (30ºC / 65% RH) conditions and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. Solvent prefilled syringes were stored in two orientations: inverted (or horizontal) and upright (or vertical). The batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Additional supportive data on batches gathered during the development were provided. These batches were stored at 25ºC ± 2ºC/ 60% RH ± 5% RH and 5ºC + 3ºC.

Samples of solvent containing pre-filled syringes were tested for appearance, water content, related compounds, sub-visible particles, sterility bacterial endotoxins and container closure integrity. The specifications and methods were the same as those used for release.

The results show that the storage position of the DMSO solvent prefilled syringe (placed into an inverted or horizontal position and an upright or vertical) is not relevant for stability. No significant changes have been observed under any conditions.

In addition, one batch of each strength of the powder filled syringes and DMSO-filled syringes was exposed to light both within and outside of secondary packaging, as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. According to the results, neither component of the finished product is photosensitive.

An in-use stability study was performed to cover the recommended in-use shelf-life defined as "immediate administration" after reconstitution. Based on the provided data, it can be concluded that the holding time for the reconstituted product should not exceed 15 minutes due to loss of homogeneity, hence supporting the recommendation of "immediate administration."

A stress study was performed for the powder filled syringes to investigate the stability-indicating power of the analytical procedures for assay and related substances. Degradation information obtained from stress studies (products of acid and base hydrolysis, thermal degradation, photolysis, and oxidation) for the active substance in the finished product demonstrates the specificity of the assay and analytical procedures for degradants.

Based on available stability data, the proposed shelf-life of 2 years when stored under 30ºC in the original package to protect from moisture as stated in the SmPC (sections 6.3 and 6.4) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The finished product is a risperidone microparticles formulation which form *in situ*, developed as a prolonged-release formulation intended for intramuscular injection for treatment of schizophrenia by maintaining the effect for 1 month (28 days) after one single injection. It has been demonstrated that the applied control strategy ensures the quality of the finished product, including the *in vivo* release properties.

During the procedure a risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed as requested by CHMP. Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary. The Major Objection was therefore resolved.

Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The nonclinical development programme of Risperidone ISM relies on information from the Risperdal® tablets (Risperdal®-SmPC, 2019) as well as additional PK and toxicology studies conducted with Risperidone ISM by the applicant. The nonclinical programme was agreed by the CHMP in a Scientific Advice held on April 28 2016 (EMA/CHMP/SAWP/270310/2016).

The pivotal non-clinical studies were performed in accordance with GLP.

2.3.2. Pharmacology

The pharmacodynamics of risperidone is well-known and thoroughly described in the literature. In summary, risperidone exhibits a combined antagonism activity on both serotonin 5-HT2 and dopamine D2 receptors with a high binding affinity. Functional dopamine D2 and serotonin 5-HT2 receptor antagonism activity of risperidone has been proven in a variety of *in vitro* and *in vivo* in animal models including mice, rats, guinea pigs and dogs. The pharmacological profile of risperidone includes interaction with histamine H1 and α1- and α2-adrenergic receptors but the compound is devoid of significant interaction with cholinergic and a variety of other types of receptors.

Hypotension and reflex tachycardia observed in dogs are considered to be predominantly consequences of vascular α1-adrenoceptor blockade and therefore, risperidone may enhance the effects of antihypertensives.

Risperidone and 9-OH-risperidone both can block IKr in HERG-transfected cells and increased ventricular action potential duration (APD) in a variety of preparations including canine Purkinje fibres, guinea pig cardiac papillary muscle, rabbit Purkinje fibres and canine ventricular myocytes. These effects occurred generally at higher concentrations and the *in vivo* data did not demonstrate a significant risk of arrhythmogenicity for risperidone since no significant effect of risperidone on QT, in either anaesthetised guinea pig or awake dog were observed.

No further pharmacology studies are required, and the applicant provides none.

2.3.3. Pharmacokinetics

The applicant has not conducted specific nonclinical studies with Risperidone ISM to evaluate the distribution, metabolism, excretion or PK drugs interactions of risperidone after IM administration of the product and no such studies are required. Reference to published data is considered adequate and sufficient.

The applicant has conducted numerous PK studies and has presented 4 single-dose PK studies in NZW rabbits and Beagle dogs to identify the lead candidate Risperidone ISM formulation for further evaluation in nonclinical studies and clinical trials.

Because risperidone presents an extensive and predominant metabolism to 9-OH-risperidone, which exhibits equivalent pharmacological activity as the parent compound, the PK evaluation of the product was based on active moiety (defined as risperidone plus 9-OH-risperidone) and not on individual risperidone or 9-OH-risperidone values.

The bioanalytical methods used for the characterisation of the nonclinical PK and toxicokinetic profile of the Risperidone ISM involved gradient elution reversed-phased high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS).

All validations were performed in accordance with the criteria laid down in the FDA guidance "Bioanalytical Method Validation, 2001". Afterwards this guidance was updated in 2018 (FDA Center for Drug Evaluation and Research (CDER), 2018) and the EMA published the Guideline for Bioanalytical Method Validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**, 2011), but the implemented changes do not affect the quality and acceptability of the results. Method validations were performed according to the principles of GLP.

The PK profile of Risperidone ISM showed that the maximum concentration (Cmax) usually, with some exceptions and with a high variability, appears during the first 24 hours post-implantation followed by a gradual decrease to sustained levels until the end of the formulation effective period (around 28 days in rabbits and 28-35 days in dogs) for all studied compositions. Overall, the nonclinical PK of these studies was consistent with that known for risperidone.

Risperidone is known to be rapidly distributed in different tissues including plasma, spleen, liver, kidney, lung, plasma and, in lesser extent, brain. The Vd after single dose of risperidone (2 mg/kg IV) was estimated at 0.32 L and 2.3 L for risperidone and 9-OH-risperidone, respectively. The protein binding of risperidone was found to average 88.2% in rat plasma and 91.7% in dog plasma. The protein binding of the metabolite 9-OH-risperidone was somehow lower, averaging 74.7% and 79.7% in rat and dog plasma, respectively. The percentage of risperidone distributed to blood cells in blood cell suspensions amounted 72% and 75% in rats and dogs, respectively.

The major metabolic pathways of risperidone in rats and dogs are the same as those in humans, namely: a) alicyclic hydroxylation, with resulting 9-OH-risperidone as the main metabolite, b) oxidative dealkylation at the piperidine nitrogen, and c) benzisoxazole scission. *In vivo* and *in vivo* studies in rat liver microsomes revealed that CYP2D and CYP3A are the major enzyme involved in the metabolism of risperidone playing both a predominant role in 9-hydroxylation of risperidone.

In rats, risperidone is mostly excreted in the faeces and in accordance to an extensive and rapid biliary excretion of metabolites; and with a limited enterohepatic circulation. In dogs, slower excretion than in rats was observed, and fractions excreted in the urine and faeces were similar. After a single oral dose a $t_{1/2}$ of ca. 1.4 hours for risperidone and 21 hours for the 9-OH-risperidone was estimated in dogs whereas t1/2 of 0.82 hours for risperidone and 5.1 hours for the 9-OH-risperidone were calculated in rats after a single IV dose and, when administered orally in rats $t_{1/2}$ reached values of 2.6 hours and 8.5 hours for risperidone and 9-OH-risperidone, respectively. A clearance of 0.27 L/h and 0.32 L/h for risperidone and 9-OH-risperidone was estimated from rat studies. In animal studies, risperidone and 9-OH-risperidone are excreted in milk.

2.3.4. Toxicology

The nonclinical toxicology programme supporting Risperidone ISM drug product is based on published data of studies evaluating risperidone and its active metabolite 9-OH-risperidone in mice, rats, and dogs via oral, intravenous (IV), and subcutaneous (SC) routes.

In addition to the public available information, the applicant has conducted sub-chronic toxicity studies (2-cycle, 28 days (rabbit) and 31 days (dogs)/cycle) and Good Laboratory Practice (GLP)-compliant chronic (12-cycle, 30 days (rabbits, dogs)/cycle) toxicity studies including toxicokinetic and local tolerance endpoints as well as an Ames Test study. These species were selected as rodents were considered too small for accurate dosing of the small injection volumes used with the ISM formulation. The findings such as somnolence, miosis, swelling mammary glands in females were mainly the result of prolactin-mediated effects or they were related to pharmacological effects of risperidone. No changes in the ECG were attributed to Risperidone ISM. The NOAELs obtained in these studies were the respective highest doses tested, of 76.7 mg/kg and 38.3 mg/kg Risperidone ISM (corresponding to 10 mg/kg and 5 mg/kg of risperidone, respectively) for rabbits and dogs in the 2-cycle repeated studies, and of 115 mg/kg and 57.5 mg/kg Risperidone ISM (corresponding to 15 mg/kg and 7.5 mg/kg of risperidone, respectively) for rabbits and dogs in the 12-cycle chronic studies.

Evaluation of local tolerance of Risperidone ISM revealed macro- and microscopically, muscular foreign body granulomatous inflammation with or without focal/multifocal multinucleated giant cells in the administration site of animals given Risperidone ISM. This effect was considered as a natural body response to the presence of a foreign substance. Reversibility of local effects at the injection site was demonstrated. Local tolerance and toxicity evaluation also included dose groups of DMSO-only at 70.0 and 35.0 mg/kg. Transient pain following injection was observed in the dog and was attributed to DMSO. No systemic toxicity attributed to DMSO was observed. The approximated clinical dose of DMSO of 10 mg/kg in the 100 mg dose of risperidone (bodyweight of 50 kg; dose of DMSO = 466.7 mg) is considered supported.

The limits for impurities of the powder prefilled syringe are below the identification thresholds and the specifications of DMSO impurities complies with the DMSO monograph according to Ph. Eur. Further toxicological qualification of impurities is not required.

The reverse mutation assay conducted by the applicant with Risperidone ISM, showed no mutagenic activity in Salmonella typhimurium and in Escherichia coli strains, with or without S9.

Published literature indicates no mutagenic potential of risperidone. In oral carcinogenicity studies of risperidone in rats and mice, increases in pituitary gland adenomas (mouse), endocrine pancreas adenomas (rat), and mammary gland adenomas (both species) were reported. This effect is thought to be related to prolonged hyperprolactinaemia resulting from dopamine D2 antagonism. The relevance for human risk of the findings of prolactin-mediated endocrine tumours in rodents is unknown.

No teratogenicity effects associated to risperidone administration was observed in rat or rabbit. In rat reproduction studies with risperidone, adverse effects were seen on mating behaviour, and on the birth weight and survival of the offspring. In rats, intrauterine exposure to risperidone was associated with cognitive deficits in adulthood similarly as observed with other antipsychotic drugs. Studies with risperidone in juvenile rats have shown a delay in physical development, with a reversible impairment of performance and memory. Dosing during lactation resulted in a reduced body weight of the high-dosed dams.

2.3.5 Ecotoxicity/environmental risk assessment

Risperidone is already used in existing marketed products and no significant increase in environmental exposure is anticipated. Since risperidone is not currently approved in Croatia an increased environmental exposure might be expected following an approval through the centralised procedure. However, since the tolerability of risperidone should be established with oral risperidone before initiating treatment in patients who have not been previously exposed to risperidone it is nevertheless agreed that there will be no increased exposure to the environment following approval of this risperidone formulation. Therefore risperidone is not expected to pose a risk to the environment.

No Environmental Risk Assessment studies were submitted. This was justified by the applicant as the introduction of Okedi manufactured by Laboratorios Farmacéuticos Rovi, S.A. is considered unlikely to result in any significant increase in the combined sales volumes for all risperidone containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar.

2.3.6. Discussion on non-clinical aspects

The bioanalytical methods used for the characterisation of the nonclinical PK and toxicokinetic profile of the Risperidone ISM (risperidone + 9-OH-risperidone) involved gradient elution reversed-phased high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS).

The toxicological profile of risperidone is well characterised with the current knowledge on nonclinical toxicity published literature and with the clinical efficacy and safety data accumulated for decades of medical usage of the RMP Risperdal®.

The studies conducted by the applicant support the safety of the risperidone LAI formulation, with no significant differences in toxicological findings between the pharmaceutical forms of the reference risperidone oral tablets and Risperidone ISM alternative LAI form. However, in the 2-cycle study in the rabbit, platelet values were increased in groups 2, 3, and 4 of females and were recognised by the applicant as not associated with the treatment. In the 12-cycle study in the dog dose levels were selected as equivalent dose for anticipated therapeutic plasma levels in humans during approximately 4 weeks. Therefore, the chosen doses are sufficient to produce pharmacodynamics or/and therapeutic effect. The observed local reactions following IM administration are considered acceptable.

The wordings in the SmPC Section 5.3 is identical to the wordings for Risperdal, except for the order and the additional text that is unique for the IM LAI formulation.

2.3.7. Conclusion on the non-clinical aspects

There are no objections for approval of Risperidone ISM from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

The clinical development programme was designed considering the following regulatory guidances and advice. The development programme has been designed in accordance with the Guideline on the pharmacokinetic (PK) and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1) 2014, the development guidance for schizophrenia (EMA/CHMP/40072/2010 Rev.1;2012). The Scientific Advice discussions were (EMA/CHMP/SAWP/270310/2016) taken into account in terms of development for acute relapse and for long term safety. However, with regard to patients medically stabilised no specific studies were conducted with an active comparator as the applicant believes the hybrid submission will account for the treatment of schizophrenia in adult patients previously stabilised with antipsychotics on the basis of the population (pop) PK analyses.

The clinical development of Risperidone ISM is composed of three Phase 1 studies (ROV-RISP-2009-01, ROV-RISP-2011-01 [PRISMA-1] and ROV-RISP-2020-02), four multiple dose studies, two comparative bioavailability study (ROV-RISP-2016-02 [BORIS, US reference product] and ROV-RISP-2020-01 [BORIS-2, EU reference product]) in stable schizophrenia, one Phase 2 study (ROV-RISP-2011-02 [PRISMA-2]) in stable schizophrenia and the Phase 3 study (ROVRISP-2016-01 [PRISMA-3]), ie the pivotal study, in acute relapse of schizophrenia, which also includes an open label extension (OLE) phase with rollover patients from the main phase as well as de novo stable patients.

Two single-dose Phase 1 studies have been conducted to characterize the PK characteristics and to evaluate the safety and tolerability of Risperidone ISM in healthy volunteers (n=17) ROV-RISP-2009-01) and in subjects with schizophrenia or schizoaffective disorder (n=36) ROV-RISP-2011-01 [PRISMA-1]), respectively. Doses evaluated (25 mg, 37.5 mg, 50 mg, 75 mg, and 100 mg) and the pop PK (11/ROV/081/1146a;2012) simulations to support them indicated that doses of Risperidone ISM 75 mg and 100 mg were the most appropriate for study in medically stable patients for maintenance and to evaluate both for the acute treatment of schizophrenia.

GCP aspect

The Clinical trials were performed in accordance with GCP as claimed by the applicant

Tabular overview of clinical studies

A listing of all clinical studies is provided below.

Table 1: Clinical Development of Risperidone ISM Completed Studies

Study Identifier	Study design / formulation	Subjects, Dose and Duration	Objectives
ROV-RISP-2020-01 BORIS-2	Phase 1, multicentre, sequential, open-label,	Medically stable schizophrenia patients on Risperdal 4 mg po **Reference**: 4 mg Risperdal PO EU	Steady-state comparative bioavailability of 100 mg Risperidone ISM

Study Identifier	Study design / formulation	Subjects, Dose and Duration	Objectives
	multiple dose Final formulation (with milling)	product, D1-D7 OD, 77 subjects **Test:** Risperidone ISM 100 mg IM, D8-D92 Q4W, 69 subjects Continued 4 mg po for 1 week to achieve steady-state. Then, Risperidone ISM was given for a total of 4 IM doses were given (each dose separated by 4 weeks). 55 subjects completed the study.	injectable every 4 weeks compared to once-daily 4 mg oral risperidone in subjects with schizophrenia stabilised on oral risperidone treatment
ROV-RISP-2020-02	Phase 1, multicentre, open-label, single dose, Final formulation (with milling)	Schizophrenia patients, 25 enrolled, 18 completed Risperidone ISM 100 mg IM single dose (gluteus)	characterize the PK of Risperidone ISM in schizophrenic patients after one intramuscular injection.
ROV-RISP-2016-02 BORIS	Phase 1, multicentre, sequential, open-label, multiple dose Final formulation (with milling)	Medically stable schizophrenia patients (20-65 years) on Risperdal 4 mg po for at least a month prior to inclusion **Reference**: 4 mg Risperdal PO US product, D1-D7 OD, 48 subjects* **Test:** Risperidone ISM 100 mg IM, D8-D92 Q4W, 58 subjects Continued 4 mg po for 1 week to achieve steady-state. Then, Risperidone ISM was given for a total of 4 IM doses were given (each dose separated by 4 weeks).	Steady-state comparative bioavailability of 100 mg Risperidone ISM injectable every 4 weeks compared to once-daily 4 mg oral risperidone in subjects with schizophrenia stabilised on oral risperidone treatment
ROV-RISP-2009-01	Phase 1, single-centre, sequential, open-label, in single scaled doses Early formulation (no milling)	Healthy volunteers (18-50 years), 21 screened, 17 included **Treatment 1 (Cohort 1) n = 9**: 25 mg Risperidone ISM, IM (gluteus) **Treatment 2 (Cohort 2) n = 8**: 37.5 mg Risperidone ISM, IM (gluteus)	PK, safety and tolerability of a new formulation of long-acting Risperidone injection using ISM
ROV-RISP-2011-01 PRISMA-1	Phase 1, open-label, randomised, single-dose,	35 subjects (18-59 years) (36 screened) with schizophrenia or schizoaffective disorder included **Treatment 1 (Group 1) n = 13**: 50	PK, safety and tolerability of Risperidone ISM in subjects with schizophrenia or

Study Identifier	Study design / formulation	Subjects, Dose and Duration	Objectives
	multicentre Early formulation (no milling)	mg Risperidone ISM **Treatment 2 (Group 2) n = 12**: 75 mg Risperidone ISM **Treatment 3 (Group 3) n = 11**: 100 mg Risperidone ISM All IM (gluteus)	schizoaffective disorder after one IM injection at different dose strengths
ROV-RISP-2011-02 PRISMA-2	Phase 2, multicentre, open-label, two-arm, parallel-design, repeat-dose Early formulation (with milling)	70 subjects (18-65 years) with schizophrenia were randomised **Treatment**: 75 mg Risperidone ISM IM Q4W, up to 4 doses Gluteus n = 20 Deltoid n = 23	PK of Risperidone ISM over four injections in the gluteal and deltoid muscle at 28-day intervals and at one dose strength; exploratory efficacy evaluation
ROV-RISP-2016-01 PRISMA-3	Phase 3, multicentre, randomised, DB, placebo-controlled, parallel groups Final formulation (with milling)	438 subjects randomised **Treatment 1 (Group 1) 75 mg Risperidone ISM**, n = 145, 25 with intense PK sampling **Treatment 2 (Group 2) 100 mg Risperidone ISM**, n = 146, 27 with intense PK sampling **Treatment 3 (Group 3) placebo**, n = 147 IM Q4W gluteal or deltoid, up to 3 doses (DB phase). OLE: Treatment 1 (n = 116) or 2 (n = 99) for up to 12 months.	Efficacy and safety of Risperidone ISM compared to placebo in subjects with schizophrenia Long term evaluation of efficacy and safety of Risperidone ISM

* total 58 subjects, 10 patients excluded as not having reached steady state at D7; DB: Double-Blind; IM: intramuscular; ISM: *in situ* microparticles; OLE: Open-Label Extension; PK: pharmacokinetic(s). Number of subjects refers to the PK population for each study. Greyed fields denote the studies performed with the final formulation.

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

The applicant intends to use pharmacokinetics for bridging to the marketed immediate release tablet. Bridging is pivotal as it is required for non-clinical data, pharmacokinetics in special populations, interactions, efficacy and safety. A similar total exposure (AUC) of active substance must be shown for

Risperidone ISM as for the German reference product. Data is generally presented for the active moiety, which is defined as risperidone plus 9-OH-risperidone.

Methods

Bioanalysis

Three different LC-MS/MS methods have been validated for risperidone and its active metabolite 9-OH-risperidone (also called paliperidone). No cross-validation was performed. Within study validation was within present acceptance criteria.

Population PK analysis

The aim of the analysis was to describe the population pharmacokinetics (Pop PK) of risperidone active moiety and to investigate relationships between clearance and several covariates (such as body size, age, race, sex).

Pop PK models have previously been developed based on exposure data of risperidone, 9-OH-risperidone (equipotent active metabolite) or the active moiety from the single-dose studies, ROV-RISP-2009-01 and ROV-RISP-2011-01 (PRISMA-1), and the multiple-dose study, ROV-RISP-2011-02 (PRISMA-2), (11/ROV/081/1146a;2012, 11/ROV/081/1146a;2015, Snoeck, 2019). The final Pop PK model (18ROV0059) was developed building on the previous models describing the PK of the active moiety and included data from five clinical studies, ROVI-RISP-2009-01, ROV-RISP-2011-01 (PRISMA-1), ROV-RISP-2011-02 (PRISMA-2), ROV-RISP-2016-01 (PRISMA-3) and ROVRISP-2016-02 (BORIS).

Simulations on different dosing schemes (switching between risperidone oral, LAI and Risperidone ISM, dose de-escalation, dose escalation, missed doses etc), including dose-dumping, were based on the final Pop PK model (SP1807266 (1381b) and SP1901640 (1146c)).

Data

The final pharmacokinetic dataset consisted of 447 subjects (25 mg (n=9 subjects); 37.5 mg (n=8 subjects); 50 mg (n=10 subjects); 75 mg (n=213 subjects) and 100 mg (n=207 subjects)) with 6288 active moiety concentrations.

Results

The final population PK model to describe active moiety PK after administration of Risperidone ISM, was a one-compartment disposition model with a complex absorption process, combining one small amount immediately dosed into the central compartment, two first-order absorption processes and one combined zero-order and first order process, and a first-order elimination from the central compartment. The final model parameter estimates are presented in Table 2.

Table 2: Pharmacokinetic Parameters of Active Moiety from the Final Population PK Model (RISPISM012)

Parameter	*Estimate*	*RSE (%)*	*IIV (%)*	*IIV RSE (%)*	*IOV (%)*	*IOV RSE (%)*
CL_{40} (L/h)	4.67	2.21	32.7	9.53	NE	NE
V_4 (L)	248	8.83	34.2	21.5	NE	NE
F_R*	0.431	3.20	20.3	21.9	33.8	9.09
F_{R1}*	0.0725	12.0	35.9	34.0	36.6	29.4
F_{R2}*	0.0873	17.9	NE	NE	170	16.5
K_{14} (1/h)	0.00583	6.04	16.8	20.2	NE	NE
Lag time 2 & lag time 3 (h)	255	2.11	NE	NE	NE	NE
K_{24} (1/h))	0.000691	8.35	109	26.2	NE	NE
D_3 (h)	308	2.23	15.1	18.7	NE	NE
K_{34} (1/h)	0.00763	6.64	25.1	49.4	36.9	24.8
F_{BA}	1 FIX	NA	NE	NE	15.2	18.5
F_5 study Boris	0.585	4.92	25.8	41.5	NE	NE
F_5 study Prisma-3	1.31	13.2	159	8.97	NE	NE
			Correlation			
Covariance CL-V	0.0909	15.1	+0.812	NA	NA	NA
Form: D3	+0.266	1.17	NA	NA	NA	NA
Injection site: F_R	+0.119	25.2	NA	NA	NA	NA
Prisma-2: Fr, F_{R1} & F_{R2}	+0.537	9.93	NA	NA	NA	NA
BMI: CL_{40}	-0.267	34.6	NA	NA	NA	NA
FORM: CL_{40}	+0.166	35.1	NA	NA	NA	NA
Sex: CL_{40}	-0.188	15.6	NA	NA	NA	NA
Residual error (%)	18.2	2.51	NA	NA	NA	NA

IIV: Inter-individual variability; IOV: Inter-occasion variability; NA: not applicable; NE: Not estimated in the model; RSE: Relative Standard Error which expresses the precision of estimation. *: IIV or IOV for Logit transformation =100*(SQRT(OMEGA2)*THETA(.)*(1-THETA(.)))/THETA(.).

CL_{40}=apparent total clearance of the active moiety; D_3=duration of the zero-order absorption process from the third depot compartment to central compartment; F_1=fraction of the dose absorbed from the first compartment computed as $F_1=F_R*(1-F_{R1})$; F_2=fraction of the dose absorbed from the second compartment computed as $F_2=(1-F_R)*F_{R2}$; F_3=fraction of the dose absorbed from the third compartment computed as $F_3=(1-FR)*(1-FR_2)$; F_4=fraction of the dose given directly into the fourth compartment computed as $F_4=FR*FR1$; F_5=fraction of oral risperidone dose given in PRISMA-3 and BORIS subjects; F_{BA}=bioavailability after IM administration (fixed to 1) and introduce for estimation of inter occasion variability; K_{14}=absorption rate constant from first depot compartment to central compartment ; K_{24}=absorption rate constant from second depot compartment to central compartment; K_{34}=absorption rate constant from third depot compartment to central compartment; $TLAG_2$=lag time from the second depot compartment; $TLAG_3$=lag time from the third depot compartment; V_4=central volume of distribution.

Epsilon shrinkage was 25.5%. The distribution of eta values for PK parameters showed that almost all random effects were centred and the η-shrinkage for FR, FR_1, K_{14}, K_{24}, K_{34} and D_3 ranged between 44,1 and 65,8 %. The η-shrinkage was < 25%, for CL, V_4 and F_5. Prediction-corrected visual predictive checks (pVPC) are shown in Figure 2.

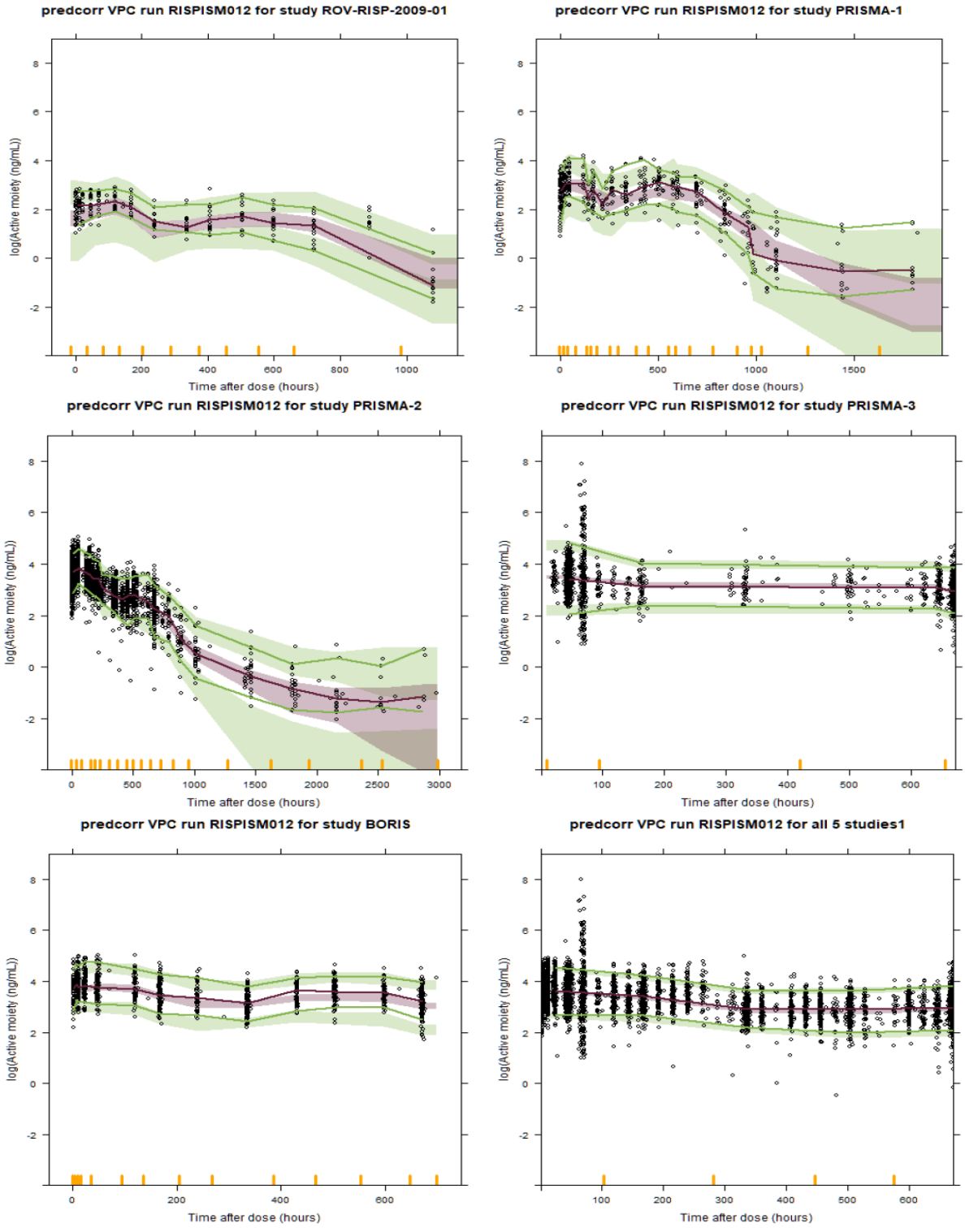


Figure 2: pcVPC comparing observed and simulated active moiety concentrations as a function of time since last dose, stratified by study and overall over a dosing interval

Black circles correspond to prediction-corrected observations (log of active moiety concentrations divided by their respective population predictions); solid plum line corresponds to the 50th percentile of prediction-corrected observations, while solid green lines correspond to 5th and 95th percentiles of prediction-corrected observations. Plum and green areas correspond respectively to the 95%-confidence interval of 50th and 5th and 95th percentiles of prediction-corrected simulations. Source: Figure 43 in report in report 18ROV0059.

Based on the stepwise covariate modelling, significant and clinical relevant (assuming a clinical relevance criterion of 15%) covariates were found to be BMI, formulation without milling (FORM) and sex on CL40. Other covariates included in the final model were galenic formulation on D3, injection site on FR and study Prisma-2 on FR, FR1 and FR2. The influence of covariates on the final pop PK model was summarised as follows:

- CL_{40} decreased when BMI increased: a 10% change in BMI leads to around 3% change in CL_{40}, with values of 5.27 and 4.17 L/h, for BMI values of 17.8 and 42.9 kg/m2, respectively. These BMI values being the extreme values in the current pop PK analysis.
- CL_{40} increased by 16.6% in subjects who received the formulation without milling leading to lower exposure in studies ROV-RISP-2009-01 and PRISMA-1 after Risperidone ISM® administration.
- CL_{40} decreased by 18.8% in female leading to higher exposure in female after Risperidone ISM® administration
- D_3 was significantly influenced by galenic formulation: indicating a 30% longer duration of the zero-order process for formulation without milling as compared to a formulation with milling
- F_R was significantly influenced by injection site: a higher fraction after injection in deltoid muscle of about 13% compared to injection in gluteus muscle
- F_R, FR_1 and FR_2 were significantly influenced by study PRISMA-2: higher after injection in patients from study PRISMA-2, about 54% increase compared to the 4 other studies

The influence of covariates on descriptive PK parameters (Cmax, Ctrough, AUCtau) was assessed by simulating the active moiety PK profile following three injections of 75 mg of Risperidone ISM, once every 28 days, using the final Pop PK model. Simulated profiles indicate the same Cmax and Ctrough for studies ROV-RISP-2009-01, PRISMA-1, PRISMA-3 and BORIS, while active moiety exposure (AUCtau) is 15% lower for ROV-RISP-2009-01 and PRISMA-1. Study PRISMA-2 had a slightly different absorption profile compare to the other studies, resulting in higher Cmax (around 27% higher), lower Ctrough (around 37% lower) but with similar exposure (AUCtau) as for PRISMA-3 and BORIS.

Simulation different dosing schemes

Different dosing schemes of Risperidone ISM were simulated and was compared to simulated profiles of oral risperidone and profiles for risperidone LAI (SP1807266 (1381b); SP1901640 (1146c)). Simulations were also performed for dose de-escalation, dose escalation, missed doses and dose-dumping.

The Pop PK model of oral risperidone was obtained from the literature. Detailed Pop PK model parameters of risperidone LAI were lacking in the literature for which reason steady-state concentration-time profiles of active moiety were digitised from a publication (Samtani et al, 2011, CNS Drugs 25 (10): 829-845).

Absorption

Following IM injection, a small amount of the drug is released resulting in an initial peak in concentration after 24 to 48 hours. A second peak occurs between Days 18 and 25.

Risperidone ISM can be administered in the gluteus or in the deltoid. Unbalanced PK sampling in the PRISMA-3 study results in minor differences in the PK profile between injection sites. No bioequivalence study was conducted to compare the early and the final formulation. The early formulations have a different release rate, with formulation being a significant covariate in the pop PK model. The studies with early formulations are therefore not further described.

An *in vivo* relative bioavailability study with the purpose of bridging to the reference product was performed (BORIS study), initially using the US 4 mg Risperdal tablets and was repeated using the EU reference product (BORIS-2 study). The primary endpoint was the steady-state AUCtau for the active moiety, as the sum of the risperidone and 9-OH risperidone concentration. An adjusted AUC was

calculated for the oral sequence, in order to adjust for the dosing interval from 1 day to 28 days. The results of the statistical analysis are presented in Table 3.

Table 3: Statistical Analysis of Comparative Bioavailability for Risperidone Active Moiety PK Parameters at Steady-State

					Treatment Comparison		
						90% CI of the Ratio	
PK Parameter	Treatment	N	Geometric LS Means	Treatment Comparison	Geometric LS Means	Lower	Upper
Adj. AUC_{tau} (day*ng/mL)	A	55	684.8	B/A	1.3887	1.2117	1.5917
	B	55	950.9				
$C_{max\ ss}$ (ng/mL)	A	55	44.57	B/A	1.3218	1.1223	1.5566
	B	55	58.90				
$C_{min\ ss}$ (ng/mL)	A	55	15.76	B/A	1.0923	0.9285	1.2849
	B	55	17.21				
C_{ave} (ng/mL)	A	55	24.46	B/A	1.3887	1.2117	1.5917
	B	55	33.96				
Fluc (%)	A	55	113.7	B/A	1.0286	0.9274	1.1409
	B	55	117.0				

Treatment A = a single oral dose of 4 mg risperidone once daily from Days 1 to 7. *Adj. AUCtau used for Treatment A Treatment B = a single intramuscular dose of 100 mg Risperidone ISM every 4 weeks from Days 8 to 92. Source: ROV-RISP-2020-01 (BORIS-2)

Distribution

Apparent volume of distribution (V/F) was determined in the population PK analysis: 248 L.

Risperidone is bound to albumin and α1-acid glycoprotein in human plasma. The plasma protein binding of risperidone is approximately 90% and is not concentration dependant up to 200 ng/mL. The protein binding of 9-OH-risperidone is 77%. The binding of risperidone increases at higher pH values. The blood to plasma concentration ratio of risperidone averages 0.67 in man. Displacement interactions of risperidone and 9-OH-risperidone with other drugs have been reported to be minimal.

Risperidone was demonstrated to pass the placental barrier, and limited data show the presence of risperidone and 9-OH-risperidone in human breast milk.

Elimination

The terminal half-life after administration of the final formulation was 556-624 h (PRISMA-3). After a single dose of 100 mg Risperidone ISM, the concentrations in the elimination phase decreased in a biphasic manner from Day 40 to Day 75, with a terminal half-life of 17 days (412h) and observed levels of risperidone active moiety generally <1 ng/mL on Day 75 (ROV-RISP-2020-02). Apparent clearance (CL/F) was determined in the population PK analysis: 4.67 L/h.

Risperidone and its metabolites are eliminated via the urine and, to a much lesser extent, via the faeces. In a mass balance study of a single 1mg oral dose of 14C-risperidone, total recovery of radioactivity at 1 week was 84%, including 70% in the urine and 14% in the faeces.

Risperidone is metabolised in the liver by cytochrome P450 (CYP)2D6 enzymes. The major metabolite is the active metabolite 9-OH-risperidone. It has a similar pharmacological activity to risperidone. The PK of

the active metabolite was studied as part of the active moiety. Another minor metabolic pathway is through N-dealkylation.

CYPs 2D6, 3A4 and 3A5 were found to be responsible for metabolizing risperidone to 9-OH-risperidone, with activities of 7.5, 0.4 and 0.2 pmol-1CYP min-1, respectively in recombinant human CYPs. Both quinidine (inhibitor of CYP2D6) and ketoconazole (inhibitor of CYP3A4) can inhibit the formation of 9-OH-risperidone. Thus, both CYP2D6 and CYP3A4 are the main enzymes for the metabolism of risperidone to 9-OH-risperidone.

Consequences of genetic polymorphisms

Although CYP2D6 extensive metabolisers have lower risperidone and higher 9-OH-risperidone concentrations than poor metabolisers, the PK of risperidone and 9-OH-risperidone combined (the active moiety), after single and multiple doses, are similar in extensive and poor metabolisers.

CYP2D6 phenotyping was performed in and classified according to a well-accepted activity score. An analysis of the AUC ratio vs CL in the pop PK model confirms that CYP2D6 has an insignificant impact on active moiety concentrations.

The CYP3A5 genotype was demonstrated not to influence risperidone, 9-OH-risperidone, or active moiety. A significant effect of CYP2D6 genotype on the steady-state plasma levels of risperidone was observed and ABCB1 polymorphisms contributed to a certain extent to the interindividual variation in steady-state plasma levels of 9-OH-risperidone and active moiety.

Dose proportionality

The PK of the active moiety is dose proportional between 75 and 100 mg Risperidone ISM.

Time dependency

Minimal accumulation was seen in repeated dose studies.

Intra- and inter-individual variability

In the BORIS study, inter-subject variability for the steady-state concentration was 40% to 65% and 38% to 52% for US sourced oral risperidone and Risperidone ISM, respectively.

Based on the population pharmacokinetic analysis, the inter-individual variability in CL_{40} and V_4 were 33 % and 34 %, respectively. The inter-individual variability in the absorption parameters, FR, FR_1, K_{14}, K_{24}, D_3, K_{34} were 20%, 36%, 17%, 109%, 15% and 25%, respectively. Inter-occasion variability on FR, FR_1, FR_2, K_{34} and F_{BA} were 34%, 37%, 170%, 37% and 15 %, respectively.

PK in target population

PK parameters from the phase III study PRISMA-3 for risperidone, 9-OH risperidone and active moiety in the patients with intense PK sampling are summarised in Table 4. The mean Cavg and AUCtau values of risperidone for a dosing interval were higher for Risperidone ISM 100 mg as compared with ISM 75 mg. The same was true for 9-OH-risperidone and the active moiety.

Table 4: Pharmacokinetic Parameters in the Phase III Study PRISMA-3

Risperidone ISM Doses / Route / # subjects	Parameter (units)	Mean[1] Risperidone PK Parameters	Mean[1] 9OH-risperidone PK Parameters	Mean[1] active moiety PK Parameters
Multiple doses of 75mg/ IM Deltoid	Derived C_{max} [ng/mL] (CV%)	9.65 (108.8)	13.93 (70.2)	23.27 (52.1)
	t_{max} [h] median (min,	48.00 (48, 648)	48.00 (48, 648)	48.00 (48, 648)

Dose 1 n = 9	max)			
	AUC_{tau} [h·ng//mL] (CV%)	1679 (69.9)	5846 (70.2)	8316 (65.1)
	$t_{½}$ [h] (CV%)	565.3 (25.9)	565.3 (25.9)	565.3 (25.9)
Multiple doses of 75mg/ IM Gluteal Dose 1 n = 16	Derived C_{max} [ng/mL] (CV%)	9.57 (67.9)	24.22 (50.3)	33.27 (47.1)
	t_{max} [h] median (min, max)	156.00 (0, 672)	108.0 (0, 672)	48.00 (0, 672)
	AUC_{tau} [h·ng//mL] (CV%)	3940 (54.6)	11900 (47.8)	16010 (41.8)
	$t_{½}$ [h] (CV%)	624.0 (18.8)	624.0 (18.8)	624.0 (18.8)
Multiple doses of 100mg/ IM Deltoid Dose 1 n = 16	Derived C_{max} [ng/mL] (CV%)	11.85 (88.4)	31.01 (64.2)	42.67 (67.4)
	t_{max} [h] median (min, max)	48.00 (48, 672)	168.0 (48, 672)	168.0 (48, 672)
	AUC_{tau} [h·ng//mL] (CV%)	4837 (85.1)	11590 (49.2)	16430 (52.0)
	$t_{½}$ [h] (CV%)	556.5 (30.9)	556.5 (30.9)	556.5 (30.9)
Multiple doses of 100mg/ IM Gluteal Dose 1 n = 11	Derived C_{max} [ng/mL] (CV%)	11.60 (62.5)	23.82 (49.3)	35.22 (42.4)
	t_{max} [h] median (min, max)	480.00 (0, 672)	108.0 (0, 672)	108 (0, 672)
	AUC_{tau} [h·ng//mL] (CV%)	4059 (50.5)	13290 (33.8)	17350 (31.5)
	$t_{½}$ [h] (CV%)	578.2 (35.6)	534.0 (46.6)	534.0 (46.6)

ISM: *in situ* microparticles; Active moiety: risperidone + 9-OH-risperidone. (Note: parameters are named as per the source reports.) [1] Values are mean values except for t_{max}, where the median values are used, as noted in the parameter column. Source: Tables 41-43, ROV-RISP-2016-01 (PRISMA-3) CSR

For the Risperidone ISM 75 mg dose, the mean risperidone active moiety estimated Cmax levels after the 1st dose were 27.61 ng/mL; which after the 2nd and 3rd dose increased and generally stabilised to 38.95 ng/mL and 37.16 ng/mL, respectively. The mean Cmin values after 1st, 2nd and 3rd doses were mostly stable and in the range of 17.46 to 20.16 ng/mL.

For the Risperidone ISM 100 mg dose, the mean risperidone active moiety estimated Cmax levels after the 1st dose were 32.00 ng/mL; which after the 2nd and 3rd dose increased and generally stabilised to 53.44 ng/mL and 50.09 ng/mL, respectively. The mean Cmin values after the 1st, 2nd and 3rd doses were mostly stable and in the range of 26.14 to 27.23 ng/mL.

The accumulation was minimal to moderate after multiple Risperidone ISM 75 mg and 100 mg doses and in the range of 1.11 to 1.27 for Cmin and 1.71 to 1.83 for estimated Cmax values.

The plasma levels of risperidone are similar for both the injection sites for Risperidone ISM 75 mg, however, 9-OH risperidone plasma levels are marginally higher compared with risperidone for the gluteal injection site; thus, the active moiety also demonstrates a similar trend. The plasma levels of risperidone are similar for both the injection sites for Risperidone ISM 100 mg, however, unlike the 75 mg dose, 9-OH risperidone plasma levels are marginally higher compared with risperidone for the deltoid injection site; thus, the active moiety also demonstrates a similar trend (Figure 3).

Overall for the active moiety, the dose-normalised AUCtau was slightly higher for injections given at the gluteal site compared with deltoid. In contrast, in the intense PK subset the dose normalised derived Cmax values were comparable for injections given at the gluteal site compared with deltoid. However, trough levels presented by dose-normalised Cmin values and peak levels presented by dose-normalised estimated Cmax values (Day 3) were similar for injections given by either gluteal or deltoid injection sites

in the PK population. The dose normalised Cmax or AUCtau was not found similar for both the gluteal and deltoid injection sites in an ANOVA analysis; the differences can be attributed to lower and unbalance 'n' for deltoid injection site, as well as Geo CV% up to 200%.

According to the activity score for CYP2D6, the majority of patients were extensive metabolizers followed by intermediate metabolizers and least poor metabolizers. Overall, extensive metabolizers reported approximately 59% and 46% less estimated Cmax (dose 1) for risperidone as compared with poor and intermediate metabolizers, respectively. For separate comparison of deltoid and gluteal injection sites, extensive metabolizers reported at least 32% less estimated Cmax (dose 1) for risperidone as compared with poor and intermediate metabolizers. For 9-OH risperidone, extensive metabolizers reported approximately 3 times higher estimated Cmax as compared with poor metabolizers.

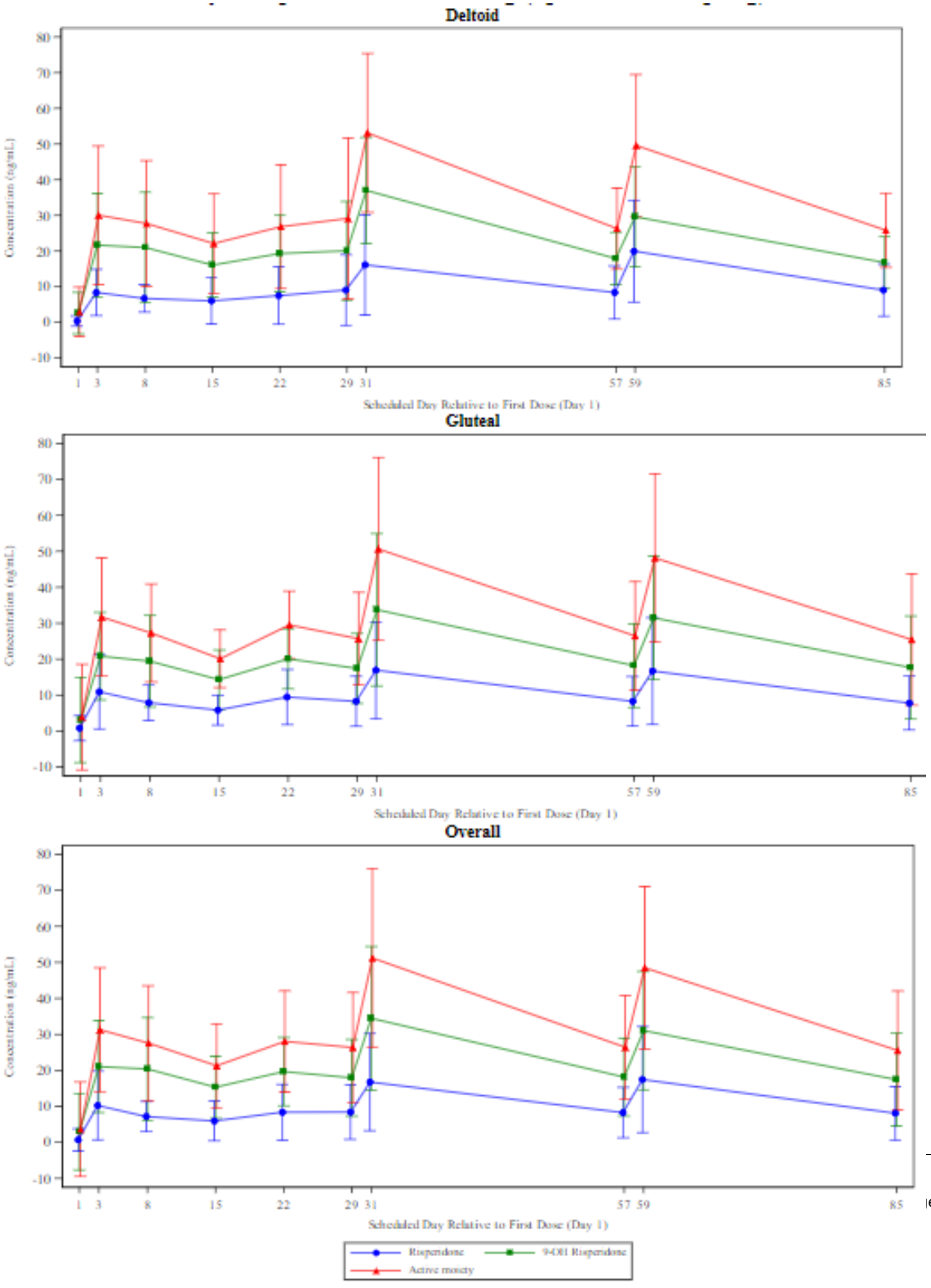


Figure 3: Mean (SD) PK profile of risperidone, 9-OH-risperidone and active moiety after administration of Risperidone ISM 100 mg (PRISMA-3 study)

Switch

Switching from oral QD 3 and 4 mg risperidone to q4w 75 and 100 mg Risperidone ISM, respectively was predicted to result in fairly similar exposures with a steady-state reached from the second injection onwards (Figure 4). The C_{max} seemed higher after administration of Risperidone ISM as compared to oral risperidone at steady state. Relatively high peak concentrations were predicted not to occur immediately after switching to Risperidone ISM.

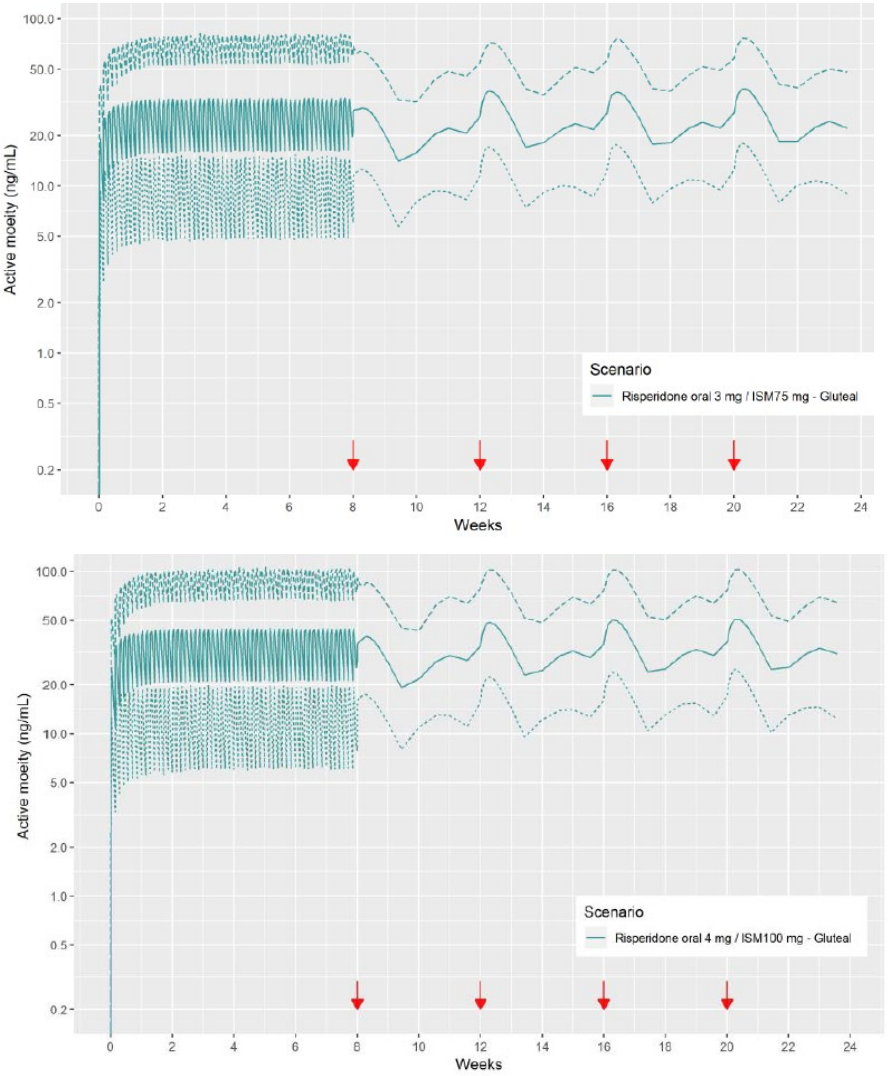


Figure 4: Switching from oral risperidone 3 and 4 mg QD to Risperidone ISM 75 and 100 mg, respectively (gluteal injections)

Green solid line is median, short- and long-dashed lines are 5th an 95th percentiles. Y-axis is in log scale. Red arrows indicate times of administration of Risperidone ISM. Source: Figures 13 and 14 in Report SP1807266 (1381b) and SP1901640 (1146c)

Switching from q4w 75 and 100 mg Risperidone ISM to oral QD 3 and 4 mg risperidone, respectively, showed that higher oral peak concentrations were observed for up to approximately 7 days following the switch (Figure 5)**.** The exposure seemed fairly similar at steady state, with a higher C_{max} after administration of Risperidone ISM as compared to oral risperidone.

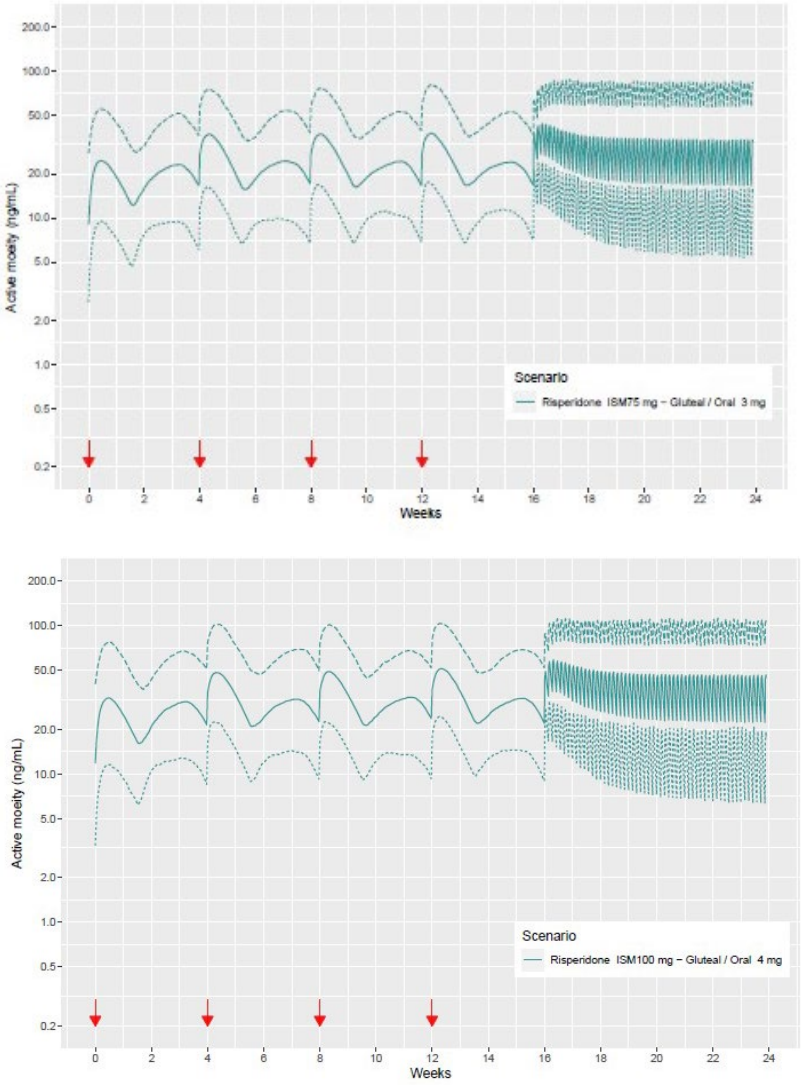


Figure 5: Switching from Risperidone ISM 75 and 100 mg to oral risperidone 3 and 4 mg QD to, respectively (gluteal injections)

Green solid line is median, short- and long-dashed lines are 5th an 95th percentiles. Y-axis is in log scale. Red arrows indicate times of administration of Risperidone ISM.

Switching from q2w 37.5 and 50 mg risperidone LAI to respectively 75 and 100 mg Risperidone ISM was predicted to result in a steady-state reached from the second ISM injection onwards (Figure 6). Higher C_{max} and lower C_{min} was observed at steady state after administration of Risperidone ISM as compared to risperidone LAI. Relatively high peak concentrations were predicted not to occur immediately after switching to Risperidone ISM.

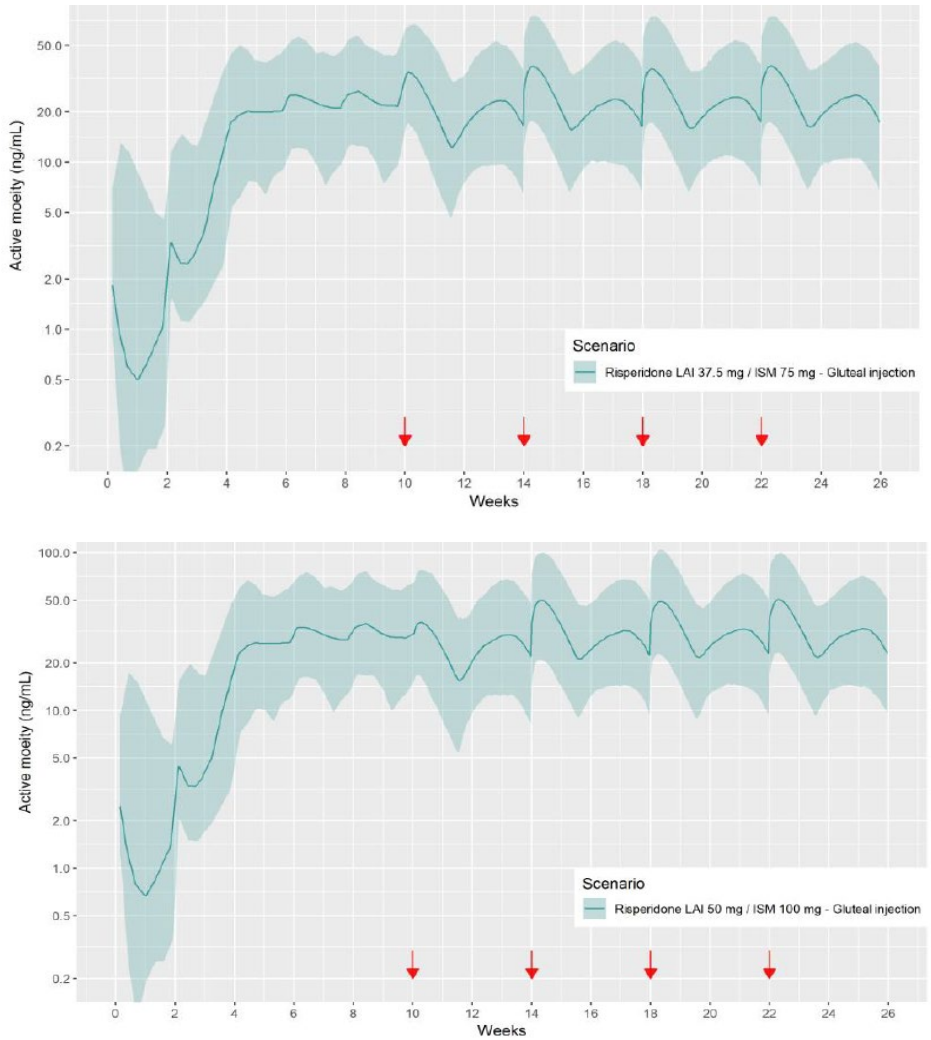


Figure 6: Switching from risperidone LAI 37.5 or 50 mg to Risperidone ISM 75 respective 100 mg using gluteal injections

Green solid lines are median, shaded areas represent 5th an 95th percentiles. Y-axis is in log scale. Red arrows indicate the times of administration of Risperidone ISM. Source: Figures 15 and 16 in Report, SP1807266 (1381b) and SP1901640 (1146c)

Special populations

There were no dedicated PK studies in elderly, children, patients with impaired renal or hepatic function. The applicant relies mainly on the information from the reference product. Risperidone ISM is not indicated in children.

84 patients with mild renal impairment were included in the pop PK analysis, demonstrating no effect on exposure compared to patients with normal renal function.

Effects of gender, race, weight and BMI on CL_{40} were studied in the pop PK analysis.

For a fixed BMI of 28 kg/m^2, active moiety exposure (AUC_{tau}) increased by 23% in females compared to male, while C_{max} increased by 19%.

No effect of weight on CL_{40} were observed. For a male with a BMI of 17.8 kg/m^2, active moiety exposure decreased by 11% compared to a male with a BMI of 28 kg/m^2, while C_{max} decreased by 9%. For a male with a BMI of 42.9 kg/m^2, active moiety exposure increased by 12% compared to a male with a BMI of 28 kg/m^2, while C_{max} increased by 10%. In an obese female (BMI of 32.1 kg/m^2), active moiety exposure

increased by 28% and could further increase in a morbid obese female (BMI of 42.9 kg/m^2) to 38% as compared to a typical subject enrolled in the current analysis (male with BMI of 28 kg/m^2).

No effect of race on CL_{40} was observed.

Interactions

The interactions of Risperidone ISM with co-administration of other medicinal products have not been studied and thus rely on the reference product oral risperidone.

Risperidone is mainly metabolised through CYP2D6, and to a lesser extent through CYP3A4. Both risperidone and its active metabolite 9-OH-risperidone are substrates of P-glycoprotein (P-gp). Substances that modify CYP2D6 activity, or substances strongly inhibiting or inducing CYP3A4 and/or P-gp activity, may influence the PK of the risperidone active antipsychotic fraction.

Exposure relevant for safety evaluation

The AUCtau,ss in stable schizophrenia patients at steady state was 325.3, 685.7 1083 day ng/mL for risperidone, 9-OH-risperidone and the active moiety, respectively (BORIS study 100 mg IM). The corresponding Cmax,ss was 24.80, 41.88 and 64.85 ng/mL, respectively.

Based on the final Pop PK model a worst-case scenario for dose dumping where the full dose entered the central compartment as a bolus were simulated. The simulated peak concentration of active moiety was about 300-400 ng/mL.

2.4.2.2. Pharmacodynamics

Exposure-efficacy

The aim was to describe the dose-concentration-response relationship for Risperidone ISM in schizophrenic patients (19/ROV/0059 report). Data were obtained from the 12-week double-blind phase in the PRISMA-3 study. An exploratory analysis was performed on PANSS and CGI-S over time, as well as their association with the active moiety concentration. Logistic regression plots were generated for the dichotomous PANSS-response and overall-response variables. A dropout model was developed using a parametric hazard model.

Data

The final dataset used for modelling the PANSS data consisted of 383 patients (receiving placebo (n=131), 75 mg Risperidone ISM (n=127), 100 mg Risperidone ISM (n=125)) with 2403 PANSS measurements. Actual records of date and time of dosing were used. The individual concentrations of active moiety at the day of a PANSS and safety measurements (used in the exposure-safety analysis) and steady state concentrations were predicted based on the population pharmacokinetic model reported in 18ROV0059.

Results

The dropout model described that the higher PANSS score, the more likely it was that a patient would dropout. Patients studied in USA had a significantly higher change of dropping out than Ukrainian patients (hazard ratio: 2.71 (95%CI: 1.81 – 4.06)). The model was only used in the PK/PD simulations.

The exploratory analysis indicated similar response (change in PANSS score, PANSS score or Overall response rate) in dose groups 75 and 100 mg. PANSS change from baseline over time are shown in Figure 7 whereas PANSS change from baseline versus active moiety concentrations are shown in Figure 8.

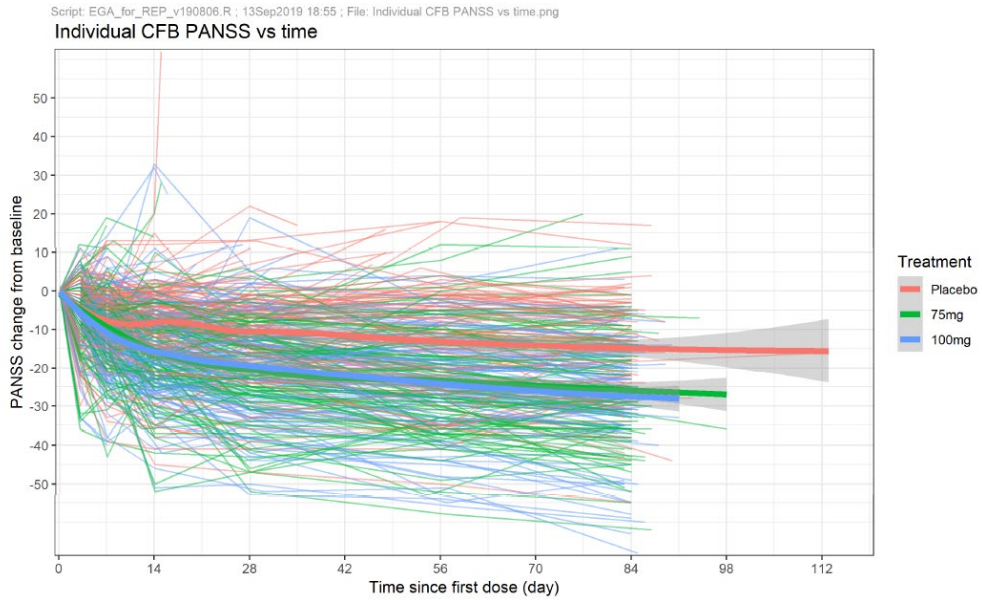


Figure 7: Individual PANSS change from baseline vs. time by treatment

The thick solid lines are LOESS smoothers together with their 95% confidence interval. Source: Figure 9 in report 19/ROV/0059

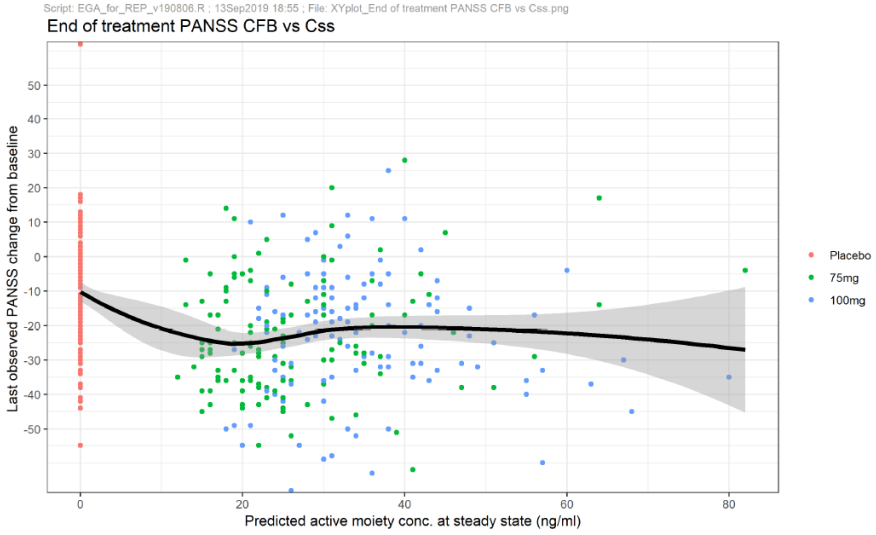


Figure 8: PANSS change from baseline at the end of treatment vs. predicted steady state concentration of active moiety

The black line is a LOESS smoother together with its 95% confidence interval. Source: Figure 12 in report 19/ROV/0059.

The proposed PK/PD model consisted of a placebo model, a drug-effect model and a time-dependent mechanism for the change in PANSS score over time. It was not possible to estimate the EC_{50}. EC_{50} was therefore fixed to a value from literature (4.6 ng/mL) where the authors also analysed the concentration response relationship of a long-acting risperidone formulation by means of modelling. Parameters estimates for the final model are given in Table 5 and VPCs are shown in Figure 9.

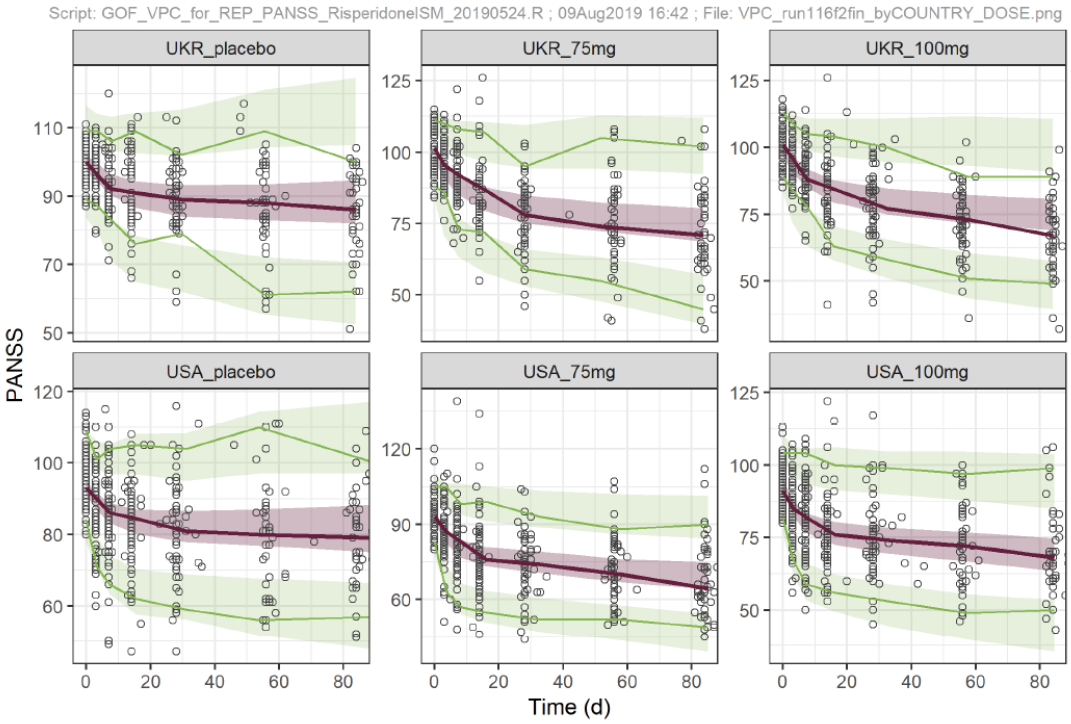
Table 5: Parameter Table of the Final PANSS Model

Source: Table 18 in report 19/ROV/0059

Parameter	Description	Estimate	RSE(%)[a]	SIR[b] 95% CI	Shr.(%)
Fixed effects parameters					
BL	PANSS at baseline	92.9	0.614	91.9 - 93.8	
TD	Time to reach 68.3% of the max. placebo effect	8.32	8.69	7.19 - 9.65	
PMAX	Maximal placebo effect (fractional reduction from BL)	0.117	9.11	0.0997 - 0.134	
POW	Shape parameter	1.39	7.76	1.22 - 1.58	
EMAX	Maximal drug effect (fractional reduction from BL and placebo effect)	0.0661	32.1	0.0368 - 0.0975	
EC50 (ng/mL)	Active moiety conc. Eliciting 50% of the maximal effect - value fixed to Ivaturi et al.	4.6 (fixed)	-	-	
DRIFT (1/day)	Slope of disease modifying effect (only when receiving active treatment)	-0.0929	17.1	-0.117 to -0.0653	
KTHL (day)	Half-life of the drug-effect delay	8.96	22.7	6.78 - 12.2	
COUNTRY~BL (%)	Percent difference of baseline for patients from Ukraine vs. US	7.27	12.1	6 - 8.79	
Inj.Site~KTHL (%)	Percent reduction of KTHL for injection in deltoid vs. gluteus	-69.1	16.1	-83.5 to -48.2	
BL~TD (%)	Percent change of TD for every unit change of BL-95	5.66	13.8	4.69 - 6.4	
Random effects parameters					
IIV_TD (CV%)[c]	Inter-individual variability on TD	58.3	15.3	43.8 - 76.6	37.8
COR_TD_BL	Correlation coefficient TD~BL	-0.264	72.5	-0.471 - 0.00801	
IIV_BL (CV%)[c]	Inter-individual variability on BL	6.51	6.26	5.86 - 7.12	16.4
COR_TD_PMAX	Correlation coefficient TD~PMAX	-0.294	62.1	-0.575 to -0.0454	
COR_BL_PMAX	Correlation coefficient BL~PMAX	0.146	72.8	0.0282 - 0.261	
IIV_PMAX (SD)	Inter-individual variability on PMAX	0.12	8.78	0.107 - 0.136	20.5
COR_TD_EMAX	Correlation coefficient TD~EMAX	0.5	36.3	0.267 - 0.685	
COR_BL_EMAX	Correlation coefficient BL~EMAX	-0.103	110	-0.218 - 0.00576	
COR_PMAX_EMAX	Correlation coefficient PMAX~EMAX	-0.278	40.5	-0.433 to -0.0759	
IIV_EMAX (SD)	Inter-individual variability on EMAX	0.169	12.4	0.142 - 0.206	33.9
COR_TD_DRIFT	Correlation coefficient TD~DRIFT	-0.102	202	-0.437 - 0.117	
COR_BL_DRIFT	Correlation coefficient BL~DRIFT	-0.126	79.7	-0.238 - 0.0199	
COR_PMAX_DRIFT	Correlation coefficient PMAX~DRIFT	0.0529	229	-0.124 - 0.235	
COR_EMAX_DRIFT	Correlation coefficient EMAX~DRIFT	0.388	33.3	0.137 - 0.56	
IIV_DRIFT (SD)	Inter-individual variability on DRIFT	0.134	7.79	0.117 - 0.153	30.7
COR_TD_KTHL	Correlation coefficient TD~KTHL	-0.827	28.5	-0.93 to -0.64	
COR_BL_KTHL	Correlation coefficient BL~KTHL	0.0105	1977	-0.236 - 0.271	
COR_PMAX_KTHL	Correlation coefficient PMAX~KTHL	0.454	75.3	0.167 - 0.692	
COR_EMAX_KTHL	Correlation coefficient EMAX~KTHL	-0.615	45.1	-0.791 to -0.357	
COR_DRIFT_KTHL	Correlation coefficient DRIFT~KTHL	-0.0829	305	-0.343 - 0.235	
IIV_KTHL (CV%)[c]	Inter-individual variability on KTHL	116	30.1	78 - 192	39.7

(R)SE: (Relative) standard error; CV: Coefficient of variation; SD: Standard deviation
a RSE on SD scale for variability estimates
b SIR settings: resamples=200,400,500,1000,1000; samples=1000,1000,1000,2000,2000
c CV = 100*sqrt(exp(variance)-1)

Model: run116f2fin with dataset: RISPISM_ER_v20190806A.CSV.



run116f2fin. Solid lines are the 5th and 95th (green lines) and 50th (median; red line) percentiles of the observed data (open circles) and the coloured areas contain 95% of the simulated quantiles.

Figure 9: VPC of the final model by country and treatment

Source: Figure 23 in report 19/ROV/0059

Exposure-safety

The aim was to perform exposure-safety analyses in order to identify and quantify a possible relationship between concentrations of active moiety and the occurrence of adverse events (19/ROV/0059 report). Data were obtained from the 12-week double-blind phase in the PRISMA-3 study.

Exploratory graphical analysis was performed on the treatment-emergent adverse event (TEAE) data, extrapyramidal, hyperprolactinaemia, and somnolence/sedation events, evaluating their association with the active moiety exposure, followed by a logistic regression analysis. Longitudinal extrapyramidal symptoms as scored by SAS (Simpson Angus Scale), AIMS8 (Item 8 of the abnormal involuntary movement scale) and BARS4 (Barnes Akathisia Rating Scale Item 4) were analysed graphically in function of time and their associations with the active moiety exposure were evaluated.

Handling of data

All TEAE data recorded during the 12-week double-blind period were included in the logistic regression analyses. If a patient had more than one AE of a given type (i.e. same AE occurring repeatedly after the 1st, 2nd and 3rd administration) only the first occurrence was included in the analysis.

For the longitudinal exploratory exposure-safety analysis of the extrapyramidal symptoms as measured by SAS, AIMS8 and BARS4, an additional focus was on a time frame within 2 weeks after dosing instead of 1 week after dosing.

The final dataset used for the exposure-safety analysis of the selected TEAE data was comprised of data from 437 subjects. For each selected TEAE, a subject was either scored as 0 (no TEAE) or 1 (TEAE).

437 subjects were included in the final dataset used for the exposure-safety analysis of longitudinal SAS, AIMS8 and BARS4 data. All three symptoms scores consisted of a total of 2683 scores: a total of 882 scores after placebo in 147 subjects, 903 scores after 75 mg Risperidone ISM in 144 subjects and 898 scores in 146 subjects after 100 mg Risperidone ISM.

Analysis of the exposure-safety data

The risk of extrapyramidal events was increased for Risperidone ISM versus placebo but no apparent relationship with active moiety exposure was present in the studied exposure range (Figure 10).

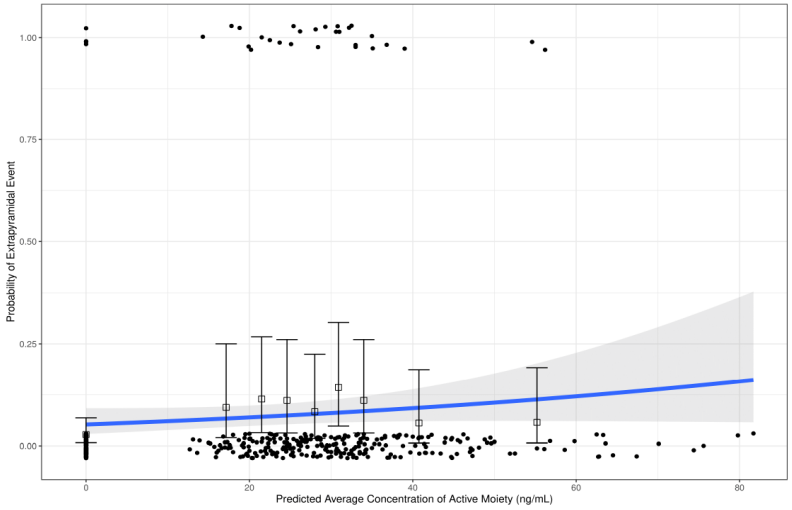


Figure 10: Logistic regression of probability of extrapyramidal events vs. predicted average active moiety concentration

The open squares and the vertical error bars are the observed event rate and the 95% confidence interval calculated in each of the concentration quantiles. The blue curve is the fit with a simple linear regression model.

The grey area is the 95% confidence interval around the regression fit. Closed black circles are observed events.

Source: Figure 36 in report 19/ROV/0059

The risk of hyperprolactinaemia events was increased for Risperidone ISM vs. placebo and this risk was predicted to increase with increasing active moiety exposure (Figure 11).

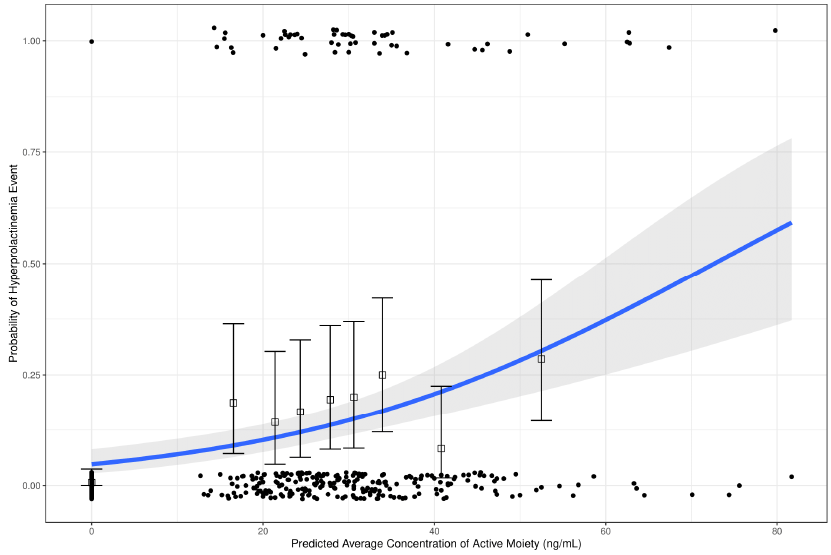


Figure 11: Logistic regression of probability of hyperprolactinaemia events vs. predicted average active moiety concentration

The open squares and the vertical error bars are the observed event rate and the 95% confidence interval calculated in each of the concentration quantiles. The blue curve is the fit with a simple linear regression model.

The grey area is the 95% confidence interval around the regression fit. Closed black circles are observed events.

Source: Figure 39 in report 19/ROV/0059

The risk of somnolence/sedation events seemed not to be increased for Risperidone ISM vs. placebo and no apparent relationship was found with active moiety exposure in the studied exposure range (Figure 12).

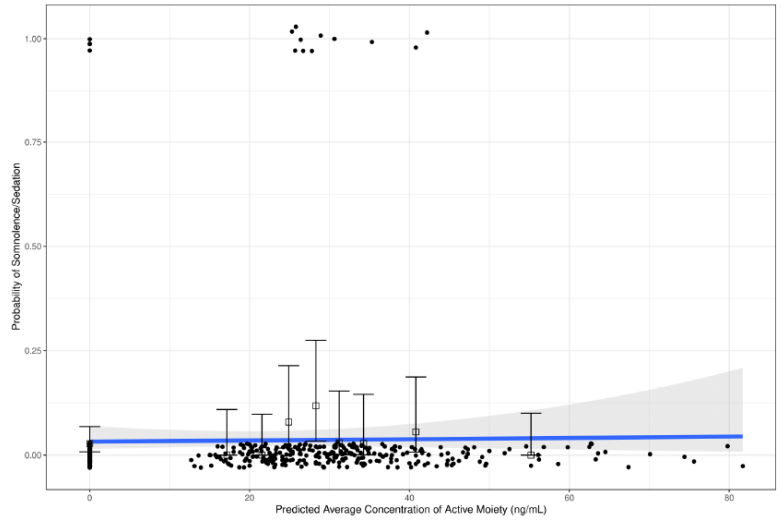


Figure 12: Logistic regression of probability of somnolence/sedation events vs. predicted average active moiety concentration

The open squares and the vertical error bars are the observed event rate and the 95% confidence interval calculated in each of the concentration quantiles. The blue curve is the fit with a simple linear regression model.

The grey area is the 95% confidence interval around the regression fit. Closed black circles are observed events.

Source: Figure 42 in report 19/ROV/0059

Measured SAS scores throughout the study appeared to be slightly higher for Risperidone ISM as compared to placebo. No relationship seemed to be present for the measured SAS scores at day 3 vs. the measured active moiety concentrations at day 2 (surrogate for C_{max}). No apparent relationship was seen for the measured SAS scores vs. the predicted active moiety concentrations, vs. the predicted active moiety concentrations during the first 2 weeks (Figure 13) or vs. the predicted average active moiety concentrations.

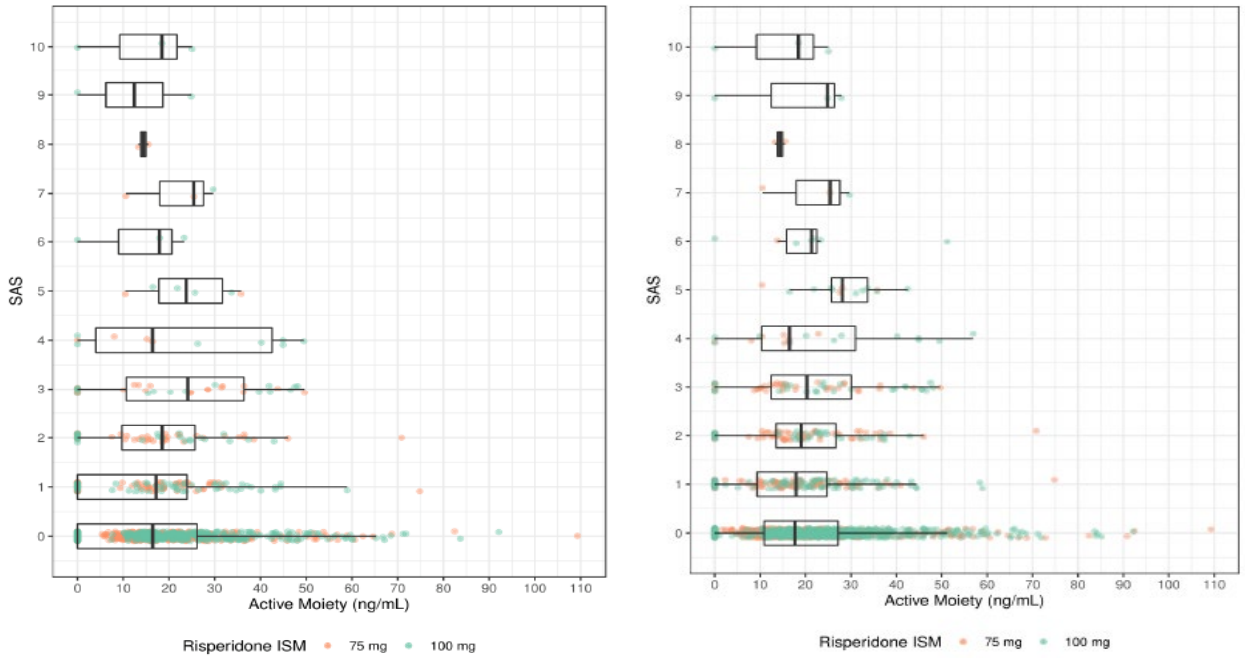


Figure 13: Box plots of the predicted active moiety concentrations split by the measured SAS scores during the first 2 weeks (left) or split by all measured SAS scores throughout the study (right)

The box covers the 25th and 75th percentile i.e. the inter-quartile range (IQR), the whiskers extent to the largest/smallest value within 1.5 x IQR in either direction. The vertical black bar with the box is the median. Closed circles are active moiety concentrations. For the purpose of the graphical exploratory analyses, one SAS baseline value of more than 10 was set to 10, five SAS baseline values of 1.25 were set to 1, and one SAS baseline value of 2.5 was set to 3. Similarly, three SAS values of more than 10 were set to 10, one SAS value of 1.11 was set to 1, 17 SAS values of 1.25 were set to 1. Source: Figures 65 and 46 in report 19/ROV/0059

Measured item 8 of AIMS scores throughout the study seemed to be similar for all three treatments. No relationship seemed to be present for the measured item 8 of AIMS scores at day 3 vs. the measured active moiety concentrations at day 2. No apparent relationship was seen for the measured item 8 of AIMS scores vs. the predicted active moiety concentrations, vs. the predicted active moiety concentrations during the first 2 weeks (Figure 14) and vs. the predicted average active moiety concentrations.

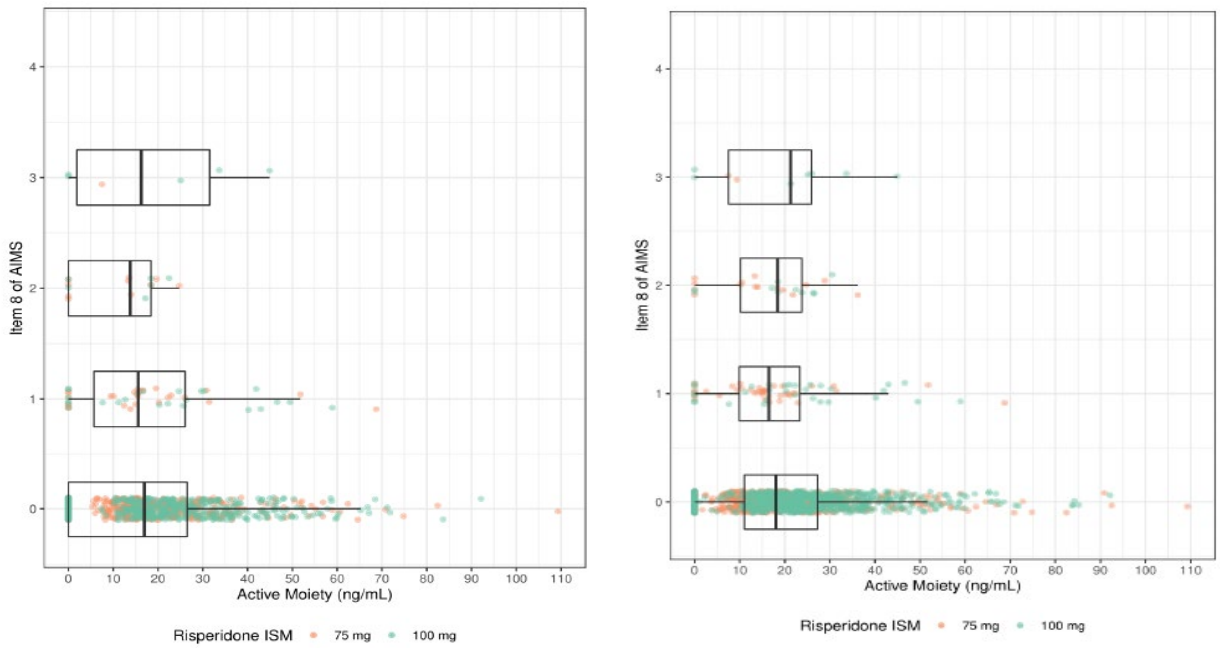


Figure 14: Box plots of the predicted active moiety concentrations split by the measured item 8 of AIMS scores during the first 2 weeks (left) or split by all measured item 8 of AIMS scores throughout the study (right)

The box covers the 25th and 75th percentile i.e. the inter-quartile range (IQR), the whiskers extent to the largest/smallest value within 1.5 x IQR in either direction. The vertical black bar with the box is the median. Closed circles are active moiety concentrations. Source: Figures 69 and 51 in report 19/ROV/0059

Measured item 4 of BARS scores throughout the study seemed to be slightly higher for Risperidone ISM as compared to placebo. No relationship appeared to be present for the measured item 4 of BARS scores at day 3 vs. the measured active moiety concentrations at day 2. No apparent relationship was seen for all measured item 4 of BARS scores vs. the predicted active moiety concentrations, vs. the predicted active moiety concentrations during the first 2 weeks (Figure 15) and vs. the predicted average active moiety concentrations.

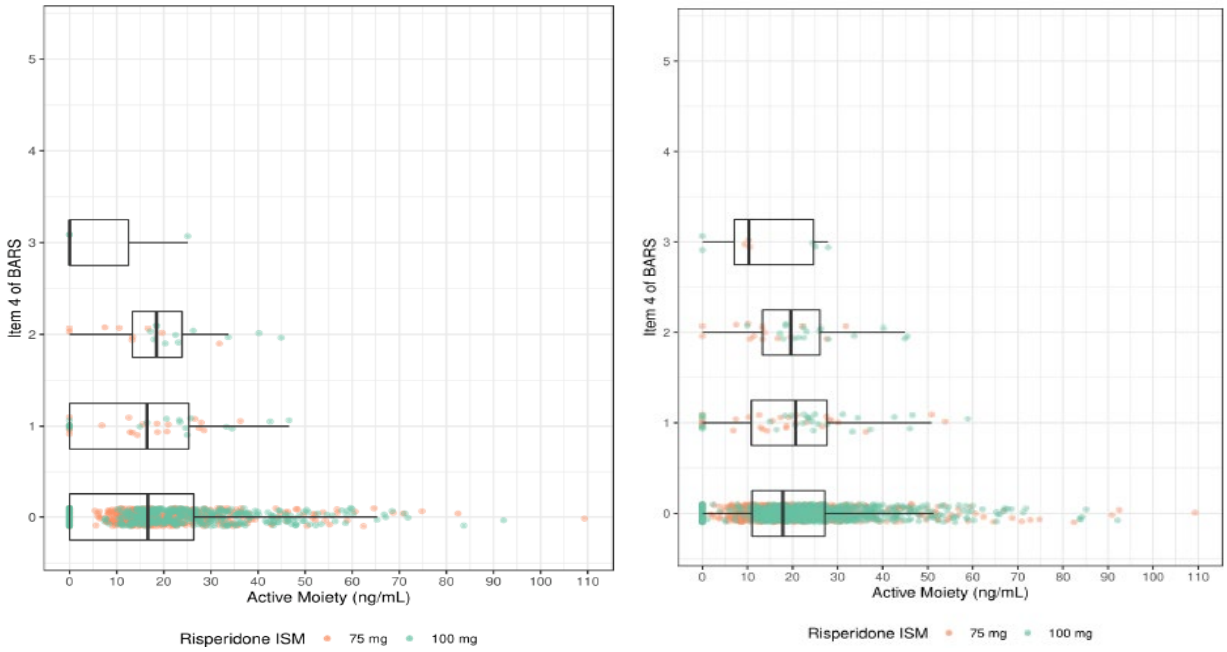


Figure 15: Box plots of the predicted active moiety concentrations split by the measured item 4 of BARS scores during the first 2 weeks (left) or by all measured item 4 of BARS scores throughout the study (right)

The box covers the 25th and 75th percentile i.e. the inter-quartile range (IQR), the whiskers extent to the largest/smallest value within 1.5 x IQR in either direction. The vertical black bar with the box is the median. Closed circles are active moiety concentrations. Source: Figures 73 and 56 in report 19/ROV/0059

2.4.2.3. Discussion on clinical pharmacology

PK Bridging

Bridging by means of pharmacokinetics is considered pivotal as it is required for non-clinical data, pharmacokinetics in special populations, interactions, efficacy and safety. For a hybrid application of an intramuscular depot formulation with a reference product with a different route of administration and release rate, clinical data and pharmacokinetic studies are required showing a similar total exposure (AUC) of active substance as for the immediate release formulation, without requirement for bioequivalence. The new formulation should be characterised in appropriate single dose and multiple dose pharmacokinetic, pharmacodynamic and clinical efficacy/safety studies. From a regulatory point of view, there is a need to establish an *in vivo* bridge against the EU reference medicinal product in the framework of article 10(3) applications (ie German Risperdal tablets).

Risperidone has an active metabolite 9-OH-risperidone, or paliperidone, which is considered to have a similar pharmacological effect (reference product SmPC). It is therefore considered acceptable to study the sum of their exposures as the active moiety.

In the context of bridging for clinical efficacy, different PK parameters may be relevant. The applicant considered several parameters for the bridging to the US reference product, namely AUC, Cmax, Cave, Cmin and peak to trough concentration (Fluctuation). This approach is agreed. According to the SmPC of oral risperidone, steady-state for risperidone is reached after 1 day and 4-5 days for 9-OH risperidone. The design of the relative bioavailability studies BORIS/BORIS-2 is therefore considered acceptable to reach steady state of both metabolite and parent. PK sampling was appropriate to characterise the respective steady state PK parameters.

The applicant provided a new PK bridging study with the EU reference product (BORIS-2), which shows that the steady-state exposure of Risperidone ISM 100mg is slightly higher than for 4 mg oral risperidone.

However, this increased exposure is within an acceptable range, as oral risperidone can be dosed up to 6 mg. The PK bridge is thus considered established.

The external validation performed by the applicant showed that the previously developed population pharmacokinetic models reasonably well described the observed active moiety concentrations in the BORIS-2 study, both after oral risperidone and Risperidone ISM injection. In addition, the Risperidone ISM model seemed to capture the terminal phase of the active moiety concentration-time profile in study ROV-RISP-2020-02. Thus, these results support that the previous popPK models are adequate, and no new simulations are needed.

For acute therapy, the applicant was asked to provide PK data or simulations supporting a similar onset of efficacy as for oral risperidone. The active moiety exposure upon administration of 100 mg Risperidone ISM from 3h onwards (prior timepoints not discernible on the graph) is higher than the Ctrough of oral risperidone. Considering 65% receptor occupancy (RO) as the relevant threshold, it is achieved after ca 4.5h following the administration of 100 mg Risperidone ISM. For oral risperidone, 65% RO is reached within 1-2h for both 3 and 4 mg. The provided simulations showed that the initial active moiety exposure and RO are in the same range for oral risperidone 4 mg and Risperidone ISM 100 mg. Therefore, bridging of the indication is supported from a PK standpoint, particularly since 100 mg is the only dose that the applicant claims for acute schizophrenia.

Given the smaller amplitude of the initial release after 75 mg Risperidone ISM, sufficient receptor occupancy is reached ca 13h later. It is unclear whether this delay would have a significant effect on PANSS or whether PANSS is sensitive enough to detect differences in tmax on day 1, when the full response is not expected until a few weeks later. In consequence, additional efficacy data would be required to support that this delay is not clinically relevant for 75 mg Risperidone ISM. This dose is however currently not claimed in the acute schizophrenia indication, the issue is therefore not pursued.

Even though the AUC after Risperidone ISM may be in the same range as for oral risperidone, it is noted, both in the BORIS study and in simulations based on literature data, that Risperidone ISM results in lower plasma concentrations of active moiety between day 10 and 15 approximately. This concentration seems to be in the range of the oral Cmin. It is however unclear whether a prolonged time at this concentration may have an impact on clinical efficacy. The applicant provided a new analysis of PANSS expressed as percentage from baseline and as function of time to investigate the effect of the lower plasma concentrations of active moiety between Day 10 and 15 with a focus on the lowest quartile of exposure. The absence of obvious trend between the PANSS score and the lower active moiety exposure between day 8-15 is agreed, however PANSS may be not sufficiently sensitive over such a timeframe. The value of the present exposure/response analysis for the information on the lack of impact on efficacy is therefore limited in this context. The SmPC section 5.2 was updated to reflect this dip in concentration.

Methods

Bioanalysis

All three individual methods were adequately validated. There was however no cross-validation between the different methods. A cross validation is not requested since the residual error between the methods was not significant according to pop PK modelling.

Within study validation reports were provided for all clinical studies. Samples were measured within their studied stability, and incurred sample reanalysis was passed where required. The measured plasma exposures are thus deemed reliable.

Population PK analysis

The model could reasonably well describe the concentration-time data of active moiety after administration of Risperidone ISM. Epsilon shrinkage was rather high (25.5%). In addition, the

η-shrinkage was high (44-66%) for many parameters (FR, FR_1, K_{14}, K_{24}, K_{34} and D_3). Lower η-shrinkage (<25%) was observed for CL, V_4 and F_5.

There were some trends in the plot of eta for CL_{40} versus dose, especially for the doses 37.5 and 50 mg. This could not be explained by a different CL in dose groups 37.5 and 50 mg. The reason for the trend in the plot is still unclear. However, these dose groups include a different formulation and lower doses (lower concentration range) than intended for clinical use, for which reason this issue is not further pursued.

The provided VPCs and pcVPC plots stratified by injection site and dose per study showed that the Pop PK model could reasonably well describe the plasma concentrations of active moiety of Risperidone ISM.

The applicant's method for handling outliers and values below the LLOQ is considered acceptable.

Different dosing schemes for the switch between risperidone oral, ISM and LAI were simulated. The oral Pop PK model of risperidone was based on a model previously reported in the literature (Vermeulen, 2007). The applicant explained that the model could initially not describe the simulated peak and trough active moiety concentrations reported by Samtani et al, 2012, and therefore the parameters (V2 and V4) were re-estimated during the development of a combined Risperidone ISM and Risperidone Oral model. The updated oral model (with the new estimates of V2 and V4) seemed to adequately describe the exposure data in the article from Samtani and in the BORIS study, and is therefore considered acceptable to use for simulations. PcVPCs based on the BORIS study and BORIS-2 study, showed that the oral Pop PK model reasonably well described the data in both the studies.

Concentration-time profiles of active moiety following the administration of Risperidone LAI were adequately digitised from simulated profiles in a publication. There was no information regarding the input data and PK model that was used in the simulations in the publication. The assessor can therefore not validate these data. However, the concentration-time data of active moiety at steady state are in the same ranges as those previously reported for risperidone LAI and the data in the publication is therefore considered to be acceptable.

Absorption

The three studies performed with early formulations (ROV-RISP-2009-01, PRISMA-1 and PRISMA-2) are considered supportive and acceptable to include in the population PK model, but should not be used alone, as the early formulations are considered to have different release properties.

Single dose PK with the final formulation is available from study ROV-RISP-2020-02. The elimination of a 100mg single dose the final formulation beyond the last day of the dosing interval was studied in the new study ROV-RISP-2020-02. This data is now reflected in the SmPC section 5.2 under elimination and absorption.

Resulting from the complex absorption upon modified release, several peaks of concentrations are seen for risperidone, 9-OH-risperidone and the active moiety. Tmax should therefore be interpreted with caution in all studies.

Comparative dissolution profiles for the EU and US sources Risperdal tablets were only performed in HCl 0.1N pH 1.2 dissolution medium and not at the range of pH 1 – 6.8 (at least pH 1.2, 4.5, and 6.8) required in the Guideline on the investigation of bioequivalence. This issue is however not pursued since it is an *in vivo* bridge that is required.

Distribution

The protein binding of risperidone and its metabolite is well-known, and the applicant did not conduct own studies.

Elimination

The excretion route and metabolism of risperidone are well known, and the applicant did not conduct own studies. The applicant provided an analysis comparing exposure and parent/metabolite ratios after oral or intramuscular administration of risperidone. The applicant did not address possible pre-systemic differences in metabolic pathways. As the systemic exposures are similar, it is agreed that the PK in special populations or interactions may be similar to those from the reference product and that these SmPC claims can be used also for Risperidone ISM.

The consequences of genetic polymorphism on the PK of risperidone are well-known and well described in the clinical studies. As it is mainly the active moiety, as a sum of risperidone and 9-OH-risperidone, that is studied here with respect to bridging to the reference product, the impact of a polymorphism of CYP2D6 is low.

Dose proportionality

Single dose data from the PRISMA-3 study showed a proportional increase in active moiety exposure (Cmax, AUC) with dose in the range 75 to 100 mg. However, the pop PK model does not support dose proportionality for doses below 75 mg. The SmPC was updated to state that dose proportionality is demonstrated between 75 and 100 mg.

Time dependency

Risperidone ISM did not demonstrate time dependency.

Intra- and inter-individual variability

The inter-individual variability is in the same range for oral and ISM risperidone.

The inter-individual variability in CL_{40}, V_4 and most of the absorption parameters (FR, FR_1, K_{14}, D_3, K_{34}) were low to moderate. A high variability was observed between the subjects based on K_{24}. Inter-occasion variability was low to moderate for FR, FR_1, K_{34} and F_{BA} and very high for FR_2.

PK in target population

Overall, the PK in the target population did not differ from other populations, as it could be described with the same population PK model.

The analysis of PRISMA-3 (ANOVA results) showed that PK for risperidone, 9-OH risperidone and risperidone active moiety, the dose normalised Cmax or AUCtau differ significantly for the gluteal and deltoid injection sites. The population PK model also identifies the injection site as a significant covariate. The differences can be attributed to lower and unbalanced sample size in group of patients receiving deltoid injection. In addition, despite statistically significant results, PKPD simulation showed negligible impact on total PANSS. No differences in safety profile of Risperidone ISM depending on the site of administration were observed. It is therefore agreed that administration in the gluteus or deltoid are similar. The SmPC has been updated accordingly and simplified. A few additional suggestions are made, see **SmPC comments**.

Overall, the approach of simulating the switch from risperidone oral or LAI to Risperidone ISM is considered acceptable.

While generally switching from 3 mg/day oral risperidone to 75 mg Risperidone ISM is agreed, it should be clear to the prescriber that the switch is not intended for patients on oral doses lower than 3 mg/day. The SmPC was amended accordingly.

The switching from oral QD 3 and 4 mg risperidone to q4w 75 and 100 mg Risperidone ISM, respectively was predicted to result in fairly similar exposures with a steady state reached from the second injection onwards. The C_{max} seemed higher after administration of Risperidone ISM as compared to oral

risperidone. The switch from oral risperidone to Risperidone ISM seems acceptable, based on exposure, using the proposed dosing regimens.

The switching from q2w 37.5 and 50 mg risperidone LAI to 75 and 100 mg Risperidone ISM, respectively was predicted to result in a steady state reached from the second injection onwards. Larger fluctuations, with a higher C_{max} and lower C_{min}, were observed for Risperidone ISM as compared to risperidone LAI. The applicant provided simulations of D2 receptor occupancy and active moiety concentrations on the switch from risperidone LAI to ISM to show the clinical consequences of the larger fluctuations after administration of Risperidone ISM. The simulations indicate lower concentrations and consequently receptor occupancy (<65%) for a few days following the switch from risperidone LAI 37.5 and 50 mg Q2W to Risperidone ISM 75 and 100 mg Q4W, respectively. The median concentrations decreased to approximately 12 ng/mL (75 mg ISM) and 15 ng/mL (100 mg ISM), which is approximately two times lower than the median steady-state Ctrough following 37.5 mg and 50 mg risperidone LAI Q2W, respectively. The proposed doses for the switch from risperidone LAI 37.5 and 50 mg Q2W to Risperidone ISM 75 and 100 mg Q4W seem adequate from a pharmacokinetic point of view.
The information about comparable active moiety concentrations at steady-state and the larger fluctuations following the switch to ISM are now included in 5.2 in the SmPC.

The applicant provided simulations from switching from Risperidone ISM to risperidone oral. Higher oral peak concentrations of active moiety were observed for up to approximately 7 days following the switch from Q4W Risperidone ISM 75 and 100 mg to oral risperidone 3 and 4 mg QD, respectively. The exposure seemed fairly similar at steady state, with a higher median C_{max} after administration of Risperidone ISM as compared to oral risperidone. The simulations indicate that the switch from Risperidone ISM to oral risperidone, based on active moiety concentrations, at the suggested doses seems adequate.

The window for administration of a dose is currently proposed as up to 3 days before or 7 days after the scheduled date. While 3 days before can be agreed upon, missing the dose by 7 days results in a decrease in concentration of approximately 50%, with its effect on efficacy being unknown. This should be reflected in the SmPC. Additionally, considering that the impact of a few days delay on efficacy is unknown, the posology should reflect the studied dosing interval, as all studies and simulations are for a 28-day interval and not a monthly interval.

Special populations

Initially, 75 mg Risperidone ISM was recommended for elderly, which was not in line with the reference product that recommends 0.5 mg twice a day with a titration to 1 or 2 mg twice daily. The exposure in patients 60-65 years was found similar to that of younger adults. The applicant refers to the referral of Risperdal Consta of CHMP (Doc. Ref. EMEA/CHMP/384879/2008), where the pharmacokinetics in the population > 65 years was considered comparable to the population < 65 years for Risperdal Consta. The oral product SmPC – which is carried through to Risperdal Consta after the harmonisation – however notes a 43% higher active antipsychotic fraction plasma concentration in elderly and entails a dose adjustment for the oral product. From a kinetic perspective, it is nevertheless agreed that elderly patients without organ impairment are expected to obtain similar exposures following a 3 mg oral dose as following a 75 mg Risperidone ISM dose, and 4mg po/100 mg ISM, respectively. A patient stabilised on an oral dose lower than 3 mg is however expected to have a higher exposure if given 75 mg Risperidone ISM. Therefore, it is suggested that only elderly on oral risperidone ≥ 3mg are considered for a switch to Risperidone ISM, starting with the lower 75 mg dose. The SmPC was amended accordingly.

In patients with renal or hepatic impairment (RI / HI), careful titration with the oral product followed by 75 mg Risperidone ISM is recommended, which is not in line with the half dose recommended with the reference product. Patients with mild (n=84) and moderate (n=3) renal impairment were included in the dataset. No conclusion can be made for moderate impairment. It is agreed that the current dataset did

not show trends of increased exposure of active moiety in mild RI patients, thus the dosing recommendations are endorsed for RI.

Patients with elevated ALT (n=11) and AST (n=3) were included. The applicant considers the dataset too small for any conclusion, and this is agreed. The dosing recommendations in patients with impaired hepatic function are in line with the reference product and are agreed. The text in section 5.2 basing on datasets too small for conclusions was removed.

The Pop PK model predicted an increase in C_{max} and AUC_{tau} of 19 respective 23% in females as compared to males. No dose-adjustment is required based on gender.

The model predicted an increase in C_{max} and AUC_{tau} of 10 respective 12% in males with a BMI of 42.9 kg/m^2 as compared to a BMI of 28 kg/m^2. Simulations showed that in obese females (BMI $\geq$ 32.1 kg/m^2) could active moiety concentrations potentially increase by 38% on average in the extreme case (morbid obese female with BMI of 42.9 kg/m2) compared to the reference patient (male with BMI of 28 kg/m^2). The reason for the higher clearance, and consequently higher exposure, in obese patients (especially females), are unclear. The applicant has not discussed the mechanistic reasons for the higher exposure in obese patients.

No differences in effect (based on PANSS score) were observed with increased BMI and the exposure in highly obese females is expected to be within the same range as approved for the oral reference product (up to 6 mg/day) (under the assumption that the requested bridging study with the EU reference product will give similar results to those from BORIS), and therefore is no dose-adjustment needed in obese subjects. Since no dose adjustment is required, no further information will be requested on the mechanistic explanation of this effect.

No effect of weight or race on CL_{40} were observed in the Pop PK analysis, and dose adjustment is therefore not required.

Interactions

At steady state, C_{max} of Risperidone ISM higher than after oral administration of 4 mg risperidone. According to its SmPC, an oral daily dose of up to 6 mg of the reference tablet can be given. Since the kinetics is dose-proportional within the therapeutic range, the steady state concentrations of Risperidone ISM would fall within the exposure expected for the approved dose of the reference product. Therefore, it is considered acceptable to refer to the reference products' SmPC for interactions where risperidone is the perpetrator and not to provide own data.

Exposure relevant for safety evaluation

At steady-state, Risperidone ISM results in slightly higher active moiety concentrations than 4 mg oral risperidone. The exposure is however not elevated to more than 150%, which is the exposure range expected for 6 mg oral Risperdal. The pharmacokinetics of the oral product is dose-proportional within the therapeutic interval, and a dose of 6 mg daily is approved. Thereby the safety data of the reference product can be extrapolated to Risperidone ISM.

Simulations of dose-dumping resulted in very high concentrations of active moiety (about 300-400 ng/mL). However, there are some assumptions made in the simulation, for instance linear PK. This scenario is a hypothetic worst-case scenario and the validity in a clinical setting is unclear.

Exposure-efficacy

No exposure-response relationship was evident based on PANSS events in the studied concentration range. Maximal effect appeared to be reached at the lowest dose (75 mg). Steady state concentrations of active moiety >20 ng/mL seemed to reach a plateau of the concentration-response relationship.

The applicant argues that the Pop PK/PD model of PANSS score can be used for predictions of PANSS score over time for doses and dosing schemes of Risperidone ISM resulting in the same active moiety exposure range as in the PRISMA-3 study. According to the applicant is the EC50 value (4.6 ng/mL) comparable to values previously reported in the literature and also supported by the results of PANSS score in the PRSIMA-3 study. The applicant's arguments are partly supported. The assessor still considers that there are some uncertainties in the proposed Pop PK/PD model, since it is based on a limited dose-range and an EC50-value with a large confidence interval. It is considered that the Pop PK/PD model can only be used to partly support discussions regarding the exposure-effect relationship of PANSS score in the exposure range studied in the PRISMA-3 study. The results from the Pop PK/PD model should not be included in the SmPC.

Exposure-safety

It would have been valuable to use safety data from all studies, however the exposure-safety analysis based on phase 3 data only is considered sufficient.

No exposure-response relationship was evident based extrapyramidal and somnolence/sedation events in the studied concentration range. The risk of hyperprolactinaemia events was predicted to increase with increasing active moiety exposure. The risk of extrapyramidal and hyperprolactinaemia events seemed to be increased for Risperidone ISM as compared to placebo, whereas the risk of somnolence/sedation events did not seem to be increased.

In the logistics regression plots of TEAE it seems like there are increased AEs at lower concentrations when based on the observed active moiety concentrations on day 2 as compared to the predicted average active moiety concentrations. The applicant discussed thoroughly why the point estimate for the observed TEAE event rate seemed to be higher at lower active moiety concentrations on day 2 as compared to the observed TEAE event rate at higher active moiety concentrations on day 2. The applicant considers that this finding is a consequence of the low number of events on day 2 with lower concentrations. The reason for this finding is still unclear. However, this is not considered to have any implications on the application and the issue is therefore not further pursued.

The scores of SAS and BARS4 seemed to be increased for Risperidone ISM vs. placebo but no apparent relationship with active moiety exposure was present in the studied exposure range. The scores of AIMS8 appeared to be similar among the three treatments.

2.4.2.4. Conclusions on clinical pharmacology

The pivotal PK bridge to the EU reference product has been established and no issues remain.

2.4.3. Clinical efficacy

The indication initially applied for was:

- *for the treatment of schizophrenia in adults.*
- *for the treatment of schizophrenia in adult patients with acute exacerbation where psychotic symptoms are moderate to severe.*
- *for the treatment of schizophrenia in adult patients previously stabilised with antipsychotics.*

During the course of the procedure the applicant changed the proposed indication to:

Okedi is indicated for the treatment of schizophrenia in adults.

The clinical development for efficacy included a short-term study with an OLE phase of 1 year (Table 6). Explorative short-term efficacy data from an open-label pharmacokinetic study was also provided.

Table 6: Clinical Development Programme or Risperidone ISM 75 mg and 100 mg

Study ID	No. of Study Centers Location (s)	Study start Enrolment status, date Total enrollment/ Enrollment goal	Design Control type	Study & Control drugs Dose, Route and Regimen	Study Objective	# subjects by arm Entered/ Completed	Duration	Gender M / F Median Age (Range)	Diagnosis Inclusion criteria	Primary Endpoint (s)
ROV-RISP-2011-02 (PRISMA-2)	4 US	26 March 2014 Completed 70 / 93	Phase 2, multicenter, open-label, two-arm, parallel-design, repeat-dose Open label	Risperidone ISM, 75 mg, injections into either the deltoid or gluteal muscle	Characterize the PK of Risperidone ISM over four injections in the gluteal and deltoid muscle at 28-day intervals and at one dose strength; exploratory efficacy evaluation	Deltoid injection 75 mg: 33 / 19 Gluteal injection 75 mg: 34 / 17	Four IM injections at 28-day intervals	Deltoid injection 75 mg: 28 M / 5 F 45 (26-61) Gluteal injection 75 mg: 27 M / 7 F, 43, (22-61)	Patients with schizophrenia Maintenance patients who have not had a relapse in the three months prior to entry onto the study	Exploratory efficacy analysis for change from baseline to 120 days after Dose 4 on the PANSS for PANSS total score, PANSS positive and negative subscales scores, PANSS individual scores, and change from baseline to 120 days after Dose 4 for CGI-S.
ROV-RISP-2016-01 (PRISMA-3) DB Phase	26 US, Ukraine	02 June 2017 Completed 438 / 438	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel groups Placebo control	Treatment 1: 75 mg Risperidone ISM Treatment 2: 100 mg Risperidone ISM Treatment 3: Placebo One injection in gluteal or deltoid muscle every 4 weeks	Evaluate the efficacy and safety of Risperidone ISM compared to that of placebo in the treatment of patients with schizophrenia	Treatment 1: 145 / 144 Treatment 2: 146 / 146 Treatment 3: 146 / 146	Up to three doses	Treatment 1: 98 M / 46 F, 43.5 (18-63) Treatment 2: 97 M / 49 F, 42.0 (22-64) Treatment 3: 98 M / 49 F, 40.0 (18-63)	Schizophrenia Patients with schizophrenia experiencing an acute exacerbation or relapses < 2 months needing treatment (not maintenance)	Endpoint was defined as study Day 85 or the last postbaseline DB assessment. The primary efficacy variable was: PANSS total score mean change from baseline to endpoint
ROV-RISP-2016-01 (PRISMA-3) OLE Phase	22 US, Ukraine	Roll-over from DB phase Completed 41/100 de novo Plus 174 rollover (215 total)	Phase 3 multicentre, randomized. Open-label	Treatment 1: 75 mg Risperidone ISM Treatment 2: 100 mg Risperidone ISM	Persistence of efficacy and safety of Risperidone ISM	Treatment 1: 90/116 Treatment 2: 71/99	Up to 13 doses	Treatment 1: 78M/38F, 39.0 (19-62) Treatment 2: 53M/46F, 39.0 (23-61)	Schizophrenia Rollover patients completed scheduled participation in DB phase OR de novo patients clinically stable and on stable oral risperidone	Endpoint was defined as study Day 385 or the last postbaseline OLE assessment. Efficacy parameters were summarized descriptively

CGI-S: Clinical Global Impression- Severity of illness; DB: double-blind; ID: identification; IM: intramuscular; ISM: *in situ* microimplants; M: male; OLE: open-label extension; PANSS: Positive and Negative Syndrome Scale; PK: pharmacokinetic; US: United States

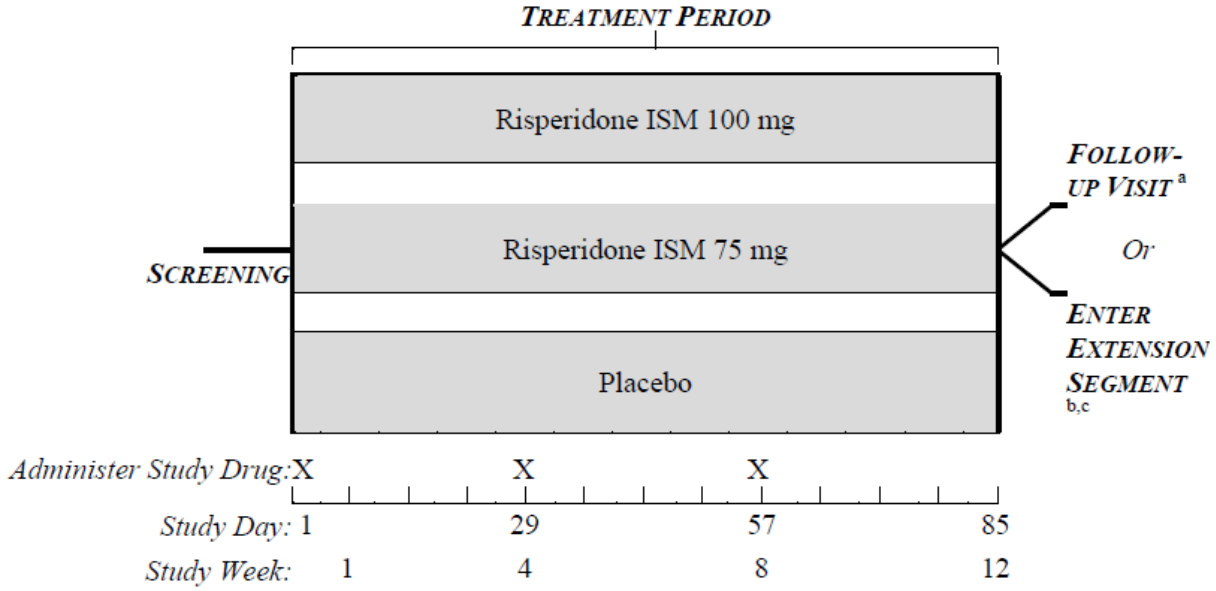
2.4.3.1. Dose-response studies and main clinical studies

No dose-response study was submitted.

2.4.3.2. Main study - ROV-RISP-2016-01 [PRISMA-3]

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)

The confirmatory efficacy study (ROV-RISP-2016-01 [PRISMA-3]) was a multicentre, randomised, double-blind (DB), placebo-controlled efficacy and safety study of Risperidone ISM in patients with acute exacerbation of schizophrenia. It was designed to meet the EMA guidance (EMA/CPMP/EWP/280/96 Corr1, and EMA/CHMP/40072/2010 Rev.1;2012) and Scientific Advice EMA/CHMP/SAWP/270310/2016.



a. If a patient did not enter the extension segment of the study, no additional doses of study drug were administered to that patient.

b. Patients who completed planned participation through to the end of the treatment period may have been eligible to enter into a long-term extension segment of the study, during which open-label Risperidone ISM (ie, 75 or 100 mg) was administered once every 4 weeks for approximately 12 months. However, to preserve the blinding condition of the double-blind stage of the study, if a participating patient entered 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 was still blinded at least up to locking the aforementioned database. Patients who entered into the extension segment began 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 continued to receive active Risperidone ISM at the same dose (ie, 75 or 100 mg) in the extension segment; patients who had been receiving placebo in the double-blind segment of the study were randomly assigned to receive either 75 or 100 mg during the extension segment.

c. De novo patients were also eligible to enter the long-term extension segment of the study. These patients were evaluated for eligibility at a screening visit and, if eligible, 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 were 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 were assigned to 100 mg Risperidone ISM every 4 weeks.

Methods

The study design included 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 entered into the long-term extension), and an optional

open-label extension (OLE) period (duration 12 months) followed by a 4-week follow-up period for all patients in the extension segment of the study.

Patients had a diagnosis of schizophrenia experiencing an acute exacerbation. Following confirmation of eligibility, each patient was randomly assigned under DB conditions to receive 1 of the following 3 study drug treatments: Risperidone ISM 75 mg, Risperidone ISM 100 mg, or placebo. The randomisation scheme ensured that an overall 1:1:1 ratio of assignments to each of these 3 study drug treatments was approximated.

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

Study Participants

A total of 565 patients were screened for the DB phase, of which 127 (22.5%) were screen failures, and 438 (22.5%) passed screening are were randomised in the DB phase. Two hundred and ninety (290) patients completed the DB phase of the study and were analysed.

A total of 174 patients signed the ICF for the OLE phase, of which 44 patients were de novo patients (did not take part in the DB phase). Three of these patients failed screening, and the rest (41 patients) continued into the OLE.

The study was conducted at 26 sites in 2 countries, with the majority of patients in the United States (61.1%) and the remainder in Ukraine (38.9%).

Main inclusion/exclusion criteria

To be eligible for enrolment into the DB part of the study, the following key inclusion criteria applied:

- Age ≥18 and ≤65 years
- Current diagnosis of schizophrenia, according to the DSM-5 criteria
    - Was experiencing an acute exacerbation or relapse with onset <2 months before screening
    - If inpatient at screening, had been hospitalised for <2 weeks for the current exacerbation
    - ≥2 years have elapsed since initial onset of active-phase schizophrenia symptoms
- Was able to achieve outpatient status for >4 months during the past year
- Had 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
- Positive and Negative Syndrome Scale (PANSS) results at the screening and baseline visits met the following criteria:
    - Total score between 80 and 120, inclusive
    - Score of ≥4 (moderate or greater) for ≥2 of the following Positive Scale items:
        i. Item 1 (P1: delusions)
        ii. Item 2 (P2: conceptual disorganisation)
        iii. Item 3 (P3: hallucinatory behaviour)
        iv. Item 6 (P6: suspiciousness/persecution)
- Clinical Global Impression – Severity (CGI-S) score of ≥4 (moderately ill or worse)

To be eligible for entry into the OLE segment of the study, a rollover patient had to

- have 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, and continued to require long-term treatment with an antipsychotic medication.

- 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

Treatments

Test Product, Dose, and Mode of Administration*:* Risperidone ISM is a long-acting formulation of risperidone that uses ISM technology. Risperidone ISM 75 mg or 100 mg were administered IM in the deltoid or gluteal muscle every 4 weeks (study days 1, 29, and 57) during the DB phase and during the OLE phase.

Reference Product, Dose, and Mode of Administration*:* Placebo was administered IM in the deltoid or gluteal muscle every 4 weeks (study days 1, 29, and 57) during the DB phase.

Duration of Treatment*:* The DB treatment period lasted 12 weeks, the follow-up period after the DB phase lasted 2 weeks (not applicable for patients who entered into the long-term extension). The OLE period lasts 12 months with a 4-week follow-up period.

Objectives

The primary objective of this study was 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

The secondary objectives of this study were 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 utilisation (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 PK characteristics of Risperidone ISM and associations with efficacy

Outcomes/endpoints

The primary efficacy variable was:

• PANSS total score mean change from baseline to endpoint

The key secondary efficacy variable was:

• CGI-S score mean change from baseline to endpoint

Other secondary efficacy variables were:

- Clinical Global Impression – Improvement (CGI-I) score mean at endpoint
- Overall response rate at endpoint
    - Overall response was 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 was 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 postbaseline 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 postbaseline assessment time point
- CGI-I score mean at each post-baseline assessment time point

Randomisation and blinding (masking)

Randomisation numbers were assigned via an interactive voice or web response system (IWRS). The randomisation scheme automatically ensured that the study drug assignment for a given patient was random and that an overall 1:1:1 ratio of assignments to each of the 3 study drug treatments (ie, blinded Risperidone ISM 75 mg, Risperidone ISM 100 mg, or placebo) was approximated.

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

An independent biostatistician maintained the randomisation scheme key, which remained unavailable to all other individuals until after study completion and subsequent locking of the study database.

On 28 September 2017, due to a noted error in the IWRS, potential accidental unblinding of treatment allocation to patients for blinded personnel was reported. It was concluded that there were 43 patients for whom the blinding was potentially compromised. The applicant has described the error that potentially led to unblinding. An error in the configuration in the IWRS information about treatment allocation was available to some personnel that should have been blinded. This may in turn have caused patients to have been unblinded. It has not been possible to determine if the potentially affected patients actually have been unblinded. The company has chosen to exclude patients based on if there was a possibility for unblinding, based on information such as logs from the IWRS. This is endorsed.

The company states that no systematic component of potential impacted patients was possible to demonstrate. The company has also provided listings of the potentially affected patients and the additional patients that were randomised to compensate.

Statistical methods

Sample size

The difference between the active treatments and placebo in the PANSS total score mean change from baseline to endpoint (primary efficacy variable) was assumed as a 9-point decrease, with a common SD of 20. In the calculation 2-group t-tests were used.

A Bonferroni adjustment was used for the two doses.

A sample size of 124 patients in the mITT population in each treatment group would have 90% power to detect a difference in means of 9 (SD = 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%. Assuming a 5% dropout rate 131

patients per treatment group, or 393 patients total was required. This assumption was re-assessed at the interim analysis and used in re-estimating the total number of randomised patients required.

As a result of the potential unblinding of 43 patients (see Randomisation and blinding), the total number of patients required was adjusted to 436.

Statistical analyses

Analysis methods

The primary efficacy analysis was designed to show superiority of active treatment versus placebo in the primary efficacy variable.

Two hypotheses were tested:

a. H0,A: μRisperidone ISM 75 mg - μplacebo = 0 vs H1,A: μRisperidone ISM 75 mg - μplacebo ≠ 0

b. H0,B: μRisperidone ISM 100 mg - μplacebo = 0 vs H0,B: μRisperidone ISM 100 mg - μplacebo ≠ 0

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

The applicant has used an MMRM model with a MAR assumption for missing data. The MMRM was fitted with country where enrolled, visit, treatment, and treatment-by-visit interaction as fixed effects and baseline PANSS total score as a covariate. This model was applied separately for patients in stage 1 (patients included in the interim analysis) and stage 2 (all subsequent patients) of the study, as well as for overall patients.

An ANCOVA model, using jump to reference imputations for missing data, was presented as a sensitivity analysis. The results of this analysis were in accordance with the MMRM. It would be preferred if the sensitivity analysis was presented in the SmPC instead of the MMRM.

A hierarchical testing was performed for the primary efficacy variable (PANSS) and the key secondary variable (CGI-S). Other secondary efficacy variables analyses were to be considered exploratory.

An interim analysis re-estimating the sample size was performed. The type I error was controlled for the sample size re-estimation by using predefined weights for the stages (Cui, Hung, Wang methodology).

The DMC received the results of the interim analysis from an unblinded statistician not part of the DMC. The company states that the unblinded statistician was not involved in other aspects of the study with the sponsor that may have affected important decisions, such as protocol amendments.

Hommel's closed testing procedure was used to control the type I error while testing two doses. This test assumes independent or positively dependent p-values. An assumption of positively dependent p-values is reasonable.

The planned main efficacy population was the ITT population. Due to an error in the IWRS (for discussion see section on blinding) some patients were potentially unblinded, and an mITT population, excluding these patients, was also defined.

Intent-to-Treat Population

The ITT population consists of all randomised patients who received at least 1 dose of study drug with a baseline measurement and ≥ 1 postbaseline evaluation of the PANSS. Analyses performed on the ITT population were as randomised. The ITT population was used for analyses of efficacy endpoints, including HEOR endpoints.

Modified Intent-to-Treat Population

The mITT population consists of all patients in the ITT population for whom blinding was not compromised. Analyses performed on the mITT population were as randomised. The mITT population was used for analyses of efficacy endpoints.

Analyses on these populations were presented for the efficacy analyses, with focus on the mITT results. Efficacy results were also presented for a PP and mPP population. In the ITT population only patients who received at least 1 dose of study drug with a baseline measurement and ≥ 1 post baseline evaluation of the PANSS were included. A strict ITT population with all randomised patients would have been preferred, but since few (5/438) patients were excluded due to this criterium, and the study was blinded, this is not likely to have affected the results.

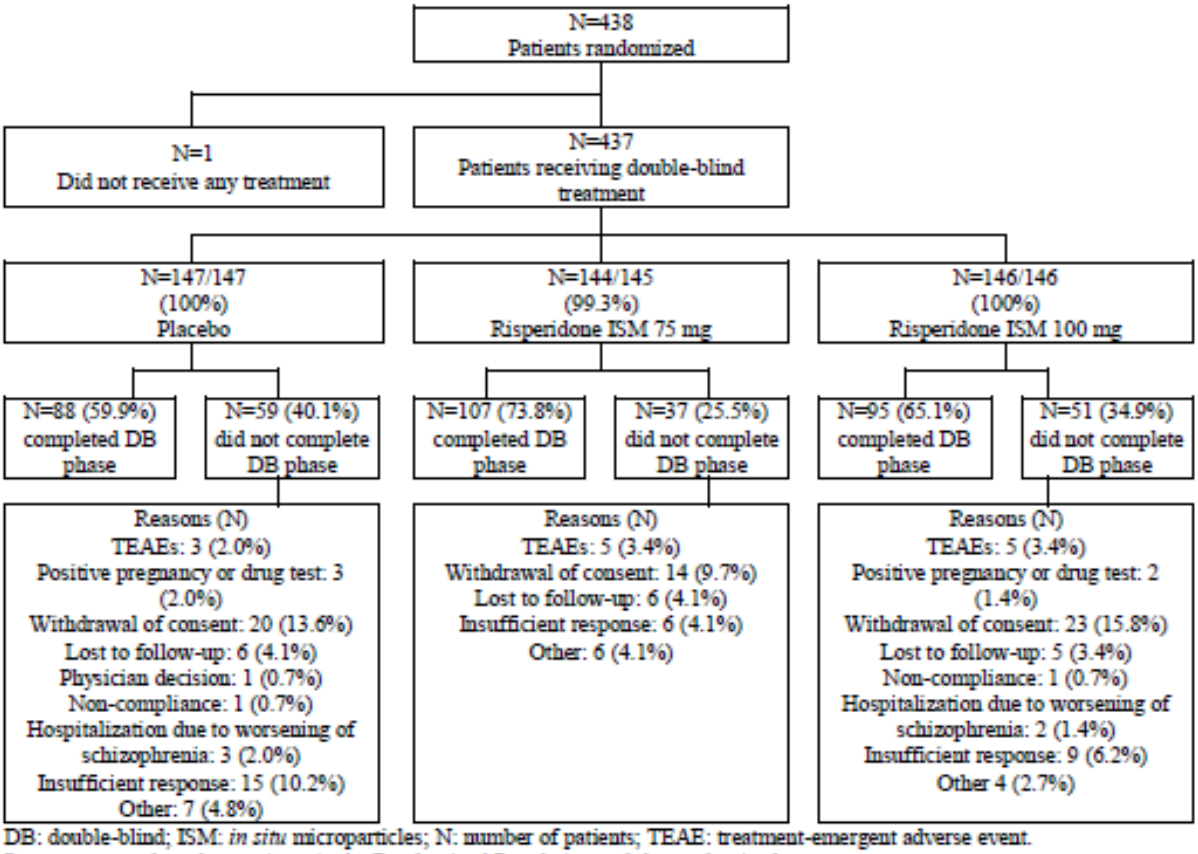
Results

Two hundred and ninety (290) patients completed the DB phase of the study and were analysed in March 2019.

A total of 174 patients signed the ICF for the OLE phase, of which 44 patients were *de novo* patients (did not take part in the DB phase). Three of these patients failed screening, and the rest (41 patients) continued into the OLE. Patient disposition for the Randomised Population is summarised in Figure 16.

Due to an error in the IWRS, 43 patients were potentially unblinded and thereby excluded and the total sample size was increased accordingly. Of the 43 potentially affected patients 13 had been assigned to placebo, 14 to Risperidone ISM 75mg and 16 to Risperidone ISM 100mg. Although the number of potentially affected patients is numerically higher in the higher dose group, there is no obvious association between assigned dose and potential unblinding, and the exclusion of the 43 patients is not considered likely to have introduced any bias.

Figure 16: Patient disposition for the Randomised Population



DB: double-blind; ISM: *in situ* microparticles; N: number of patients; TEAE: treatment-emergent adverse event.
Percentages are based on patients in the Randomized Population and the randomized treatment.
Source: ROV-RISP-2016-01 PRISMA-3 CSR, Table 14.1.1.2

Patients were evenly distributed across the treatment groups, with 147 patients in the placebo group, 145 patients in the Risperidone ISM 75 mg group, and 146 patients in the Risperidone ISM 100 mg group. One patient (84010013) was assigned treatment (assigned to the Risperidone ISM 75 mg group) but did not receive study treatment because they withdrew consent before receiving a dose of study drug.

The OLE phase

At the time of reporting, 215 patients received at least 1 dose in the OLE phase (OL population). Of these 215 patients, 26 patients (12.1%) had completed the OLE phase, 46 patients (21.4%) did not complete the OLE phase, and 143 (66.5%) were ongoing. The most common reasons for not completing the OLE phase was withdrawal of consent (24 patients, 11.2%), AEs (7 patients, 3.3%), and hospitalisation for worsening, relapse, or exacerbation of schizophrenia symptoms (5 patients, 2.3%). Other reasons for not completing were lost to follow-up (4 patients, 1.9%); and insufficient clinical response (2 patients, 0.9%); and death, noncompliance, and other (1 patient each).

Baseline data

Demographics and baseline characteristics are presented in Table 7.

Table 7: Demographic and Baseline Characteristics (mITT Population)

Baseline Variable		Risperidone ISM	Risperidone ISM	Risperidone ISM	
	Placebo	75 mg	100 mg	All	Overall
Statistic/Category	N=132	N=129	N=129	N=258	N=390
Age (years)					
N	132	129	129	258	390
Mean (SD)	40.0 (11.35)	42.6 (10.63)	42.6 (11.14)	42.6 (10.87)	41.7 (11.08)
Min	18	19	22	19	18
Max	63	63	64	64	64
Sex, n (%)					
Male	85 (64.4)	88 (68.2)	84 (65.1)	172 (66.7)	257 (65.9)
Race, n (%)					
White	71 (53.8)	69 (53.5)	65 (50.4)	134 (51.9)	205 (52.6)
Black or African American	59 (44.7)	58 (45.0)	63 (48.8)	121 (46.9)	180 (46.2)
Asian	1 (0.8)	1 (0.8)	1 (0.8)	2 (0.8)	3 (0.8)
Other	1 (0.8)	1 (0.8)	0	1 (0.4)	2 (0.5)
Ethnicity, n (%)					
Hispanic or Latino	10 (7.6)	6 (4.7)	3 (2.3)	9 (3.5)	19 (4.9)
Not Hispanic or Latino	122 (92.4)	123 (95.3)	126 (97.7)	249 (96.5)	371 (95.1)
Country, n (%)					
Ukraine	56 (42.4)	57 (44.2)	57 (44.2)	114 (44.2)	170 (43.6)
United States	76 (57.6)	72 (55.8)	72 (55.8)	144 (55.8)	220 (56.4)
BMI (kg/m²)					
N	132	129	129	258	390
Mean (SD)	28.19 (4.715)	27.77 (5.226)	28.26 (5.268)	28.02 (5.243)	28.07 (5.065)
Min	18.4	18.9	18.7	18.7	18.4
Max	39.8	40.1	40.0	40.1	40.1
Baseline Variable		**Risperidone ISM**	**Risperidone ISM**	**Risperidone ISM**	
	Placebo	**75 mg**	**100 mg**	**All**	**Overall**
Statistic/Category	N=132	N=129	N=129	N=258	N=390

Years since Schizophrenia Diagnosis					
N	132	129	129	258	390
Mean (SD)	14.3 (9.74)	16.1 (10.67)	15.7 (10.43)	15.9 (10.53)	15.4 (10.29)
Median	12.5	15.0	14.0	14.0	13.0
Min	0	0	2	0	0
Max	40	42	50	50	50
Time since Acute Exacerbation or relapse (weeks)					
N	132	129	129	258	390
Mean (SD)	0.4 (0.22)	0.4 (0.26)	0.4 (0.49)	0.4 (0.39)	0.4 (0.34)
Median	0.4	0.3	0.4	0.3	0.3
Min	0	0	0	0	0
Max	1	1	5	5	5
Baseline CGI-S					
1 = Normal	0	0	0	0	0
2 = Borderline ill	0	0	0	0	0
3 = Mildly ill	0	0	0	0	0
4 = Moderately ill	28 (21.2)	32 (24.8)	33 (25.6)	65 (25.2)	93 (23.8)
5 = Markedly ill	92 (69.7)	77 (59.7)	88 (68.2)	165 (64.0)	257 (65.9)
	Placebo	**75 mg**	**100 mg**	**All**	**Overall**
6 = Severely ill	12 (9.1)	20 (15.5)	8 (6.2)	28 (10.9)	40 (10.3)
7 = Extremely ill	0	0	0	0	0
Mean (SD)	4.9 (0.54)	4.9 (0.63)	4.8 (0.53)	4.9 (0.58)	4.9 (0.57)
Median	5.0	5.0	5.0	5.0	5.0
Min	4	4	4	4	4
Max	6	6	6	6	6

BMI: body mass index; ISM: *in situ* microimplants; mITT: modified intent-to-treat; N: number of patients; SD: standard deviation.
Note: Presented statistics, frequencies and the denominator used for percentages are based on patients in the mITT Population and the randomized treatment.
- BMI (kg/m^2) is calculated as BMI = 100 x Weight (kg)/ [Height $(cm)^2$].

The primary analysis population for the DB phase (mITT) consisted of 390 patients. Forty percent of 147 placebo patients did not complete the DB phase with 18/147 (12.3%) discontinuing to due insufficient response or worsening of schizophrenia, whilst 26% of the 144 Risperidone ISM 75 mg patients did not complete the DB phase with 6 /144 (4.1%) being withdrawn for insufficient response and in the Risperidone ISM 100 mg group 35% of the 146 patients did not complete the DB phase with 11/146 (7%) discontinuing to due insufficient response or worsening of schizophrenia.

Numbers analysed

The planned total number of randomised patients in the DB segment of the study was approximately 436 (approximately 145 in each of the 3 treatment groups). Note: due to a potential accidental unblinding quality issue, it was considered that 43 patients were potentially compromised and were therefore removed; the sample size was subsequently increased from 393 to 436 to compensate for these removed patients. Approximately 100 *de novo* patients were planned to be enrolled in the extension segment of the study, in addition to rollover patients.

The number of patients in each analysis population is summarised in Table 8.

Table 8

Analysis Population	Placebo N=147 n (%)	Risperidone ISM 75 mg N=145 n (%)	Risperidone ISM 100 mg N=146 n (%)	Overall N=438 n (%)
Safety (SAF) population	147	144	146	437
Modified Safety (mSAF) population	134 (91.2)	130 (90.3)	130 (89.0)	394 (90.2)
Intent-To-Treat (ITT) population	145 (98.6)	143 (98.6)	145 (99.3)	433 (98.9)
Modified Intent-To-Treat (mITT) population	132 (89.8)	129 (89.0)	129 (88.4)	390 (89.0)
Per-Protocol (PP) population	119 (81.0)	126 (86.9)	121 (82.9)	366 (83.6)
Modified Per-Protocol (mPP) population	109 (74.1)	114 (78.6)	112 (76.7)	335 (76.5)
Pharmacokinetic (PK) population *	0	144 (100)	146 (100)	290 (66.4)
Intense PK subset	0	25 (17.4)	28 (19.2)	53 (12.1)
Open-label (OL) population (rollovers)	55 (37.4)	58 (40.0)	61 (41.8)	174 (39.7)
De novo patients		31 (26.7)	10 (10.1)	
OL population (rollovers)+ de novo		116 (100)	99 (100)	

Modified SAF, ITT, and PP populations were analyzed because of a potential unblinding incident.

Outcomes and estimation

PANSS total score mean change from baseline to Day 85 in the mITT population

The PANSS total score at baseline was comparable between the Risperidone ISM groups. The PANSS total score LS mean change from baseline was significantly larger for both Risperidone ISM 75 mg and Risperidone ISM 100 mg compared to placebo (Table 9). A sensitivity analysis using ANCOVA supported the primary analysis.

The mean change from baseline was significant for both Risperidone ISM groups in each of the participating countries as well as for patients with a baseline PANSS score <95 and those with baseline PANSS score ≥95.

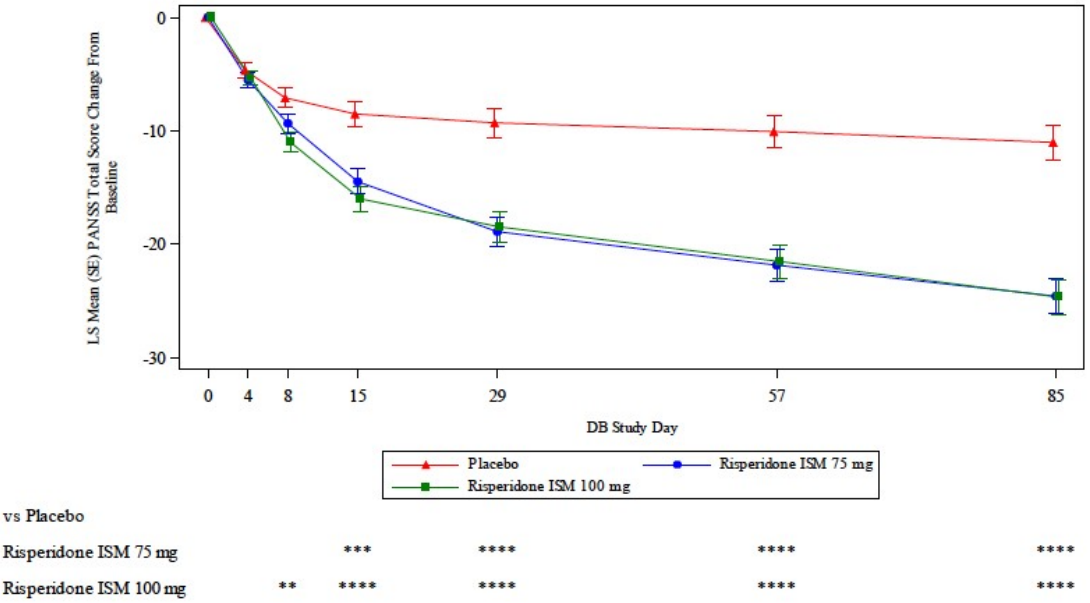
Table 9: PANSS Total Score Change From Baseline to Day 85 (mITT Population)

Time point Statistic	Placebo N=132	Risperidone ISM 75 mg N=129	Risperidone ISM 100 mg N=129
Day 85			
LS Means (SE), 95% CI	-11.0 (1.56), -14.1 to -8.0	-24.6 (1.51), -27.5 to -21.6	-24.7 (1.54), -27.7 to -21.6
Risperidone ISM v Placebo:			
LS Means Difference (SE), 95% CI		-13.6 (2.17), -17.8 to -9.3	-13.6 (2.19), -17.9 to -9.3
P-value		<0.0001	<0.0001
LH Mean Difference (SE), 95% CI [1]		-13.0 (2.19), -17.3 to -8.8	-13.3 (2.21), -17.6 to -8.9
CHW Adjusted p-value [1]		<0.0001	<0.0001
Hommel Adjusted p-value [2]		<0.0001	<0.0001

CHW: Cui, Hung, Wang (1999); CI: confidence interval; ISM: *in situ* microparticles; mITT: modified intent-to-treat; LH: Lawrence and Hung (2003); LS: least squares; MMRM: mixed model with repeated measures; PANSS: Positive and Negative Syndrome Scale; SE: standard error.
[1] CHW and LH methods combine results from stage 1 and stage 2 (ROV-RISP-2016-01 PRISMA-3 CSR, Table 4.2.1.1.1.3)
[2] Hommel adjustment of CHW p-values. These are the primary p-values of the study and are used to assess confirmatory superiority of each Risperidone ISM dose over Placebo if p <0.05 and if the corresponding p-value from the ITT analysis (ROV-RISP-2016-01 [PRISMA-3] CSR, Table 14.2.1.1.2.2) is also p <0.05
Notes: Presented statistics are based on all patients in the mITT population and the randomised treatment.

In order to evaluate further change from baseline in the first 29 days, mean change from baseline in PANSS total score at each post-baseline assessment time point was evaluated as a secondary efficacy outcome (Figure 17 and Table 10).

Figure 17: PANSS Total Score Change From Baseline at Each Time Point (mITT Population)



mITT: modified intent-to-treat; LS: least squares; PANSS: Positive and Negative Syndrome Scale; SE: standard error. Profile of LS Mean at each time point. Error bars represent SE. * p<0.05, ** p<0.01, *** p<0.001, **** p<0.0001.

Table 10: PANSS Total Score Change From Baseline at Each Time Point (mITT Population)

Time point Statistic	Placebo N=132	Risperidone ISM 75 mg N=129	Risperidone ISM 100 mg N=129
Day 4			
LS Means (SE), 95% CI	-4.7 (0.64),-5.9 to -3.4	-5.5 (0.65), -6.8 to -4.2	-5.4 (0.65), -6.6 to -4.1
Risperidone ISM v Placebo:			
LS Means Difference (SE), 95% CI		-0.9 (0.91),-2.7 to 0.9	-0.7 (0.91),-2.5 to 1.1
P-value		0.343	0.443
Day 8			
LS Means (SE), 95% CI	-7.1 (0.86),-8.8 to -5.4	-9.3 (0.87), -11.1 to -7.6	-11.0 (0.87), -12.7 to -9.3
Risperidone ISM v Placebo:			
LS Means Difference (SE), 95% CI		-2.3 (1.22),-4.7 to 0.2	-3.9 (1.22),-6.4 to -1.5
P-value		0.066	0.001
Day 15			
LS Means (SE), 95% CI	-8.5 (1.10),-10.7 to -6.3	-14.5 (1.11), -16.6 to -12.3	-16.0 (1.11), -18.2 to -13.8
Risperidone ISM v Placebo:			
LS Means Difference (SE), 95% CI		-6.0 (1.56),-9.0 to -2.9	-7.5 (1.56),-10.6 to -4.4
P-value		<0.001	<0.0001
Day 29			
LS Means (SE), 95% CI	-9.3 (1.31),-11.9 to -6.7	-18.9 (1.31), -21.5 to -16.3	-18.5 (1.31), -21.0 to -15.9
Risperidone ISM v Placebo:			
LS Means Difference (SE), 95% CI		-9.6 (1.85),-13.2 to -6.0	-9.2 (1.85),-12.8 to -5.6
P-value		<0.0001	<0.0001
Day 57			
LS Means (SE), 95% CI	-10.1 (1.47),-13.0 to -7.2	-21.8 (1.44), -24.7 to -19.0	-21.5 (1.45), -24.4 to -18.7
Risperidone ISM v Placebo:			
LS Means Difference (SE), 95% CI		-11.8 (2.06),-15.8 to -7.7	-11.4 (2.06),-15.5 to -7.4
P-value		<0.0001	<0.0001
Day 85[1]			
LS Means (SE), 95% CI	-11.0 (1.56),-14.1 to -8.0	-24.6 (1.51), -27.5 to -21.6	-24.7 (1.54), -27.7 to -21.6
Risperidone ISM v Placebo:			
LS Means Difference (SE), 95% CI		-13.6 (2.17),-17.8 to -9.3	-13.6 (2.19),-17.9 to -9.3
P-value		<0.0001	<0.0001
LH Mean Difference (SE), 95% CI [2]		-13.0 (2.19),-17.3 to -8.8	-13.3 (2.21),-17.6 to -8.9
CHW Adjusted p-value [2]		<0.0001	<0.0001
Hommel Adjusted p-value [3]		<0.0001	<0.0001

CI: Confidence Interval;, DB = Double-blind, mITT = Modified Intent-To-Treat, KM = Kaplan-Meier, CHW = Cui, Hung, Wang (1999), CI = Confidence Interval, mITT = Modified Intent-To-Treat, LH = Lawrence and Hung (2003), LS = Least Squares, MMRM = Mixed Model with Repeated Measures, PANSS = Positive and Negative Syndrome Scale, SE = Standard Error
[1] Analyzed for the primary endpoint
[2] HW and LH methods combine results from stage 1 and stage 2
[3] Hommel adjustment of CHW p-values. These are the primary p-values of the study and are used to assess confirmatory superiority of each Risperidone ISM dose over Placebo if $p < 0.05$ and if the corresponding p-value from the ITT analysis is also $p < 0.05$
Notes: Presented statistics are based on all patients in the mITT population and the randomised treatment.

There was a progressive decrease in PANSS score from baseline to Day 85 in all treatment groups. These results support efficacy across the entire duration of treatment and improvement in PANSS.

PANSS Response Rate

The PANSS response was defined as a decrease from baseline in PANSS total score of ≥30% and is shown for the mITT population in Table 11.

Table 11: PANSS Response Rate (mITT Population)

Time point Statistic	Placebo N=132	Risperidone ISM 75 mg N=129	Risperidone ISM 100 mg N=129
Day 85, n [1]	132	129	129
Responders, n (%)	11 (8.3)	49 (38.0)	40 (31.0)
95% CI (%) [2]	4.2 to 14.4	29.6 to 46.9	23.2 to 39.7
Risperidone ISM v Placebo:			
Difference in proportions (%)		29.7	22.7
95% CI [3]		19.6 to 38.9	13.0 to 31.6
p-value [3]		<0.0001	<0.0001
Endpoint, n	132	129	129
Responders, n (%)	12 (9.1)	54 (41.9)	45 (34.9)
95% CI (%) [2]	4.8 to 15.3	33.2 to 50.9	26.7 to 43.8
Risperidone ISM v Placebo:			
Difference in proportions (%)		32.8	25.8
95% CI [3]		22.5 to 42.2	15.8 to 35.0
p-value [3]		<0.0001	<0.0001

CI=confidence interval; DB=Double-blind; ISM=in situ microparticles; mITT=modified intent-to-treat; PANSS=Positive and Negative Syndrome Scale; SE=standard error.
[1] Dropouts prior to a presented time point are treated as non-responders
[2] Clopper Pearson Exact CI
[3] Mantel-Haenzel Test stratified by country and baseline PANSS [<95, >=95] with stratified Newcombe Cis Notes:- Those patients who do not achieve a response are censored on the day of withdrawal/completion from the DB treatment.- Presented statistics, frequencies and denominator used for percentages are based on all patients in the mITT population and the randomised treatment.

At Day 85, the difference in proportions compared with the placebo group was 29.7% (95% CI:19.6, 38.9) for the Risperidone ISM 75 mg group, and 22.7% (95% CI: 13.0, 31.6) for the Risperidone ISM 100 mg group.

Taking into account censored observations, at endpoint (Day 85 or last postbaseline DB assessment the difference in proportions compared with the placebo group was 32.8% (95% CI: 22.5, 42.2) for the Risperidone ISM 75 mg group, and 25.8% (95% CI: 15.8, 35.0) for the Risperidone ISM 100 mg group.

Time to PANSS Response

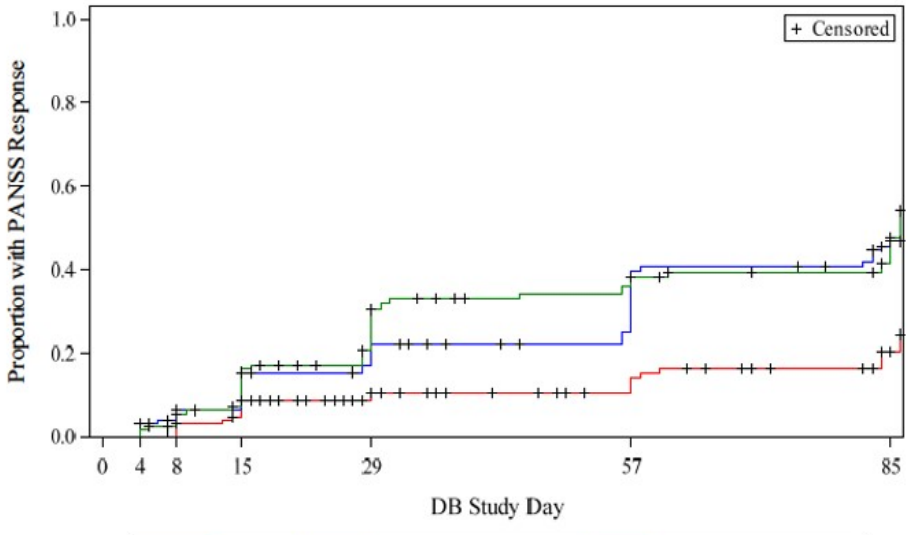
Time to reach PANSS response was a key secondary efficacy variable and the data are displayed in Table 12 and Figure 18.

Table 12: Time to PANSS Response (mITT Population)

Time point Statistic	**Placebo** N=132	**Risperidone ISM 75 mg** N=129	**Risperidone ISM 100 mg** N=129
Time to 1st response			
Responders/Non-Responders/Censored			
(KM % With 1st Response [95% CI])			
4 days	0/132/0	4/124/1	2/127/0
	(NE [NE])	(3.1 [1.2 to 8.1])	(1.6 [0.4 to 6.1])
≤8 days	4/123/5	8/116/5	7/116/6
	(3.1 [1.2 to 7.9])	(6.3 [3.2 to 12.2])	(5.5 [2.6 to 11.1])
≤15 days	11/111/10	19/100/10	20/101/8
	(8.6 [4.9 to 15.1])	(15.3 [10.1 to 23.0])	(16.2 [10.8 to 24.0])
≤29 days	13/92/27	27/90/12	36/77/16
	(10.5 [6.2 to 17.5])	(22.2 [15.8 to 30.7])	(30.3 [22.9 to 39.5])
≤57 days	16/76/40	46/65/18	44/59/26
	(13.9 [8.7 to 21.9])	(39.8 [31.5 to 49.4])	(38.1 [29.9 to 47.8])
≤85 days	21/19/92	53/14/62	51/16/62
	(20.2 [NE])	(46.8 [38.0 to 56.5])	(47.6 [38.1 to 58.0])
KM Median [95% CI] [1] (days)	NE [91.0 to NE]	87.0 [58.0 to 99.0]	86.0 [84.0 to NE]
p-value [5]		<0.0001	<0.0001

CI: confidence interval; DB: double-blind; ISM: in situ microparticles; KM: Kaplan-Meier; mITT: modified intentto-treat; NE: not estimable; PANSS: Positive and Negative Syndrome Scale
[1] Log-Rank Test stratified by country and baseline PANSS [<95, ≥95] versus Placebo
Notes:
- Those patients who do not achieve a response are censored on the day of withdrawal/completion from the DB treatment.
- Presented statistics, frequencies and denominator used for percentages are based on all patients in the mITT population and the randomised treatment.

Figure 18: Kaplan Meier Plot of Time to PANSS Response at Each Time Point (mITT Population)



At Risk							P-Value*
Placebo	132	132	131	119	97	79	45	
Risperidone ISM 75mg	129	129	121	114	96	81	45	<0.0001
Risperidone ISM 100mg	129	129	124	112	89	63	39	<0.0001

DB=Double-blind; ISM=in situ microparticles; mITT=modified intent-to-treat; PANSS=Positive and Negative Syndrome Scale.
P-values refer to Log Rank Test of Kaplan-Meier median time to PANSS response compared with placebo.

Kaplan-Meier percentage with first response was higher in both Risperidone ISM groups than in the placebo group at all time points. The percentage with first response was similar for the 2 Risperidone ISM groups at all time points other than ≤29 days, where it was 22.2 (95% CI: 15.8, 30.7) for the Risperidone ISM 75 mg group, and 30.3 (95% CI: 22.9, 39.5) for the Risperidone ISM 100 mg group. The Kaplan-Meier median time to PANSS response was not estimable for the placebo group, 87.0 (95% CI: 58.0, 99.0) days for the Risperidone ISM 75 mg group, and 86.0 (95% CI: 84.0, not estimable) days for the Risperidone ISM 100 mg group.

The PANSS response rate at each post-baseline assessment time point was measured on days 4, 8, 15, 29, 57, and 85. In the placebo group, the PANSS response rate increased at each time point up to Day 57, where it reached a high of 10.6% (14 responders; 95% CI: 5.9, 17.2). In both Risperidone ISM groups, the PANSS response rate increased at each time point and was highest at Day 85.

During the first two weeks the response is modest but gradually increase over time.

CGI-S

CGI-S score mean change from baseline to Day 85 was the key secondary efficacy variable. The difference in the change from baseline to Day 85 between placebo and both Risperidone ISM groups in mITT population was significant (Table 13).

Table 13: Change From Baseline in CGI-S Score to Day 85 (mITT Population)

Time point Statistic	**Placebo** N=132	**Risperidone ISM 75 mg** N=129	**Risperidone ISM 100 mg** N=129
Day 85			
LS Means, 95% CI	-0.6, -0.8 to -0.4	-1.3, -1.5 to -1.2	-1.3, -1.5 to -1.2
Risperidone ISM v Placebo:			
LS Means Difference, 95% CI		-0.7, -1.0 to -0.5	-0.7, -1.0 to -0.5
P-value		<0.0001	<0.0001
LH Mean Difference, 95% CI [1]		-0.7, -1.0 to -0.5	-0.7, -1.0 to -0.5
CHW Adjusted p-value [1]		<0.0001	<0.0001
Hommel Adjusted p-value [2]		<0.0001	<0.0001

CGI-S: Clinical Global Impression – Severity Scale; CHW: Cui, Hung, Wang (1999); CI: confidence interval; ISM: in situ microparticles; LH: Lawrence and Hung (2003); LS: Least Squares; mITT: modified intent-to-treat; PANSS: Positive and Negative Syndrome Scale; SE: standard error.
[1] CHW and LH methods combine results from stage 1 and stage 2
[2] Hommel adjustment of CHW p-values. These are the p-values of the study used to assess confirmatory superiority of each Risperidone ISM dose over Placebo if p < 0.05 and if both doses were superior to Placebo in the primary analysis of the study for both the mITT and ITT population Notes: Presented statistics are based on all patients in the mITT population and the randomised treatment.

Mean change from baseline in CGI-S score at each postbaseline assessment time point was a secondary efficacy variable. Change from baseline increased at each time point in all treatment groups.

Table 14: Change From Baseline in CGI-S Score at Each Time Point to Day 15 (mITT Population)

Time point Statistic	**Placebo** N=132	**Risperidone ISM 75 mg** N=129	**Risperidone ISM 100 mg** N=129
Day 4			
LS Means, 95% CI	-0.2, -0.2 to -0.1	-0.2, -0.3 to -0.2	-0.2, -0.3 to -0.2
Risperidone ISM v Placebo:			
LS Means Difference, 95% CI		-0.1, -0.2 to 0.0	-0.1, -0.2 to 0.0
P-value		0.155	0.118
Day 8			
LS Means, 95% CI	-0.2, -0.3 to -0.1	-0.4, -0.5 to -0.3	-0.6, -0.7 to -0.4
Risperidone ISM v Placebo:			
LS Means Difference, 95% CI		-0.2, -0.4 to -0.1	-0.3, -0.5 to -0.2
P-value		0.004	<0.0001
Day 15			
LS Means, 95% CI	-0.4, -0.5 to -0.2	-0.8, -1.0 to -0.7	-0.8, -0.9 to -0.7

Time point Statistic	**Placebo** N=132	**Risperidone ISM 75 mg** N=129	**Risperidone ISM 100 mg** N=129
Risperidone ISM v Placebo:			
LS Means Difference, 95% CI		-0.5, -0.6 to -0.3	-0.5, -0.6 to -0.3
P-value		<0.0001	<0.0001

CGI-S: Clinical Global Impression – Severity of illness; CHW=Cui, Hung, Wang (1999); CI: confidence interval; ISM: in situ microparticles; ITT: intent-to-treat; LH: Lawrence and Hung (2003); LS: Least Squares; mITT: modified ITT; N: Number of patients; SE: standard error.
[1] CHW and LH methods combine results from stage 1 and stage 2
[2] Hommel adjustment of CHW p-values. These are the p-values of the study used to assess confirmatory superiority of each Risperidone ISM dose over Placebo if p < 0.05 and if both doses were superior to Placebo in the primary analysis of the study for both the mITT and ITT population
Notes: Presented statistics are based on all patients in the mITT population and the randomised treatment.

Change from baseline increased at each time point in all treatment groups.

CGI-I

The change from baseline between placebo and both Risperidone ISM groups in mITT population was significant. Mean change from baseline in CGI-I score at each postbaseline assessment time point was a secondary efficacy variable and was significant compared to placebo from Day 8 onwards for both Risperidone ISM groups.

Change from Baseline in PANSS Subscale Score

The mean **PANSS positive subscale score** at baseline was 25.3 for the placebo group, 25.1 for the Risperidone ISM 75 mg group, and 25.5 for the Risperidone ISM 100 mg group. The change from baseline increased at each time point in all treatment groups. At Day 8, the LS means difference from placebo was -1.0 (95% CI: -1.9, -0.1) for the Risperidone ISM 75 mg group, and -1.8 (95% CI: -2.7, -0.9) for the Risperidone ISM 100 mg group.

The difference from the placebo group increased at each time point for both Risperidone ISM groups. At Day 85, the difference from placebo was -3.9 (95% CI: -5.3, -2.5) for the Risperidone ISM 75 mg group, and -4.6 (95% CI: -6.0, -3.2) for the Risperidone ISM 100 mg group. The data were similar for the two Risperidone ISM groups.

The mean **PANSS negative subscale score** at baseline was 23.5 for the placebo group, 23.3 for the Risperidone ISM 75 mg group, and 23.1 for the Risperidone ISM 100 mg group. The change from baseline increased at each time point in all treatment groups. At Day 15, the LS means difference from placebo was -0.9 (95% CI: -1.6, -0.2) for the Risperidone ISM 75 mg group, and -0.9 (95% CI: -1.7, -0.2) for the Risperidone ISM 100 mg group.

The difference from the placebo group increased at each time point for both Risperidone ISM groups. At Day 85, the difference from placebo was -2.1 (95% CI: -3.1, -1.0) for the Risperidone ISM 75 mg group, and -2.0 (95% CI: -3.1, -0.9) for the Risperidone ISM 100 mg group. The data were similar for the two Risperidone ISM groups.

The mean **PANSS general psychopathology subscale score** at baseline was 47.7 for the placebo group, 47.8 for the Risperidone ISM 75 mg group, and 47.4 for the Risperidone ISM 100 mg group. The change from baseline increased at each time point in all treatment groups. At Day 15 the LS means difference from placebo was -3.0 (95% CI: -4.8, -1.3) for the Risperidone ISM 75 mg group, and -3.7

(95% CI: -5.4, -2.0) for the Risperidone ISM 100 mg group. The difference from the placebo group increased at each time point for both Risperidone ISM groups. At Day 85, the LS means difference from placebo was -7.3 (95% CI: -9.5, -5.0) for the Risperidone ISM 75 mg group, and -6.8 (95% CI: -9.1, -4.6) for the Risperidone ISM 100 mg group. The results were similar for the two Risperidone ISM groups.

The OLE phase

The main study (ROV-RISP-2016-01 [PRISMA-3]) included an optional, OLE phase after completion of the DB phase, to assess durability of the effect of Risperidone ISM. The OLE phase was not powered to determine statistical significance and no formal statistical testing was performed. Descriptive results of the efficacy endpoints are summarised by treatment group and overall.

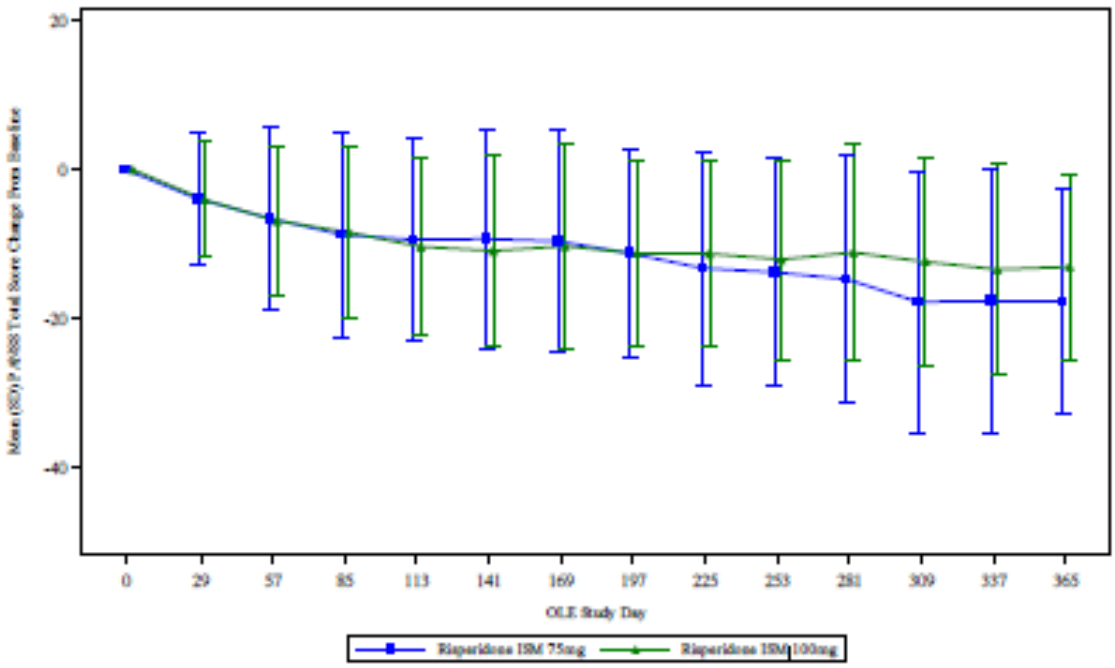
One hundred seventy-four patients (39.7%) who participated in the DB phase signed informed consent for participation in the OLE phase of the study. An additional 41 de novo patients were assigned to treatment. The OL population consisted of 215 patients who received at least 1 dose of Risperidone ISM in the OLE phase of the study.

After at least 365 days of treatment in the OLE phase, **early treatment discontinuation** was reported for 24.6% of patients in the OL population, 22.6% of patients in the Risperidone ISM 75 mg group and 26.9% of patients in the Risperidone ISM 100 mg group.

The **mean PANSS score at baseline** was 71.3 for the entire OL population; 70.7 for the Risperidone ISM 75 mg group (N=116), and 72.0 for the Risperidone ISM 100 mg group (N=99).

Decreases in the PANSS total score indicative of improvement were recorded for the overall OL population and all subgroups. The mean change from baseline to endpoint (the last postbaseline OLE assessment), in the PANSS total score was -10.7 for the OL population (N=209), -10.3 for the Risperidone ISM 75 mg group and -11.1 for the Risperidone ISM 100 mg group (Figure 19).

Figure 19: Mean (SD) Profile of PANSS Total Score Change From Baseline in Open-Label Extension Phase by Open-Label Extension Treatment (Open-Label Population)



ISM: *in situ* microparticles; OLE: open-label extension; PANSS: Positive and Negative Syndrome Scale; SD: standard deviation.

OLE: open-label extension; PANSS: Positive and Negative Syndrome Scale; SD: standard deviation.

As could be expected, placebo patients who entered the OLE phase showed the most pronounced change from baseline in the PANSS total score.

PANSS response, defined as a decrease of at least 30% from baseline in the PANSS total score, was reported at the endpoint in the OLE phase for 32 (14.9%) patients. This included 22 (19.0%) patients in the Risperidone ISM 75 mg group and 10 (10.1%) patients in the Risperidone ISM 100 mg group.

The **mean CGI-S score** at baseline was 3.5 for the OL population, 3.4 for the Risperidone ISM 75 mg group and 3.5 for the Risperidone ISM 100 mg group. The mean change from baseline to endpoint was -0.5 for the OL population, -0.6 for the Risperidone ISM 75 mg group and -0.5 for the Risperidone ISM 100 mg group. The mean CGI-I score at the endpoint during the OLE phase was 3.0 for the OL population, 3.1 for the Risperidone ISM 75 mg group and 2.8 for the Risperidone ISM 100 mg group.

Overall response, defined as either a ≥30% decrease (improvement of symptoms) from baseline in the PANSS total score or a CGI-I score of 2 (much improved) or 1 (very much improved), was reported at the endpoint in the OLE phase for 90 (41.9%) patients. This included 43 (37.1%) responders in the Risperidone ISM 75 mg group and 47 (47.5%) responders in the Risperidone ISM 100 mg group.

Relapse, defined as either a ≥30% increase from baseline in PANSS total score, rehospitalisation for psychotic symptoms or use of adjunctive antipsychotic medication after stabilisation, was recorded for 20 (9.3%) patients during the OLE phase. This included 12 (10.3%) patients in the Risperidone ISM 75 mg group and 8 (8.1%) patients in the Risperidone ISM 100 mg group.

Remittance, defined as the simultaneous attainment of a score of ≤3 for 6 months or more on 8 main items of the PANSS, was achieved after at least 365 days of treatment in the OLE phase, in 61.9% of the

OL population, 61.2% for the Risperidone ISM 75 mg group, and 62.4% for the Risperidone ISM 100 mg group.

Summary of main efficacy results

A tabulated summary of the most relevant information to describe the efficacy data generated in the main trial(s) is presented below.

Table 15

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)**			
Study id	ROV-RISP-2016-01		
Design	This was a multicentre, randomised, double-blind (DB) study designed to evaluate the efficacy and safety of Risperidone ISM, a new long-acting injectable form of the licensed drug risperidone, in patients with schizophrenia experiencing an acute exacerbation.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 weeks 1 to 8 days 12 months, followed by a 4-week follow-up period.
Hypothesis	To evaluate the efficacy and safety of Risperidone ISM compared to that of placebo in the treatment of patients with schizophrenia. Superiority of active treatment versus placebo was examined.		
Treatments groups	Treatment 1		75 mg Risperidone ISM IM every 4 weeks (study days 1, 29, and 57) Entered/completed: 145/144
	Treatment 2		100 mg Risperidone ISM IM every 4 weeks (study days 1, 29, and 57) Entered/completed: 146/146
	Treatment 3		Placebo IM every 4 weeks (study days 1, 29, and 57) Entered/completed: 146/146
Endpoints and definitions	Primary endpoint	PANSS total score mean change from baseline to endpoint	Primary endpoint was defined as study Day 85 or the last post-baseline DB assessment.
	Key Secondary endpoint	CGI-S score mean change from baseline	CGI-S score mean change at endpoint
	Secondary Endpoints	CGI-I score mean	CGI-I score mean at endpoint

		Overall response rate	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 total score ⩾ 30% decrease (improvement of symptoms) from baseline at endpoint
		Time to reach PANSS response	
Database lock	8 March 2019		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	The modified intent-to-treat (mITT) population consists of all patients in the ITT population for whom blinding was not compromised Day 85			
Descriptive statistics and estimate variability	Treatment group	**Risperidone ISM 75 mg**	**Risperidone 100 mg**	**Placebo**
	Number of subj	129	129	132
	PANSS LS mean	-24.6	-24.7	-11
	95% CI	-27.5 to 21.6	-27.7 to 21.6	-14.1 to -8.0
	CGI-S LS mean	-1.3	-1.3	-0.6
	95% CI	-1.5 to -1.2	-1.5 to -1.2	-0.8 to -0.4
	PANSS response rate Responders, n (%)	49 (38)	40 (31)	11 (8.3)
	95% CI (%)	29.6 to 46.9	23.2 to 39.7	4.2 to 14.4

Effect estimate per comparison	**Primary endpoint** (PANSS) LS means diff	**Risperidone ISM 75 mg vs Placebo**	**Risperidone ISM 100 mg vs Placebo**
	95% CI	-13.6	-13.6
		-17.8 to -9.3	-17.9 to -9.3
		P<0.0001	P<0.0001
	Key Secondary endpoint (CGI-S)		
	LS means diff	-0.7	-0.7
	95% CI	-1 to 0.5	-1 to 0.5
		P<0.0001	P<0.0001
	PANSS response rate		
	Responders, %	29.7	22.7
	95% CI	19.6 to 38.9	13.0 to 31.6
		P<0.0001	P<0.0001
Notes			
Analysis description	**Primary Analysis**		

Analysis population and time point description	Modified SAF, ITT, and PP populations were analysed because of a potential unblinding incident. The planned total number of randomised patients in the DB segment of the study was approximately 436 (approximately 145 in each of the 3 treatment groups). Due to a potential accidental unblinding quality issue, 43 patients were potentially compromised and therefore removed; the sample size was subsequently increased from 393 to 436 to compensate for this. Approximately 100 de novo patients were planned to be enrolled in the extension segment of the study, in addition to rollover patients. The number of patients in each analysis population is summarised below:			
Descriptive statistics and estimate variability	Treatment group	Risperidone ISM 75 mg	Risperidone ISM 100 mg	Placebo
	Number of subjects	145	146	147

2.4.3.3. Supportive study - Study ROV-RISP-2011-02 (PRISMA-2)

This was a multicentre, open label, two-arm, parallel design, repeat-dose Phase 2 clinical trial with an exploratory objective of evaluating the PK and efficacy of once every four weeks of the injectable formulation Risperidone ISM after four IM injections in the gluteal muscle or deltoid muscle at 28-day (±1 day) intervals at one dose strength (75 mg) in patients with schizophrenia. The mean efficacy parameters (PANSS and CGI-S) did not change from baseline values with mean CGI-I values of 3 (minimal improvement) by Visit 48, indicating a continuation of psychiatric stability. There was no apparent difference in efficacy parameters between the two injection site groups.

2.4.3.4. Clinical studies in special populations

None.

2.4.3.5. Analysis performed across trials (pooled analyses and meta-analysis)

The clinical efficacy development plan of Risperidone ISM is limited to one Phase 3 study.

2.4.3.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The CHMP guideline for medicinal products including depot preparations in the treatment of schizophrenia (EMA/CHMP/40072/2010 Rev. 1), states that "*depot preparations are meant for maintenance treatment once a patient is stabilised satisfactorily on oral preparation"* and "*it would be very rare to start a patient on a depot preparation, as e.g. dose titration is not possible, an acute effect may be needed or undesirable effects may occur, in which case the preparation cannot be withdrawn"*. Furthermore, "*non-inferiority of a new depot formulation needs to be demonstrated vs. the oral formulation, or another antipsychotic LAI product can be considered"*. "*Clinical studies to compare efficacy of the oral depot preparation are deemed necessary unless a clear pharmacokinetic/pharmacodynamic relationship is demonstrated for the oral formulation." It is also stated that, "If the efficacy and safety of the compound are known and it is not necessary to show this in itself for the depot formulation, provided no new claims are made. However, it is of importance to know whether the new formulation affects efficacy or safety in comparison to the oral formulation."*

In the scientific advice (EMA/CHMP/SAWP/ 270310/2016), the applicant's proposal for the study design was not supported. "*In conclusion, the CHMP consider that the differences in PK, the expected differences in TEAEs and the intention to show the new claim of treatment of acutely exacerbated schizophrenia patients the Applicant should follow the CHMP guideline for medicinal products including depot preparations in the treatment of schizophrenia (EMA/CHMP/40072/2010 Rev. 1) and the different proposals of clinical development programme including comparator arm such as risperidone.*"

It is noted that neither the CHMP guideline nor the recommendations in the advice were fully followed by the applicant. From an efficacy perspective, the initial main concerns were lack of ability to titrate the dose, to switch to another antipsychotic, and the lack of a direct comparison to the reference product.

This hybrid marketing authorisation application is based on the reference product of oral risperidone and an established clinical effect. The PRISMA 3 study lacks active comparator which is a limitation.

Efficacy data and additional analyses

In the phase 3 study (PRISMA 3) 438 patients were randomised to receive 3 doses of IM Risperidone ISM (75 mg or 100 mg) or placebo every 28 days. No supplemental oral risperidone was permitted during the study. The rates of discontinuations do not raise concern. Due to an error in the IWRS, 43 patients were potentially unblinded and thereby excluded and the total sample size was increased accordingly. Of the 43 potentially affected patients 13 had been assigned to placebo, 14 to Risperidone ISM 75mg and 16 to Risperidone ISM 100mg. Although the number of potentially affected patients is numerically higher in the higher dose group, there is no obvious association between assigned dose and potential unblinding, and the exclusion of the 43 patients is not considered likely to have introduced any bias. The statistical methodology used in the study is in general considered appropriate.

The primary endpoint in the PRISMA 3 study was the change in PANSS total score from baseline to end of study (Day 85). Both Risperidone ISM 75 and 100 mg doses demonstrated a gradually increasing and mean difference over time compared with placebo, with no notable differences between the doses. In the key secondary efficacy endpoint mean change of the CGI-S score from baseline to Day 85 both Risperidone ISM treatment groups demonstrated better CGI-S scores versus placebo from Day 8 onwards. Mean changes from baseline in efficacy rating scales were generally limited. Comparable CGI-S changes have been reported in similar populations in the literature.

Risperidone ISM achieves therapeutic levels from the first hours after drug administration and provides a sustained release following multiple IM injections. Risperidone ISM 100 mg is near to being bioequivalent to 4 mg PO US Risperdal at steady state based on exclusion of non-compliant subjects (see clinical pharmacology sections). No relationship between the active moiety concentrations and the PANSS measurements was evident and some uncertainties were identified regarding Pop PK/PD model (see clinical pharmacology sections).

The study included patients with a current diagnosis of schizophrenia and an acute exacerbation or relapse, who had a PANSS score at the baseline period between 80 and 120. At the screening visit, all risperidone-naïve patients received 2 mg/day oral risperidone for 3 days to ensure a lack of any clinically significant hypersensitivity reactions before the trial. Patients with previous history of being treated with risperidone did not receive oral risperidone at the screening and started directly with Risperidone ISM (75 mg or 100 mg) or placebo after randomisation.

Maintenance of effect of Risperidone ISM in previously stabilised patients has not been studied, except for in the open label prolongation phase of the main study and to some extent in study PRISMA 2. Support for maintenance is therefore based on extrapolation of efficacy and safety from the reference product. The CHMP scientific advice that concluded that "*considering the differences in pharmacokinetic profile for this new formulation compared with previously established formulations of risperidone, safety and efficacy*

needs to be confirmed in the phase III programme for treatment of acute exacerbation as well as for maintenance treatment". It is agreed that steady state active moiety concentrations over 20 ng/ml are likely at the plateau of the exposure-response relation and it is unlikely that small differences in PK would meaningfully impact the clinical response. The results of the OLE part of the PRISMA-3 study indicated a continued therapeutic effect of Risperidone ISM over a period of more than 1 year.

Patients who have not previously been exposed to risperidone may not respond to, or may not tolerate, this substance. There may be genetic differences of metabolism, individual differences in responsiveness and tolerability, individual preferences, as well as other reasons why treatment is not tolerated. Efficacy endpoints in the main study, including the primary endpoint, aimed to demonstrate effect at Day 85. It was noted that clinically relevant effect may not be reached during the first 3 weeks. There is similar to the oral reference product.

Patients with an acute exacerbation may require titration of an oral or parenteral immediate-release antipsychotic, as well as concomitant treatment with other drugs. Treatment with modified-release risperidone with 4 weeks duration will diminish the flexibility to provide other treatments if required.

Efficacy was not assessed earlier than Day 4 and no subgroup analysis on risperidone-naïve patients was provided. Data on efficacy variables during the first 3 weeks is either probably not clinically relevant or not available due to limited numbers of time points for assessment. Full effect of oral risperidone is not received until after a few weeks of treatment. However, supplemental doses are not going to be administered during Risperidone ISM treatment, which is an issue. Based on pop PK simulations, active moiety exposure upon administration of 100 mg Risperidone ISM from 3 hours onwards is higher than the C_{trough} of oral risperidone. Furthermore, 65% receptor occupancy is achieved after ca 4.5 hours following the administration of 100 mg Risperidone ISM and within 1-2 hours for both 3 and 4 mg oral risperidone. The provided simulations showed that the initial active moiety exposure and receptor occupancy are in the same range for oral risperidone 4 mg and Risperidone ISM 100 mg, supporting bridging of the acute indication from a PK standpoint (based on exclusion of non-compliant subjects).

There is a dip in blood plasma concentrations of active moiety around Day 14 after each administration of Risperidone ISM. This is not accompanied by a corresponding dip in median PANSS total Score or CGI. Median C_{ave} for the active moiety is approximately 7 ng/mL following 4 mg of oral risperidone, and for individuals with C_{pl} below this concentration there is a risk of sub-optimal treatment effect. The plasma concentrations are also low at the end of the dosing interval. The applicant provided detailed analyses revealing that the observed dips in plasma concentrations has not contributed to a potential lack of efficacy. No relevant increase in PANSS has been observed in relation to plasma concentration dips.

The efficacy appeared to be similar irrespective of site of administration. However, the dose-normalised AUC_{tau} was slightly higher for injections given at the gluteal site compared with deltoid.

Additional expert consultation

None

Assessment of paediatric data on clinical efficacy

Not applicable.

2.4.3.7. Conclusion on clinical efficacy

This hybrid marketing authorisation application is based on a bridge to an oral risperidone reference product which has an established clinical effect. The main basis for assessment of efficacy (and safety) is therefore based on bridging from oral risperidone. In addition, one phase 3 placebo-controlled study has

been performed comparing Risperidone ISM to placebo. The main contribution from this study would be the specific impact on efficacy (and safety) from the specific modified-release formulation and related consequences for treatment strategy.

The lack of an adequate active control in the phase 3 study complicates the interpretation of the results with regards to both acute and maintenance treatment.

The indication initially proposed by the applicant was:

- *for the treatment of schizophrenia in adults.*
- *for the treatment of schizophrenia in adult patients with acute exacerbation where psychotic symptoms are moderate to severe.*
- *for the treatment of schizophrenia in adult patients previously stabilised with antipsychotics.*

Initiating treatment with a long-acting risperidone product in patients where efficacy of and tolerability for risperidone has not been justified by the data provided. Appropriate recommendations for a run-in period on immediate-release risperidone of at least 6 days for risperidone-experienced patients and at least 14 days for risperidone-naïve patients have therefore been introduced in the SmPC. In patients stabilised on other oral antipsychotics (different from risperidone) stabilisation and tolerance with oral risperidone should be confirmed before initiating treatment with RISPERIDONE ISM.

Regarding "*Patients never treated before with oral Risperidone"* the applicant's proposal is partially supported. The provided justification for the proposed 14 days period with respect to the demonstration of efficacy is acknowledged. However, to ensure satisfactory tolerability and safety, longer period of treatment may be requited. Therefore, the SmPC now states that a minimum period of 14 days is required, but that the period should be sufficiently long to confirm the tolerability and responsiveness to risperidone.

The subpopulation referred to in section 4.2 of the SmPC as "*Patients with history of previous response to Risperidone who are not currently stabilised with oral antipsychotics (moderate to severe psychotic symptoms)"* are patients with acute symptoms ("*not currently stabilised")* and this indication was not endorsed. Therefore, patients who are not stabilised should not be included in section 4.2 of the SmPC.

The following wording of the indication was finally agreed:

> *Okedi is indicated for the treatment of schizophrenia in adults for whom tolerability and effectiveness has been established with oral risperidone.*

2.4.4. Clinical safety

This hybrid marketing authorisation application is based on oral risperidone as reference product and the established safety profile of oral and LAI risperidone formulations. The adverse event profile of oral risperidone is well established. The European Union reference date (EURD) is 01/06/1993. In the PSUSA 2017 the post-marketing exposure is estimated at over 52 million patient-years cumulatively for risperidone.

2.4.4.1. Patient exposure

Overall, 579 patients were exposed to Risperidone ISM in the initially submitted application. 185 patients received at least 6 doses of Risperidone ISM (6 months treatment). 118 patients received at least 12 doses (12 months treatment).

- In the healthy volunteer study (**Study ROV-RISP-2009-01**), 17 subjects were administered either 25 mg (9 subjects) or 37.5 mg (8 subjects) Risperidone ISM as a single dose.

- In Study ROV-RISP-2011-01 (**PRISMA-1**), 36 subjects received a single IM injection of Risperidone ISM (13 subjects in the 50 mg group, 12 subjects in the 75 mg group, and 11 subjects in the 100 mg group).
- Eighty-one subjects in Study ROV-RISP-2016-02 (**BORIS**) received 4 mg oral risperidone for 7 days and of those subjects, 73 received 100 mg Risperidone ISM every 4 weeks from Days 8 to 92.
- In Study ROV-RISP-2011-02 (**PRISMA-2**), 67 subjects received multiple (4-weekly) doses of 75 mg Risperidone ISM.
- In the DB and OL phases of Study ROV-RISP-2016-01 (**PRISMA-3**), 202 subjects received 75 mg (n=144) and 184 received 100 mg (n=146) Risperidone ISM, or placebo (n=147). Of the 386 subjects treated, 111 subjects received at least 13 doses of Risperidone ISM during the DB and OLE phases, including 40 patients (10.4%) who received 13 doses, 7 patients (1.8%) who received 14 doses, 4 patients (1.0%) who received 15 doses, and 60 patients (15.5%) who received 16 doses of Risperidone ISM.

Seventy subjects (32.6%) of the 215 subjects in the OL population completed the OLE phase of Study ROV-RISP-2016-01 (PRISMA-3), and 93 subjects (43.3%) were ongoing in the OLE phase as of the 30 May 2019 data cut-off. Among the 52 subjects (24.2%) who did not complete the OLE phase, the most commonly reported primary reasons for discontinuation were withdrawal of consent (25 subjects; 11.6%), a TEAE (7 subjects; 3.3%), and hospitalisation for worsening, relapse, or exacerbation of schizophrenia symptoms (6 subjects; 2.8%).

Table 16: Multiple Dose Studies: Summary of Subject Disposition

	Number (%) of subjects						
	ROV-RISP-2016-02 (BORIS)	ROV-RISP-2011-02 (PRISMA-2)			ROV-RISP-2016-01 (PRISMA-3) DB phase		
	Total	Deltoid 75 mg	Gluteal 75 mg	Overall	75 mg	100 mg	Placebo
	N=104			N=93	N=145	N=146	N=147
Randomized	81	35	35	70	145	146	147
Not Treated	23 (22.1)	2 (5.7)	1 (2.9)	3 (4.3)	1 (0.69)	-	-
Treated	81 (77.9)	33 (94.3)	34 (97.1)	67 (95.7)	144 (99.3)	146 (100)	147 (100)
Completed	58 (55.8)	19 (54.3)	17 (48.6)	36 (51.4)	107 (73.8)	95 (65.1)	88 (59.9)
Reasons for discontinuation from treatment							

	Number (%) of subjects						
	ROV-RISP-2016-02 (BORIS)	ROV-RISP-2011-02 (PRISMA-2)			ROV-RISP-2016-01 (PRISMA-3) DB phase		
	Total	Deltoid 75 mg	Gluteal 75 mg	Overall	75 mg	100 mg	Placebo
	N=104			N=93	N=145	N=146	N=147
Adverse event	5 (6.2)	2 (5.7)	2 (5.7)	4 (5.7)	5 (3.4)	5 (3.4)	3 (2.0)
Positive pregnancy or urine drug screen test result	-	-	-	-	-	2 (1.4)	3 (2.0)
Lost to follow-up	3 (3.7)	3 (8.6)	5 (14.3)	8 (11.4)	6 (4.1)	5 (3.4)	6 (4.1)
Consent withdrawn	14 (17.3)	3 (8.6)	3 (8.6)	6 (8.6)	14 (9.7)	23 (15.8)	20 (13.6)
Investigator decision	-	-	-	-	-	-	1 (0.7)
Sponsor decision	1 (1.2)	-	-	-	-	-	-
Death	-	1 (2.9)	-	1 (1.4)	-	-	-
Non-compliance	-	-	-	-	-	1 (0.7)	1 (0.7)
Hospitalization for worsening, relapse, or exacerbation of schizophrenia symptoms	-	-	-	-	-	2 (1.4)	3 (2.0)
Insufficient clinical response	-	-	-	-	6 (4.1)	9 (6.2)	15 (10.2)
Other	-	7 (20.0)	8 (22.8)	15 (21.4)	6 (4.1)	4 (2.7)	7 (4.8)

2.4.4.2. Adverse events

The adverse events observed were in line with the established safety profile for oral risperidone and Risperdal Consta. Sixty-seven percent of the TEAEs were mild and only 5 subjects (2.3%) in the OL population reported a severe TEAE.

Subjects in Study ROV-RISP-2011-02 (PRISMA-2) (dosed with 75 mg) experienced a higher number of both TEAEs and related TEAEs (88%) compared to both ROV-RISP-2016-02 (BORIS) (dosed with 100 mg [57%]) and ROV-RISP-2016-01 (PRISMA-3) (dosed with either 75 mg [42%] and 100 mg [53%]).

Safety results for the 3 multiple dose studies have not been pooled as Study ROV-RISP-2016-01 (PRISMA-3) is the only study in subjects with acute relapse (PANSS score between ≥80 and ≤120, and a CGI score of ≥4) compared to subjects who were medically stable in Studies ROV-RISP-2016-02 (BORIS) and ROV-RISP-2011-02 (PRISMA-2) (PANSS <70 and CGI score of <4), and due to differences in study designs.

Table 17: Multiple Dose Studies: Analysis of TEAEs Reported

	Number (%) of Subjects [Number of TEAEs]					
	ROV-RISP-2016-02 (BORIS)	ROV-RISP-2011-02 (PRISMA-2)		ROV-RISP-2016-01 (PRISMA-3) DB Phase		
	100 mg	Gluteal 75 mg	Deltoid 75 mg	75 mg	100 mg	Placebo
	N=73	N=34	N=33	N=144	N=146	N=147
Subjects with TEAEs	39 (53.4)	32 (94.1)	31 (93.9)	80 (55.6)	94 (64.4)	65 (44.2)
Number of TEAEs	77	214	185	192	225	128
Subjects with Related TEAEs	34 (46.6) [49]	30 (88.2) [119]	29 (87.9) [125]	60 (41.7) [100]	77 (52.7) [130]	32 (21.8) [47]
Subjects with Serious TEAEs	2 (2.7) [4]	5 (14.7)[a]	7 (21.2)[a]	2 (1.4) [2]	5 (3.4) [6]	5 (3.4) [6]
Deaths	0	0	1	0	0	0
Subjects Discontinued Due to TEAEs	3 (4.1) [4]	2 (5.9)[a]	2 (6.1)[a]	6 (4.2)	9 (6.2)	11 (7.5)
Severity (All TEAEs)						
Mild	32 (43.8) [56]	32 (94.1) [192]	30 (90.9) [146]	56 (38.9) [149]	60 (41.1) [175]	46 (31.3) [101]
Moderate	12 (16.4) [18]	12 (35.3) [18]	16 (48.5) [34]	23 (16.0) [42]	30 (20.5) [46]	14 (9.5) [21]
Severe	3 (4.1) [3]	3 (8.8) [4]	4 (12.1) [5]	1 (0.7) [1]	4 (2.7) [4]	5 (3.4) [6]
Severity (related to study treatment)						
Mild	28 (38.4) [39]	28 (82.4) [108]	28 (84.8) [105]	44 (30.6) [77]	53 (36.3) [98]	25 (17.0) [40]
Moderate	8 (11.0) [9]	5 (14.7) [8]	9 (27.3) [19]	16 (11.1) [23]	21 (14.4) [29]	6 (4.1) [6]
Severe	1 (1.4) [1]	2 (5.9) [3]	1 (3.0) [1]	-	3 (2.1) [3]	1 (0.7) [1]

DB: Double-Blind; N: number of subjects in each treatment group; TEAE: treatment-emergent adverse event

[a] Number of TEAEs are not available.

During the OLE phase of the Study ROV-RISP-2016-01 (PRISMA-3; data cut-off 30 May 2019), at least 1 TEAE was reported for 134 subjects (62.3%) in the OL population. The majority (67.2%; 213/317) of the TEAEs were mild and only 5 subjects (2.3%) in the OL population reported a severe TEAE.

A low number of patients were exposed for at least 12 months to Risperidone ISM in the clinical trial programme. The applicant provided updated data over the course of the assessment from OLE period of study PRISMA-3 and discussed satisfactorily the findings in relation to the known safety profile for risperidone.

Table 18 Multiple Dose Studies: All TEAEs Occurring at ≥5% by SOC and PT

	Number (%) of Subjects [Number of TEAEs]						
	ROV-RISP-2016-02 (BORIS) (Medically Stable PANSS <70)		ROV-RISP-2011-02 (PRISMA-2) (Medically Stable PANSS ≤70)		ROV-RISP-2016-01 (PRISMA-3) – DB Phase Acute relapse (PANSS ≥80-≤120)		
	Oral 4 mg N=81	ISM 100 mg N=73	Gluteal 75 mg N=34	Deltoid 75 mg N=33	Placebo N=147	75 mg N=144	100 mg N=146
MedDRA System Organ Class/ Preferred Term	**N=81**	**N=73**	**(N = 34)**	**(N = 33)**	**N=147**	**N=144**	**N=146**
All TEAE	**31 (38.3) [42]**	**39 (53.4) [77]**	**32 (94.1) [214]**	**31 (93.9) [185]**	**65 (44.2) [128]**	**80 (55.6) [192]**	**94 (64.4) [225]**
Cardiac disorders	**0**	**0**	**1 (2.9) [1]**	**2 (6.1) [4]**	**0**	**3 (2.1) [3]**	**6 (4.1) [6]**
Tachycardia	0	0	0	2 (6.1) [3]	0	2 (1.4) [2]	4 (2.7) [4]
Endocrine disorders	**10 (12.3) [10]**	**5 (6.8) [5]**	**19 (55.9) [55]**	**17 (51.5) [41]**	**1 (0.7) [1]**	**8 (5.6) [8]**	**13 (8.9) [13]**
Hyperprolactinaemia	10 (12.3) [10]	5 (6.8) [5]	19 (55.9) [55]	17 (51.5) [41]	1 (0.7) [1]	8 (5.6) [8]	13 (8.9) [13]
Eye disorders	**0**	**0**	**6 (17.6) [6]**	**1 (3.0) [1]**	**1 (0.7) [1]**	**1 (0.7) [1]**	**2 (1.4) [3]**
Cataract	0	0	2 (5.9) [2]	0	0	0	0
Cataract cortical	0	0	0	0	0	0	1 (0.7) [1]
Gastrointestinal disorders	**4 (4.9) [6]**	**4 (5.5) [7]**	**6 (17.6) [12]**	**4 (12.1) [9]**	**15 (10.2) [18]**	**17 (11.8) [18]**	**10 (6.8) [12]**
Abdominal discomfort	0	0	2 (5.9) [3]	0	2 (1.4) [2]	2 (1.4) [2]	1 (0.7) [1]
Dry mouth	1 (1.2) [1]	2 (2.7) [2]	0	2 (6.1) [3]	3 (2.0) [3]	1 (0.7) [1]	1 (0.7) [1]
Vomiting	1 (1.2) [1]	0	2 (5.9) [2]	0	2 (1.4) [2]	2 (1.4) [2]	1 (0.7) [1]
General disorders and administration site conditions	0	0	**18 (52.9) [56]**	**13 (39.4) [41]**	**9 (6.1) [12]**	**14 (9.7) [17]**	**8 (5.5) [10]**
Chest pain	0	0	2 (5.9) [2]	1 (3.0) [1]	0	0	0
Fatigue	0	0	1 (2.9) [1]	2 (6.1) [2]	0	0	1 (0.7) [2]
Injection site erythema	0	0	7 (20.6) [12]	3 (9.1) [6]	2 (1.4) [2]	1 (0.7) [1]	0

	Number (%) of Subjects [Number of TEAEs]						
	ROV-RISP-2016-02 (BORIS) (Medically Stable PANSS <70)		ROV-RISP-2011-02 (PRISMA-2) (Medically Stable PANSS ≤70)		ROV-RISP-2016-01 (PRISMA-3) – DB Phase Acute relapse (PANSS ≥80-≤120)		
	Oral 4 mg N=81	ISM 100 mg N=73	Gluteal 75 mg N=34	Deltoid 75 mg N=33	Placebo N=147	75 mg N=144	100 mg N=146
MedDRA System Organ Class/ Preferred Term	**N=81**	**N=73**	**(N = 34)**	**(N = 33)**	**N=147**	**N=144**	**N=146**
Injection site induration	0	0	1 (2.9) [2]	4 (12.1) [4]	0	0	0
Injection site pain	0	0	12 (35.3) [31]	10 (30.3) [25]	5 (3.4) [7]	8 (5.6) [10]	4 (2.7) [5]
Injection site warmth	0	0	2 (5.9) [2]	1 (3.0) [1]	0	0	0
Pain	0	0	3 (8.8) [4]	1 (3.0) [1]	0	0	0
Infections and infestations	**2 (2.5) [2]**	**4 (5.5) [4]**	**7 (20.6) [8]**	**5 (15.2) [5]**	**7 (4.8) [8]**	**10 (6.9) [10]**	**15 (10.3) [21]**
Nasopharyngitis	0	0	2 (5.9) [2]	1 (3.0) [1]	0	5 (3.5) [5]	4 (2.7) [4]
Upper respiratory tract infection	1 (1.2) [1]	4 (5.5) [4]	1 (2.9) [2]	0	1 (0.7) [1]	1 (0.7) [1]	2 (1.4) [2]
Injury, poisoning and procedural complications	**0**	**4 (5.5) [4]**	**4 (11.8) [5]**	**5 (15.2) [7]**	**3 (2.0) [4]**	**3 (2.1) [3]**	**4 (2.7) [5]**
Excoriation	0	0	1 (2.9) [1]	2 (6.1) [2]	0	0	0
Scratch	0	0	0	2 (6.1) [2]	0	0	0
Investigations	**0**	**16 (21.9) [20]**	**1 (2.9) [1]**	**4 (12.1) [9]**	**10 (6.8) [16]**	**28 (19.4) [45]**	**39 (26.7) [57]**
Blood prolactin increased	0	0	0	0	0	13 (9.0) [15]	21 (14.4) [22]
Electrocardiogram QT prolonged	0	0	0	2 (6.1) [3]	0	0	0
Heart rate increased	0	0	1 (2.9) [1]	2 (6.1) [2]	0	1 (0.7) [1]	0
Weight increased	0	15 (20.5) [15]	0	1 (3.0) [1]	3 (2.0) [3]	10 (6.9) [10]	8 (5.5) [8]

	Number (%) of Subjects [Number of TEAEs]						
	ROV-RISP-2016-02 (BORIS) (Medically Stable PANSS <70)		ROV-RISP-2011-02 (PRISMA-2) (Medically Stable PANSS ≤70)		ROV-RISP-2016-01 (PRISMA-3) – DB Phase Acute relapse (PANSS ≥80-≤120)		
	Oral 4 mg N=81	ISM 100 mg N=73	Gluteal 75 mg N=34	Deltoid 75 mg N=33	Placebo N=147	75 mg N=144	100 mg N=146
MedDRA System Organ Class/ Preferred Term	**N=81**	**N=73**	**(N = 34)**	**(N = 33)**	**N=147**	**N=144**	**N=146**
Musculoskeletal and connective tissue disorders	**2 (2.5) [2]**	**3 (4.1) [4]**	**9 (26.5) [17]**	**7 (21.2) [7]**	**5 (3.4) [10]**	**12 (8.3) [12]**	**5 (3.4) [10]**
Arthralgia	0	0	2 (5.9) [2]	0	1 (0.7) [2]	1 (0.7) [1]	0
Musculoskeletal stiffness	0	1 (1.4) [1]	2 (5.9) [2]	2 (6.1) [2]	1 (0.7) [1]	0	0
Pain in extremity	0	1 (1.4) [1]	2 (5.9) [2]	1 (3.0) [1]	0	1 (0.7) [1]	1 (0.7) [1]
Nervous system disorders	**16 (19.8) [17]**	**16 (21.9) [18]**	**16 (47.1) [27]**	**19 (57.6) [35]**	**15 (10.2) [19]**	**33 (22.9) [40]**	**38 (26.0) [51]**
Akathisia	0	4 (5.5) [4]	0	2 (6.1) [2]	3 (2.0) [3]	6 (4.2) [6]	11 (7.5) [13]
Dizziness	0	0	4 (11.8) [4]	2 (6.1) [2]	4 (2.7) [4]	5 (3.5) [5]	6 (4.1) [6]
Drooling	0	0	0	3 (9.1) [3]	0	0	1 (0.7) [1]
Extrapyramidal disorder	0	0	2 (5.9) [3]	0	0	0	1 (0.7) [1]
Headache	2 (2.5) [2]	2 (2.7) [2]	4 (11.8) [7]	1 (3.0) [1]	5 (3.4) [6]	15 (10.4) [17]	12 (8.2) [12]
Oromandibular dystonia	0	0	2 (5.9) [2]	7 (21.2) [8]	0	1 (0.7) [1]	2 (1.4) [2]
Sedation	1 (1.2) [1]	0	6 (17.6) [7]	4 (12.1) [5]	0	1 (0.7) [1]	1 (0.7) [1]
Somnolence	14 (17.3) [14]	11 (15.1) [11]	2 (5.9) [2]	7 (21.2) [8]	4 (2.7) [4]	4 (2.8) [5]	8 (5.5) [8]
Psychiatric disorders	**0**	**0**	**8 (23.5) [10]**	**5 (15.2) [6]**	**18 (12.2) [25]**	**13 (9.0) [14]**	**13 (8.9) [19]**
Anxiety	0	0	2 (5.9) [2]	0	3 (2.0) [4]	1 (0.7) [1]	2 (1.4) [4]
Insomnia	1 (1.2) [1]	1 (1.4 [1])	2 (5.9) [3]	1 (3.0) [1]	6 (4.1) [8]	4 (2.8) [4]	6 (4.1) [8]
Schizophrenia	0	0	2 (5.9) [2]	3 (9.1) [3]	7 (4.8) [7]	3 (2.1) [3]	3 (2.1) [4]

	Number (%) of Subjects [Number of TEAEs]						
	ROV-RISP-2016-02 (BORIS) (Medically Stable PANSS <70)		ROV-RISP-2011-02 (PRISMA-2) (Medically Stable PANSS ≤70)		ROV-RISP-2016-01 (PRISMA-3) – DB Phase Acute relapse (PANSS ≥80-≤120)		
	Oral 4 mg N=81	ISM 100 mg N=73	Gluteal 75 mg N=34	Deltoid 75 mg N=33	Placebo N=147	75 mg N=144	100 mg N=146
MedDRA System Organ Class/ Preferred Term	**N=81**	**N=73**	**(N = 34)**	**(N = 33)**	**N=147**	**N=144**	**N=146**
Respiratory, thoracic and mediastinal disorders	**0**	**0**	**5 (14.7) [6]**	**2 (6.1) [3]**	**4 (2.7) [4]**	**4 (2.8) [4]**	**6 (4.1) [7]**
Cough	0	0	3 (8.8) [3]	0	1 (0.7) [1]	1 (0.7) [1]	1 (0.7) [1]
Skin and subcutaneous tissue disorders	**0**	**2 (2.7) [2]**	**4 (11.8) [5]**	**5 (15.2) [6]**	**4 (2.7) [5]**	**3 (2.1) [3]**	**1 (0.7) [1]**
Rash	0	0	2 (5.9) [2]	2 (6.1) [2]	0	1 (0.7) [1]	0
Vascular disorders	**0**	**0**	**2 (5.9) [2]**	**4 (12.1) [7]**	**1 (0.7) [1]**	**1 (0.7) [1]**	**3 (2.1) [3]**
Hypertension	0	0	0	2 (6.1) [2]	1 (0.7) [1]	0	2 (1.4) [4]
Hypotension	0	0	1 (2.9) [1]	3 (9.1) [5]	0	1 (0.7) [1]	0

DB: Double-Blind; ISM: *in situ* microparticles; MedDRA: Medical Dictionary for Regulatory Activities; N: number of subjects in each treatment group; PANSS: Positive and negative syndrome scale for schizophrenia; PT: preferred term; SOC: System Organ Class; TEAE: treatment-emergent adverse event

[a] Data for All TEAEs includes SOCs and PTs which have an incidence <5% and are therefore not included in the table.

[b] Data for SOC includes TEAEs from PTs which have an incidence <5% and are therefore not included in the table. Complete PT data are presented in Appendix

It is noted, that frequency of AE was higher during DB period in patients treated with Risperidone ISM 100 mg compared to Risperidone ISM 75 mg. The applicant presented also the number and proportion of most prevalent TEAEs in relation to numbers of administered doses and time after administration during DB period in PRISMA-3 for each study month (week 1-4, week 5-8, and week 9-12). The applicant compared early to late phase after each injection (one column with week 1-2 + week 5-6 + week 9-10. Compared with week 3-4 + week 7-8 + week 11-12).

Injection site reactions - Study ROV-RISP-2016-01 (PRISMA-3) DB phase

Redness, swelling, and induration of the injection side were evaluated by designated study site personnel after each injection; patients assessed injection site pain after each dose using a VAS. Across all 733 Risperidone ISM injections (290 at baseline, 232 at Day 29, 211 at Day 57) assessed for a reaction, 42 (17 at baseline, 13 at Day 29, 12 at Day 57) had any reaction reported. During the DB phase, the frequency of injection site reactions was low in all treatment groups. Overall, 8.0% of patients experienced any reaction of redness, swelling, or induration. In all 3 treatment groups, redness was the most frequent injection site reaction (6.2% of patients), followed by swelling (1.8%). Few patients (0.7%) only had induration. Among treatment groups, the frequency of injection site reactions ranged from 6.1% in the placebo group, to 8.3% in the Risperidone ISM 75 mg and 9.6% in the Risperidone ISM 100 mg group.

2.4.4.3. Serious adverse events and deaths

Deaths

There were 2 deaths in the 5 completed studies: one subject (Study ROV-RISP-2011-02 [PRISMA-2], 75 mg Risperidone ISM to the deltoid muscle), a 56-year old , died from a sudden cardiac arrest, approximately 10 days after the third dose of Risperidone ISM, secondary to serious TEAEs of alcohol poisoning and drug abuse (acute cocaine intoxication). The subject died the same day (Day 66). The cause of the death was due to acute cocaine and alcohol intoxication with no relationship to Risperidone ISM. The closest measure active moiety concentration to the event was 23.62 ng/mL, which are within the therapeutic range, so a correlation between an unexpected high risperidone plasma level delivery, due to the nature of the depot injection and the death can be ruled out. One subject (ROV-RISP-2016-01 [PRISMA-3, OLE]) took an intentional overdose (took approximately 60 pills of perindopril to commit suicide) and committed completed suicide (suicidal attempt, death). The event occurred 20 days after the most recent dose of investigational product (dose of 75 mg by IM injection in the left gluteus). The subject received 75 mg Risperidone ISM in the DB phase of the study. The closest measured active moiety concentration to the event was 20.30 ng/mL. This concentration was determined 20 days before the onset day of the SAE.

The two deaths in the study programme do not raise any safety concern of relevance for this application.

Other Serious Adverse Events

There were in total 26 SAEs reported from the multiple-dose studies (Table 19). The only serious TEAE occurring in more than 1 subject per treatment group was schizophrenia (placebo: 4 subjects, 2.7%; Risperidone ISM 100 mg: 2 subjects, 1.4%). Also, in the OLE phase of study ROV-RISP-2016-01 (PRISMA-3) schizophrenia (6 subjects; 2.8%) was the most commonly reported SAE. Intentional overdose, completed suicide, insomnia, suicidal ideation, and chronic obstructive pulmonary disease were reported as SAEs for 1 subject each (0.5%).

The reported other SAEs do not raise any new safety concern.

Table 19: Multiple Dose Studies: All SAEs by SOC and PT

MedDRA System Organ Class/ Serious Adverse Event	Number (%) of Subjects [Number of TEAEs]					
	ROV-RISP-2016-02 (BORIS)	ROV-RISP-2011-02 (PRISMA-2)		ROV-RISP-2016-01 (PRISMA-3) DB Phase		
	100 mg (N=73)	Gluteal 75 mg (N=34)	Deltoid 75 mg (N=33)	Placebo (N=147)	75 mg (N=144)	100 mg (N=146)
Any SAE	**2 (2.7) [4]**	**5 (14.7) [5]**	**7 (21.2) [8]**	**5 (3.4) [6]**	**2 (1.4) [2]**	**5 (3.4) [6]**
Gastrointestinal disorders	**1 (1.4) [1]**			**1 (0.7) [1]**		
Lower gastrointestinal hemorrhage				1 (0.7) [1]		
Incarcerated inguinal hernia	1 (1.4) [1]					
Infections and infestations				**1 (0.7) [1]**	**1 (0.7) [1]**	**1 (0.7) [1]**
Appendicitis					1 (0.7) [1]	
Pneumonia				1(0.7) [1]		
Skin infection						1 (0.7) [1]
Injury, poisoning and procedural complications			**1 (3.0) [1]**			**1 (0.7) [2]**
Alcohol poisoning			1 (3.0) [1]			
Fall						1 (0.7) [1]
Humerus fracture						1 (0.7) [1]
Investigations	**1 (1.4) [1]**					
Blood bilirubin increased	1 (1.4) [1]					
Metabolism and nutrition disorders	**1 (1.4) [2]**	**1 (2.9) [1]**	**1 (3.0) [1]**			
Hypokalemia	1 (1.4) [1]					
Hypomagnesemia			1 (3.0) [1]			
Hyponatremia	1 (1.4) [1]	1 (2.9) [1]				
Musculoskeletal and connective tissue disorders		**1 (2.9) [1]**				
Rhabdomyolysis		1 (2.9) [1]				
Neoplasms benign, malignant and unspecified (incl			**1 (3.0) [1]**			
Throat cancer			1 (3.0) [1]			

MedDRA System Organ Class/ Serious Adverse Event	Number (%) of Subjects [Number of TEAEs]					
	ROV-RISP-2016-02 (BORIS)	ROV-RISP-2011-02 (PRISMA-2)		ROV-RISP-2016-01 (PRISMA-3) DB Phase		
	100 mg (N=73)	Gluteal 75 mg (N=34)	Deltoid 75 mg (N=33)	Placebo (N=147)	75 mg (N=144)	100 mg (N=146)
Nervous system disorders			**1 (3.0) [1]**			
Oromandibular dystonia			1 (3.0) [1]			
Psychiatric disorders		**3 (8.8) [3]**	**4 (12.1) [4]**	**4 (2.7) [4]**	**1 (0.7) [1]**	**3 (2.1) [3]**
Agitation						1 (0.7) [1]
Anxiety		1 (2.9) [1]				
Drug abuse			1 (3.0) [1]			
Psychotic disorder		1 (2.9) [1]				
Schizophrenia			3 (9.1) [3]	4 (2.7) [4]	1 (0.7) [1]	2 (1.4) [2]
Suicidal ideation		1 (2.9) [1]				

DB: Double-Blind; MedDRA: Medical Dictionary for Regulatory Activities; N: number of subjects in each treatment group; PT: Preferred Term; SAE: serious adverse event; SOC: System Organ Class; TEAE: treatment-emergent adverse event

2.4.4.4. Laboratory findings

Hyperprolactinaemia

The SmPC for oral risperidone shows increased blood prolactin is a common (>1%-10%) adverse drug reaction and there is a footnote for hyperprolactinaemia stating that it can, in some cases, lead to gynecomastia, menstrual disturbances, amenorrhea, galactorrhoea. Hyperprolactinaemia is one of the most common TEAEs reported in clinical trials with all antipsychotics. The highest prevalence of hyperprolactinaemia and severity of hyperprolactinaemia are found in association with risperidone and amisulpride. There is evidence that the major active metabolite of risperidone, 9-hydroxyrisperidone (paliperidone), is responsible for the prolactin elevation. The rates of hyperprolactinaemia reported are often as high as 80-90% of all female subjects. When data are reported in a categorical manner, there is evidence that almost all subjects receiving oral risperidone (72-100%) and risperidone long-acting intramuscular injection (LAIM) (53-67%) have hyperprolactinaemia.

Table 20: Study ROV-RISP-2016-02 (BORIS): Treatment-Related Hyperprolactinaemia TEAEs

MedDRA System Organ Class/ Preferred Term	No. (%) of Subjects [No. of TEAEs]		
	Oral 4 mg (N=81)	ISM 100 mg (N=73)	Total (N=81)
All TEAEs	**26 (32.1) [35]**	**34 (46.6) [49]**	**46 (56.8) [84]**
Endocrine disorders	**10 (12.3) [10]**	**5 (6.8) [5]**	**15 (18.5) [15]**
Hyperprolactinemia	10 (12.3) [10]	5 (6.8) [5]	15 (18.5) [15]

ISM: *in situ* microparticles; MedDRA = Medical Dictionary for Regulatory Activities, N: number of subjects in each treatment group; TEAE: treatment-emergent adverse event

Note: A TEAE was defined as an AE that occurred or worsened after the first dose of study drug. At each level of subject summarization, a subject was counted once if the subject was reported to have 1 or more events.

AEs were coded using MedDRA Version 21.0.

Treatment A = a single oral dose of 4 mg risperidone once-daily from Days 1 to 7.

Treatment B = a single intramuscular dose of 100 mg risperidone ISM every 4 weeks from Days 8 to 92.

In Study ROV-RISP-2011-02 (**PRISMA-2**), hyperprolactinaemia was detected in 59/67 subjects (Table 21). The high incidence of events reported in this study was due to the frequency of sampling.

Table 21: Study ROV-RISP-2011-02 (PRISMA-2): Treatment-Related Hyperprolactinaemia TEAEs

MedDRA System Organ Class/ Preferred Term	No. (%) of Subjects [No. of TEAEs]		
	75 mg IM Injection Risperidone ISM in Gluteal Muscle (N=34)	75 mg IM Injection Risperidone ISM in Deltoid Muscle (N=33)	Overall (N=67)
All TEAEs	**30 (88.2) [119]**	**29 (87.9) [125]**	**59 (88.1) [244]**
Endocrine disorders	**19 (55.9) [55]**	**17 (51.5) [41]**	**36 (53.7) [96]**
Hyperprolactinemia	19 (55.9) [55]	17 (51.5) [41]	36 (53.7) [96]

For study ROV-RISP-2016-01 (**PRISMA-3**), all reported TEAEs (preferred terms of blood prolactin increased and hyperprolactinaemia) in the DB and OLE phases are listed in Table 22. Applying the protocol definition of a TEAE of hyperprolactinaemia to the DB phase, 36 rather than 55 of the 290 subjects in the DB phase had TEAEs that qualified as hyperprolactinaemia.

Table 22: Study ROV-RISP-2016-01 (PRISMA-3; DB Phase): All Reported TEAEs (First Occurrences)

	Number (%) of Subjects		
	Risperidone ISM 75 mg (N=144)	**Risperidone ISM 100 mg (N=146)**	**All Risperidone ISM (N=290)**
Blood prolactin increased	13 (9.0%)	21 (14.4%)	34 (11.7%)
Hyperprolactinemia	8 (5.6%)	13 (8.9%)	21 (7.2%)
Total	**21 (14.6%)**	**34 (23.3%)**	**55 (19.0%)**

DB: Double-Blind; ISM: *in situ* microparticles; N: number of subjects in each treatment group; TEAE: treatment-emergent adverse event

Hyperprolactinaemia is a known adverse reaction to risperidone and is expected in a high proportion of exposed subjects. The detected incidence/prevalence will depend on timing/frequency of measurement and definition of the event. The overall incidence of hyperprolactinaemia in the study PRISMA-3 was only 7%, and the overall incidence of blood prolactin increased was 12% which is seen as substantially lower than expected, and also notably lower compared to the findings in the PRISMA-2 study. The applicant argues in the PRISMA-3 study, 124 out of 518 patients (24%) had prolactin levels above the upper limit of normal at screening; therefore 7% of TEAEs of hyperprolactinaemia and 12% of TEAEs blood prolactin increase represent new events. They further argue that the different incidence of hyperprolactinaemia in PRISMA-3 and PRISMA-2 studies is a consequence of the different study designs and patient populations. It is agreed that this may, at least partly, explain the discrepancy.

That there is a difference may also potentially be related to the conduct and integrity of the study. According to the applicant audits described only four minor findings regarding the collection of adverse events, in 4 sites of 18 sites audited, no one related to the recording of hyperprolactinaemia/blood prolactin increase. It is further argued that the most common adverse reactions of risperidone, (dry mouth, vomiting, sedation/somnolence, akathisia, headache, insomnia, etc.) had a very similar incidence in all 3 studies. This latter statement requires a comment. It is noted from the provided table above that for most SOCs the proportion of subjects reporting adverse events is notably higher in the PRISMA-2 study compared to the PRISMA-3 study. There is, however, no major difference between the frequency of adverse events reported from PRISMA-3 compared to the known safety profile of risperidone. Consequently, no major issue suggesting a problem with the integrity of the PRISMA-3 study has been identified.

2.4.4.5. Safety in special populations

Age

No dose adjustments for Risperidone ISM are recommended for elderly people. In the pivotal trial ROV-RISP-2016-01 (PRISMA-3), however, only patients aged ≥18 and ≤65 years were included. The renal function normally decreases with age and chronic disease, such as cardiovascular disease and diabetes, have increased prevalence with age. Acute clinical events with a potential sudden reduction of renal

function are increasingly common with increasing age. Patients with renal impairment have less ability to eliminate the active antipsychotic fraction compared to patients with normal renal function. Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death and the indication does not include this population.

Considering the absence of study data in patients >65 years old, the short duration of run-in on oral risperidone proposed, and the long duration of exposure from with this formulation, it is not obvious that this product is appropriate to use in an elderly population.

It can be agreed that there is a clinical need for a prolonged release formulation also in the elderly. In general, however, the use of antipsychotics in an elderly population may be a concern regarding potential age-related pharmacokinetic and pharmacodynamic factors, comorbidity and interactions with concomitant medication. Elderly patients are particularly vulnerable to the adverse effects of antipsychotic agents, such as extrapyramidal and anticholinergic effects.

The uncertainty regarding RISPERIDONE ISM concerns the safety of such a long-acting formulation in the elderly, without supporting study data. Exposure cannot be quickly reduced/discontinued in case of adverse effects and poor tolerability. Tolerance should be reliably established on oral risperidone before initiating treatment with a prolonged-release formulation.

The applicant refers to an observational study (Lin 2020) comparing the effectiveness of long-acting injectable antipsychotics in elderly patients with schizophrenia with oral antipsychotics on time to rehospitalisation. The interpretation of this study is not fully agreed. The results indicated that the long-acting injectable antipsychotics group had a significantly lower rehospitalisation rate and a significantly longer time to rehospitalisation within 1 year of discharge than the oral antipsychotics group. While these results seem encouraging, this was a non-interventional study and the adjustments made for baseline differences were not exhaustive. It is expected that the group of elderly patients in the long-acting injectable antipsychotics group were selected by prescribers as particularly suitable for that treatment. This may have confounded the comparison.

For oral risperidone the recommendation is to titrate the dose more cautiously to approximately half the dose used in younger adults. In the article 30 referral for Risperdal Consta in 2008 (EMEA/CHMP/384879/2008) the CHMP also assessed the dosing in the elderly population and concluded that it was shown that the pharmacokinetics in the population >65 years are comparable to the population <65 years.

Due to the absence of data on efficacy and safety of this prolonged-release formulation in elderly >65 years, and in line with the SmPC for Risperdal Consta agreed in the referral 2008 (EMEA/CHMP/384879/2008), a statement regarding the absence of data and recommending caution in the elderly is warranted in the SmPC.

Hepatic and Renal Impairment

No studies in subjects with hepatic or renal dysfunction were performed. Patients with renal impairment have less ability to eliminate the active antipsychotic fraction than adults with normal renal function. In patients with moderate to severe renal disease (creatinine clearance 59 to 15 mL/min), clearance of the risperidone and its active metabolite decreased by 60%, compared to young healthy patients. Therefore, risperidone doses should be reduced in patients with severe renal disease (creatinine clearance <30 mL/min).

Patients with impaired hepatic function have increases in plasma concentration of the free fraction of risperidone. While the PK of risperidone in patients with liver disease were comparable to those in young healthy patients, the mean free fraction of risperidone in plasma was increased by about 35% because of

the diminished concentration of both albumin and α1-acid glycoprotein. Based on this, risperidone doses should be reduced in patients with severe liver disease (10-15 points on Child Pugh System).

Dementia-Related Psychosis

The risperidone labelling includes a warning on increased mortality in elderly patients with dementia-related psychosis. The applicant has included the same information for Risperidone ISM.

2.4.4.6. Immunological events

N/A

2.4.4.7. Safety related to drug-drug interactions and other interactions

The interaction of Risperidone ISM with other drugs is expected to show a similar pattern as seen with oral risperidone. The safety aspect to be considered regarding potential interactions is the inevitably long remaining exposure to risperidone the patient will be subjected to if an interaction occurs that require discontinuation or dose reduction. The use of this type of product in patients with multiple comorbidities and anticipated need of multiple co-medications may not be appropriate. The applicant has added a warning in section 4.4 in the SmPC.

2.4.4.8. Discontinuation due to AES

Safety concerns potentially specific for the Risperidone ISM formulation are of particular interest. The applicant reports 6 events in 6 subjects leading to discontinuation in the Risperidone ISM 75 mg arm, one being a limb abscess. The abscess was on the thigh and the injection was given in the deltoid muscle, consequently distant and unrelated to the abscess.

2.4.4.9. Post marketing experience

Risperidone ISM has never been marketed and therefore no post-marketing data are available. Risperidone was first approved in 1993 as oral tablets. The safety profile for risperidone is considered well characterised.

For risperidone, the most frequently reported events were in the central nervous system, psychiatric disorders and gastrointestinal system (European Medicines Agency 2008). The most common adverse reactions (ADRs) in clinical trials (>5% and twice placebo) were parkinsonism, akathisia, dystonia, tremor, sedation, dizziness, anxiety, blurred vision, nausea, vomiting, upper abdominal pain, stomach discomfort, dyspepsia, diarrhoea, salivary hypersecretion, constipation, dry mouth, increased appetite, increased weight, fatigue, rash, nasal congestion, upper respiratory tract infection, nasopharyngitis, and pharyngo-laryngeal pain. Somnolence was higher following administration into the deltoid muscle (21% for each event) compared to the gluteal muscle (6% for each event).

Antipsychotic drugs can cause a potentially fatal symptom complex referred to as *Neuroleptic Malignant Syndrome* (NMS). Clinical manifestations of NMS include hyperpyrexia, muscle rigidity, altered mental status, and autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria, rhabdomyolysis, and acute renal failure (European Medicines Agency 2008). In the clinical trials conducted to date with Risperidone ISM, no cases of NMS have been reported.

Tardive dyskinesia is characterised by potentially irreversible, involuntary, dyskinetic movements. The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to

increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. Importantly, the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn (European Medicines Agency 2008). Tardive dyskinesia has not been reported with Risperidone ISM in the clinical trials conducted for this application.

2.4.4.10. Discussion on clinical safety

The safety profile of oral risperidone is well characterised and clinical experience is extensive. The international birth date for risperidone is December 1992 based on first approval in United Kingdom. Risperidone is currently registered in approximately 120 countries worldwide.

The established immediate-release posology aims to individualise treatment and use the lowest effective dose for each patient with a target dose of 4 to 6 mg/day. Risperidone ISM provides an exposure profile in the studied populations that slightly exceeds what is seen with an oral dose of 4 mg but below what is seen with a daily dose of 6 mg. The overall safety profile of Risperidone ISM is therefore not expected to be different from the well-known safety profile of oral risperidone. This is largely confirmed by the clinical trial data from the Risperidone ISM development programme. There are, however, some observations that require further discussion.

Due to the limited size of the trials with Risperidone ISM it is not unexpected that the severe adverse reactions NMS and tardive dyskinesia were not observed in these trials. These risks should, however, be considered in the context of a depot formulation where exposure will continue for a long period if such a severe adverse reaction occur. This is an important complicating factor when the risk profile is evaluated.

Risperidone is metabolised to 9-hydroxy-risperidone, which has a similar pharmacological activity to risperidone. Steady-state of risperidone is reached within 1 day in most patients while steady-state of 9-hydroxy-risperidone is reached within 4-5 days of dosing. Further, it cannot be assumed that all important adverse events occur immediately after maximum exposure is reached. The data from PRISMA-3 contains only 12 risperidone-naïve subjects allocated to received Risperidone ISM. No meaningful conclusion can be drawn from so few patients regarding the risk associated with initiating treatment with Risperidone ISM in risperidone-naïve patients. The need for a run-in period on immediate-release risperidone before initiation of RISPERIDONE ISM has been introduced in the SmPC, recommending a period of 6 days for risperidone-experienced patients and 14 days for risperidone-naïve patients.

Only patients aged ≥18 and ≤65 years were included in the pivotal trial ROV-RISP-2016-01 (PRISMA-3). Considering the absence of study data in *patients >65 years old*, the limited ability to adjust the exposure level, and the long duration of exposure with this formulation, it may be questioned how appropriate this formulation is for an older population. For oral risperidone the recommendation is to titrate the dose more cautiously to approximately half the dose used in younger adults. In the article 30 referral for Risperdal Consta in 2008 (EMEA/CHMP/384879/2008) the CHMP also assessed the dosing in the elderly population and concluded that it was shown that the pharmacokinetics in the population >65 years are comparable to the population <65 years. Due to the absence of data on efficacy and safety of this prolonged release formulation in elderly >65 years, and in line with the SmPC for Risperdal Consta agreed in the referral 2008 (EMEA/CHMP/384879/2008), a statement regarding the absence of data and recommending caution in older patients has been introduced in the SmPC.

Hyperprolactinaemia is a known and frequent adverse reaction caused by risperidone. It is noted that the overall incidence of hyperprolactinaemia in the study PRISMA-3 was substantially lower than expected. It is also notably lower compared to the findings in the ROV-RISP-2011-02 (PRISMA-2) study. The finding may raise concerns regarding the integrity of PRISMA-3 and the process of capturing adverse events. The

applicant argues that the different incidence of hyperprolactinaemia in PRISMA-3 and PRISMA-2 studies is a consequence of the different study designs and patient populations. It is agreed that this may, at least partly, explain the discrepancy. It is noted that the cut-off serum prolactin level used to define hyperprolactinaemia (above 1000 mIU/L without clinical symptoms, above 530 mIU/L if clinical symptoms of hyperprolactinaemia were present) was higher than in some recent studies on hyperprolactinaemia.

That there is a difference may also potentially be related to the conduct and integrity of the study. For most SOCs the proportion of subjects reporting adverse events is notably higher in the PRISMA-2 study compared to the PRISMA-3 study. There is, however, no major difference between the frequency of adverse events reported from PRISMA-3 compared to the known safety profile of risperidone. Consequently, no major issue suggesting a problem with the integrity of the PRISMA-3 study has been identified.

Safety concerns potentially specific for the Risperidone ISM formulation are also of particular interest. *Injection site reactions* are expected and overall do not raise a particular concern.

The table in section 4.8 of the SmPC has been harmonised with the formal reference product (oral Risperdal). This can be accepted but for injection site reactions the information is based on data from the development programme for Risperidone ISM. Since treatment always should be titrated with oral risperidone before initiating Risperidone ISM, some adverse reactions are expected to differ in frequency compared to oral Risperdal, and harmonisation with Risperdal Consta is more appropriate. This has been applied to "Sedation/somnolence", "Unresponsive to stimuli, depressed level of consciousness", and "Rales, pneumonia aspiration, pulmonary congestion, dysphonia, respiratory disorder".

2.4.4.11. Conclusions on clinical safety

While the exposure levels seen with Risperidone ISM are within those expected from the approved dose interval for oral risperidone, and a similar adverse reaction profile is expected. The patient should be titrated on immediate-release risperidone and tolerability established before treatment with the Risperidone ISM formulation is initiated. The formulation still offers a challenge regarding handling of rare, but potentially serious, late adverse reactions. This should be considered in the overall benefit-risk balance.

2.4.5. Conclusions on clinical aspects

Based on the presented bioequivalence study(ies) Okedi is considered bioequivalent with Risperdal, 4 mg, Coated tablet.

Enough bridge has been established to efficacy and safety characteristics of the reference product. It has been clarified that treatment should only be initiated in adults for whom tolerability and effectiveness has been established with oral risperidone. No major safety concerns remain unresolved.

2.5. Risk Management Plan

2.5.1. Safety concerns

Table 23: Summary table of the safety concerns

Important identified risks	None

Important potential risks	None
Missing information	None

Considering the very well-known safety profile safety, there are no important safety concerns for risperidone.

2.5.2. Pharmacovigilance plan

Routine pharmacovigilance (PV) is sufficient to identify and characterise the risks of the product and to monitor the effectiveness of the risk minimisation measures (RMMs). Therefore, no additional PV activities are required.

2.5.3. Risk minimisation measures

In line with the reference product, routine RMMs are adequate to minimise the risks of the product in the agreed indication.

2.6. Pharmacovigilance

2.6.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.6.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Non-conformity of paediatric studies

Not applicable

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

Comments were made during the assessment on the package leaflet and by some user test participants. The applicant updated the package leaflet accordingly and the user test was then considered acceptable.

3. Benefit-risk balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Risperidone *in situ* microparticles (ISM) (Okedi) is a new injectable long-acting formulation of risperidone claimed to provide therapeutic plasma concentrations early and adequate concentrations during the entire dose interval for efficacy without any supplemental oral dosing. A monthly dosing interval is proposed.

The indication applied for is:

> *Okedi is indicated for the treatment of schizophrenia in adults for whom tolerability and effectiveness has been established with oral risperidone.*

3.1.2. Available therapies and unmet medical need

The need for long-acting antipsychotics (LAI) as a maintenance treatment for individuals with a history of non-adherence with oral antipsychotics is recognised. While there are several clinical advantages to depot administration of antipsychotic medications, the most important is improved patient adherence to treatment.

A number of second-generation LAI have been previously approved for use either every 2 weeks, every month or every three months. Risperidone LAI (i.e. Risperdal Consta), is a q2w LAI of risperidone. Due to the inherent lag phase of this microsphere product, it takes approximately 3 weeks for sufficient amounts of risperidone to be released into systemic circulation and therefore, it has to be supplemented with oral risperidone for 3 weeks. No LAI has previously been approved for treatment of patients with acute exacerbations.

3.1.3. Main clinical studies

The legal basis for the application is 10:3 (hybrid application) with Risperdal, 4 mg, Coated tablet as reference product. The pivotal studies performed by the applicant to support the application are;

ROV-RISP-2020-01 [BORIS-2]. This was a Phase 1, multicentre, sequential, open-label study to evaluate the steady-state comparative bioavailability of 100 mg Risperidone ISM injectable every 4 weeks compared to once-daily 4 mg oral risperidone in subjects with schizophrenia stabilised on oral risperidone treatment. Subjects on existing oral risperidone treatment (4 mg) continued the oral regimen for 1 week to achieve steady-state concentrations of risperidone. Then, a single IM dose of Risperidone ISM was administered. A total of 4 IM doses were given (each dose separated by 4 weeks).

PRISMA 3. This was a Phase 3, multicentre, randomised, DB, 12-week long, placebo-controlled study evaluating efficacy and safety of Risperidone ISM (75 mg and 100 mg) in adults experiencing an acute exacerbation or relapse of schizophrenia. At the screening visit, all risperidone naïve patients received 2 mg/day oral risperidone for 3 days to ensure a lack of any clinically significant hypersensitivity reactions before the trial. Patients with previous history of being treated with risperidone started directly with RISPERIDONE ISM (75 mg or 100 mg) or placebo after randomisation.

Four hundred and thirty-eight (438) patients were randomised to receive 3 doses of IM Risperidone ISM (75 mg or 100 mg) or placebo every 28 days. No supplemental oral risperidone was permitted during the

study. After the main part of the study 40% who participated in the DB phase continued into the open-label single-arm phase of the study. An additional 41 *de novo* patients were included at this stage.

PRISMA 2 was a phase 2, multicentre, open-label, two-arm (deltoid or gluteus maximus muscle), parallel-design, repeat-dose study. The aim was to characterize the PK of Risperidone ISM over four injections in the gluteal and deltoid muscle at 28-day intervals and at one dose strength. There was also an exploratory efficacy evaluation included.

3.2. Favourable effects

The **BORIS-2** study results showed that exposure of Risperidone ISM 100 mg is generally similar to 4 mg po EU Risperdal at steady state. PK simulations of the initial active moiety exposure and receptor occupancy are in the same range for oral risperidone 4 mg and Risperidone ISM 100 mg; thus in principal constituting a sufficient bridge to the reference product.

In the **PRISMA 3** study both Risperidone ISM 75 and 100 mg demonstrated a statistically significant mean difference in PANSS total score from baseline to end of study (Day 85) compared with placebo (-13.6 95% CI -17.8- -9.3 for the 100 mg dose) with no differences between the doses. The curves started separating at day 4 and there was a gradual increase in difference over time.

The proportions of PANSS responders (decrease in PANSS total score of ≥30%) were 38% in the 75 mg group and 31% in the 100mg group, compared to 8% in the placebo group. In both Risperidone ISM groups, the PANSS response rate increased at each time point and was highest at Day 85. During the first two weeks the response is modest but gradually increase over time. The median time to PANSS response was not estimable for the placebo group, 87.0 (95% CI: 58.0, 99.0) days for the Risperidone ISM 75 mg group, and 86.0 (95% CI: 84.0, not estimable) days for the Risperidone ISM 100 mg group.

The secondary endpoints showed similar and consistent results, with no relevant difference between the two dosage levels. The CGI-S score mean change from baseline to Day 85 was the key secondary efficacy variable. The difference in the change from baseline to Day 85 between placebo and both Risperidone ISM groups in mITT population was -0.7 (95% CI -1.0 to -0.5) in both Risperidone ISM dosage groups.

The change in mean PANSS positive subscale score increased at each time point in all treatment groups. At Day 8, the LS means difference from placebo was -1.0 (95% CI: -1.9, -0.1) for the Risperidone ISM 75 mg group, and -1.8 (95% CI: -2.7, -0.9) for the Risperidone ISM 100 mg group. At Day 85, the difference from placebo was -3.9 (95% CI: -5.3, -2.5) for the Risperidone ISM 75 mg group, and -4.6 (95% CI: -6.0, -3.2) for the Risperidone ISM 100 mg group.

For the mean PANSS negative subscale score at Day 15, the LS means difference from placebo was -0.9 (95% CI: -1.6, -0.2) for the Risperidone ISM 75 mg group, and -0.9 (95% CI: -1.7, -0.2) for the Risperidone ISM 100 mg group. At Day 85, the difference from placebo was -2.1 (95% CI: -3.1, -1.0) for the Risperidone ISM 75 mg group, and -2.0 (95% CI: -3.1, -0.9) for the Risperidone ISM 100 mg group.

Among the 386 subjects treated in the open-label extension of PRISMA 3, 111 subjects received at least 13 doses of Risperidone ISM.

In the open-label study **PRISMA 2** of patients with schizophrenia on maintenance therapy was no substantial change from baseline in the PANSS scores or CGI-S scores over the duration of the study (Day 120 post-dose 4).

3.3. Uncertainties and limitations about favourable effects

Even though the AUC after Risperidone ISM may be in a similar range as for oral risperidone, it is noted, both in the BORIS (2) studies and in simulations based on literature data, that Risperidone ISM results in lower plasma concentrations of active moiety between day 10 and 15 approximately. This concentration seems to be in the range of the oral C_{min}. It is however unclear whether a prolonged time at this concentration may have an impact on clinical efficacy. There is no obvious trend between the PANSS score and the lower active moiety exposure between day 8-15, however PANSS may not be sufficiently sensitive over such a timeframe. The value of the present exposure/response analysis for the information on the lack of impact on efficacy is therefore limited in this respect. The observed dips in plasma concentrations have not contributed to lack of efficacy as measured by the PANSS assessment.

It is noted that neither the CHMP guideline nor the recommendations in the CHMP scientific advice were fully adhered to by the applicant. From an efficacy perspective the difficulty to titrate the dose, to switch to another antipsychotic and the non-negligible reduction of exposure if a dose administration is delayed remain noted as potential concerns with the product.

In the group-wise comparison the 100 mg dose did not demonstrate any benefit over the 75 mg dose. An increase in the dose from 75 mg to 100 mg, when not titrated on oral risperidone, carries a potential risk. Failure to tolerate the increased dose will be accompanied by many weeks of continued exposure. This type of up-titration of long-acting antipsychotics has, however, been approved previously by the CHMP and is therefore accepted.

3.4. Unfavourable effects

The safety profile of oral risperidone is well characterised and clinical experience extensive. Risperidone ISM provides an exposure profile in the studied populations that slightly exceeds what is seen with an oral dose of 4 mg but below what is seen with an oral daily dose of 6 mg. The overall safety profile of Risperidone ISM is therefore not expected to be different from the well-known safety profile of oral risperidone. This is largely confirmed by the clinical trial data from the Risperidone ISM development programme.

The most frequently reported events are in the central nervous system, psychiatric disorders and gastrointestinal system. The most common ADRs in clinical trials (>5% and twice placebo) were parkinsonism, akathisia, dystonia, tremor, sedation, dizziness, anxiety, blurred vision, nausea, vomiting, upper abdominal pain, stomach discomfort, dyspepsia, diarrhoea, salivary hypersecretion, constipation, dry mouth, increased appetite, increased weight, fatigue, rash, nasal congestion, upper respiratory tract infection, nasopharyngitis, and pharyngo-laryngeal pain.

Antipsychotic drugs can cause a potentially fatal symptom complex referred to as *Neuroleptic Malignant Syndrome* (NMS). Clinical manifestations of NMS include hyperpyrexia, muscle rigidity, altered mental status, autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia), elevated creatine phosphokinase, myoglobinuria, rhabdomyolysis, and acute renal failure.

Tardive dyskinesia is characterised by potentially irreversible, involuntary, dyskinetic movements. The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. Importantly, the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Tardive dyskinesia has not been reported with Risperidone ISM in the clinical trials conducted for this application. In the clinical trials conducted to date with Risperidone ISM, no cases of NMS or tardive dyskinesia have been reported.

3.5. Uncertainties and limitations about unfavourable effects

The main remaining uncertainties are the risks from the very prolonged exposure if discontinuation of therapy is required, if a rare but severe adverse reaction such as NMS or tardive dyskinesia develops. Due to the limited size of the trials with Risperidone ISM it is not unexpected that the severe adverse reactions NMS and tardive dyskinesia were not observed in the trials. These risks should, however, be considered in the context of a depot formulation such as Risperidone ISM, where exposure will continue for a long period if such a severe adverse reaction occur. This is an important complicating factor when the risk profile is evaluated.

While there is clinical experience from treatment of older individuals with oral immediate-release risperidone, the appropriateness of this specific formulation for older individuals remains uncertain.

3.6. Effects Table

N/A – efficacy of the new formulation mainly determined from bridging to the reference product.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Other available LAI of antipsychotic substances are mainly approved for maintenance treatment of patients with schizophrenia. However, Risperidone ISM has a different PK profile compared to other LAI. It has demonstrated comparative bioavailability to 4-6 mg oral risperidone in a supportive study, producing adequate plasma levels within 24 hours. PK simulations of the initial active moiety exposure and receptor occupancy is supporting a similar bioavailability of Risperidone ISM 100 mg and the reference product.

The PRISMA 3 study cannot on its own support treatment of acute exacerbations, even though this was the target population for the study. It is inadvisable to start treatment with such a long-acting formulation in risperidone-naïve patients (see *CHMP guideline for medicinal products including depot preparations in the treatment of schizophrenia (EMA/CHMP/40072/2010 Rev. 1*)). It has been established that there is a need for a run-in period on immediate-release risperidone before initiation of RISPERIDONE ISM, and such guidance is now provided in the SmPC, with a period of at least 6 days for risperidone-experienced patients and at least 14 days for risperidone-naïve patients.

Maintenance treatment with Risperidone ISM in previously stabilised patients has not been studied directly, except for in the open-label extension of the PRISMA 3 study and to some extent in the PRISMA 2 study. Thus, this part of the indication is based on extrapolation of efficacy and safety from the reference product. This is not fully in line with the CHMP scientific advice that "considering the differences in pharmacokinetic profile for this new formulation compared with previously established formulations of risperidone, safety and efficacy needs to be confirmed in the phase III programme for treatment of acute exacerbation as well as for maintenance treatment". It is agreed that steady-state active moiety concentrations over 20 ng/ml are likely at the plateau of the exposure-response relation, and that it is unlikely that small differences in PK would meaningfully impact the clinical response. In addition, the 3-months assessments of efficacy and the results of the OLE part of the PRISMA 3 study indicated a continued therapeutic effect of Risperidone ISM over a period of more than 1 year.

Unfavourable effects

Risperidone ISM 100 mg provides an exposure profile in the studied populations that slightly exceeds what is seen with an oral dose of 4 mg but is below what is seen with an oral daily dose of 6 mg. Considering that oral risperidone is used in this dosing interval, these results seem reassuring both with respect to efficacy and safety. The overall safety profile of Risperidone ISM is therefore not expected to be different from the well-known safety profile of oral risperidone. This is largely confirmed by the clinical trial data from the Risperidone ISM development programme. It is the long duration of effect, the very purpose with this presentation of risperidone, that might generate particular safety concerns, should severe adverse reactions occur. Establishing tolerability using short-acting formulations is therefore an essential risk minimisation measure.

As another consequence of the long duration of exposure, it should be used with caution in an elderly population, and only after reliably having established tolerability on oral risperidone with daily doses of ≥3 mg.

3.7.2. Balance of benefits and risks

Enough bridge has been established to efficacy and safety characteristics of the reference product. It has been clarified that treatment should only be initiated in adults for whom tolerability and efficacy has been established with oral risperidone. No concerns remain unresolved and a positive benefit/risk ratio can therefore be concluded.

3.8. Conclusions

A bridge was established between the data for the test formulation and the data for the reference formulation based by means of studies and through a scientific rationale.

The benefit risk balance for Risperidone ISM is positive for the proposed indication.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Okedi is favourable in the following indication:

Treatment of schizophrenia in adults for whom tolerability and effectiveness has been established with oral risperidone.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- ***Periodic Safety Update Reports***

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.