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Long-term efficacy and safety of once-monthly Risperidone ISM® in the treatment of schizophrenia: Results from a 12-month open-label extension study

Yuriy Filts [a], Robert E. Litman [b,c], Javier Martínez [d], Lourdes Anta [d,*], Dieter Naber [e], Christoph U. Correll [f,g,h]

[a] Communal Noncommercial Enterprise of Lviv Regional Council, Lviv Regional Clinical Psychiatric Hospital, Lviv, Ukraine
[b] CBH Health LLC, Gaithersburg, MD, USA
[c] Department of Psychiatry, Georgetown University Medical School, Washington, DC, USA
[d] Medical Department, Laboratorios Farmacéuticos ROVI, S.A., Calle Alfonso Gómez, 45-A, 28037 Madrid, Spain
[e] Department of Psychiatry and Psychotherapy, Hamburg-Eppendorf University, Hamburg, Germany
[f] Department of Psychiatry Research, The Zucker Hillside Hospital, Glen Oaks, NY, USA
[g] Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Department of Psychiatry and Molecular Medicine, Hempstead, NY, USA
[h] Charité Universitätsmedizin Berlin, Department of Child and Adolescent Psychiatry, Berlin, Germany

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ABSTRACT

Objective: To evaluate long-term efficacy, safety and tolerability of Risperidone ISM® in patients with schizophrenia, a multicenter, open-label extension of the PRISMA-3 study was conducted.
Methods: Eligible placebo (unstable) and Risperidone ISM® (stabilized) rollover patients from a previous 12-week double-blind phase and de novo stable patients received once-monthly intramuscular injections of Risperidone ISM® 75 or 100 mg for 12 months. The long term-efficacy assessment included the Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression-Severity (CGI-S) and Clinical Global Impression-Improvement (CGI-I) scales. Safety evaluation included treatment-emergent adverse events (TEAEs), injection site reactions (ISR), laboratory tests and several safety scales.
Results: Altogether, 215 patients entered the study (55 unstable, 119 stabilized and 41 stable patients). Most patients (74.9%) completed, and discontinuation rates were broadly similar across the study subgroups, mainly due to withdrawal of consent (12.1%). PANSS total and subscales scores decreased from baseline to endpoint in all groups, with the largest decrease for unstable patients. Improvement from baseline to 12 months was also shown for CGI-S and CGI-I scores for both unstable and stabilized patients; the CGI-S and CGI-I scores remained almost unchanged for the stable group. At least one treatment-related TEAE was reported in 39.1% of patients; the most common were headache (12.1%), hyperprolactinemia (9.8%) and asthenia (5.1%). ISR were reported in 8 (0.3%) patients; injection site pain score was low across the 2355 doses assessed.
Conclusion: Risperidone ISM® is an effective, safe, and well-tolerated long-term treatment of schizophrenia in adults, regardless of the initial disease severity or whether patients were previously treated with Risperidone ISM® during an acute exacerbation or switched from stable doses of oral risperidone.

1. Introduction

Schizophrenia is a leading cause of disability worldwide with similar incidence rates between men and women (Vos et al., 2015). Compared with the general population, patients with schizophrenia have a 14- to 15-year shorter average life-span, with a higher negative impact in men

Abbreviations: AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; CGI-I, Clinical Global Impression-Improvement; CGI-S, Clinical Global Impression-Severity; C-SSRS, Columbia-Suicide Severity Rating Scale; DB, double blind; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ECG, electrocardiogram; EPS, extrapyramidal symptoms; IM, intramuscular; ISR, injection site reactions; LAI, long-acting injectable; OLE, open-label extension; PANSS, Positive and Negative Syndrome Scale; SAS, Simpson-Angus Scale; TEAE, treatment-emergent adverse event; VAS, visual analog scale.

* Corresponding author at: Laboratorios Farmacéuticos ROVI, S.A., Calle Alfonso Gómez, 45A, 28037 Madrid, Spain.
E-mail address: lanta@rovi.es (L. Anta).

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than women (Hjorthøj et al., 2017).

Suboptimal adherence to treatment and relapse rates are directly related and contribute to the patient's functional deterioration (Carbon and Correll, 2014; Jeong and Lee, 2013; Liu-Seifert et al., 2005). Thus, long-term treatment with antipsychotics is crucial for the prevention of relapse and functional decline (Correll et al., 2018); however, despite extensive pharmacologic research over the last 50 years, there is still a gap in evidence for the long-term safety and the risk-benefit profile for antipsychotic treatments in schizophrenia (Hasan et al., 2015; Kishimoto et al., 2019; Nasrallah et al., 2019).

The reasons for suboptimal adherence in schizophrenia are many and varied, but include patients' lack of insight into their illness, medication beliefs, and substance abuse (Higashi et al., 2013; Kane et al., 2013).

In addition to poor adherence, the specific clinical challenges associated with the management of schizophrenia include adverse events, environmental elements, such as family support, and the limited efficacy of antipsychotic therapy in relieving negative, cognitive and residual positive symptoms (Correll and Schooler, 2020; Kahn et al., 2015; Krogmann et al., 2019; Liu-Seifert et al., 2005). Long-acting injectable (LAI) antipsychotics help to overcome some of these challenges, and seem to be an effective alternative to oral treatments, especially in patients with poor adherence (Correll et al., 2016; Kishimoto et al., 2021; Ostuzzi et al., 2021).

Risperidone ISM® (Laboratorios Farmacéuticos ROVI) is a new LAI injectable risperidone that uses the ISM® technology, which provides immediate and sustained drug plasma levels without loading doses or oral risperidone supplementation (Anta et al., 2018; Anta et al., 2020; Llaudó et al., 2016b).

The previously published double-blind (DB) phase of the PRISMA-3 study demonstrated that monthly (every 4 weeks) intramuscular (IM) doses of 75 mg or 100 mg Risperidone ISM® can be an effective therapeutic strategy for patients with schizophrenia suffering from an acute episode with severe or moderate psychotic symptoms (Correll et al., 2020). Patients who correctly completed this DB phase were invited to enter an open-label extension (OLE) study along with newly enrolled patients (de novo) to assess the long-term efficacy, safety and tolerability of monthly IM injections of Risperidone ISM®. This report describes the main results of this OLE study. We hypothesized that Risperidone ISM® would be a safe and effective long-term treatment for patients with schizophrenia, independent of degree of stability, coming either from the placebo or Risperidone ISM® arm of the acute 12-week study or being de novo enrolled patients stabilized on oral risperidone (Correll et al., 2020).

2. Materials and method

2.1. Study design

This study (NCT03870880) was an OLE of the phase III, 12-week, DB, placebo-controlled PRISMA-3 study (Correll et al., 2020), conducted in 26 centers in the United States and Ukraine between August 2017 and January 2020, in accordance with the Declaration of Helsinki, and Good Clinical Practice principles outlined in the International Conference on Harmonization. The protocol, amendments, and informed consent were approved by an Ethics Committee at each site, and written informed consent was obtained from all patients before study participation.

2.2. Patients

The OLE study included a screening period during which patients were evaluated for eligibility and were consecutively allocated to receive monthly (every 4 weeks) injections in the gluteal or deltoid muscle of either 75 or 100 mg of Risperidone ISM® for approximately 12 months, followed by a 4-week follow-up period.

Eligible patients were 18–65 years old, with a current diagnosis of schizophrenia, according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria. Those who completed the DB phase of the PRISMA-3 study according to the protocol (Correll et al., 2020) and had been receiving placebo in the DB phase ("unstable patients") were randomly assigned to Risperidone ISM® at a dose of either 75 or 100 mg. Patients treated with Risperidone ISM® in the DB phase continued to receive monthly Risperidone ISM® in the OLE study at the same dose (75 or 100 mg) as during the DB phase ("stabilized patients"; Fig. 1, Supplementary Fig. 1).

In addition, patients who had not participated in the DB phase (de novo patients), were newly enrolled into the OLE study if they met the age and diagnostic criteria, and were clinically stable at screening, which was defined as a Positive and Negative Syndrome Scale (PANSS) total score of <70, a Clinical Global Impression-Severity (CGI-S) score of ≤ 3 (mild), without significant symptom exacerbation or hospitalizations due to relapses in the 3 months prior to screening, and were on a stable maintenance dose of oral risperidone 4–6 mg daily for at least the last 4 weeks prior ("stable patients"). Patients on 4 mg/day of oral risperidone were assigned to the 75 mg dose of Risperidone ISM® whereas those on oral risperidone ≥ 4–≤ 6 mg/day were assigned to the 100 mg dose of Risperidone ISM® (Fig. 1, Supplementary Fig. 1).

The exclusion criteria for the OLE study were similar to those in the previously published DB study (Correll et al., 2020).

Antidepressants, antipsychotics (other than Risperidone ISM®), lithium and other mood stabilizers were not permitted during the study. Benzodiazepines, anticholinergics and propranolol were allowed as rescue medication."

2.3. Assessments

The long-term efficacy of Risperidone ISM® was evaluated at each scheduled monthly visit using the PANSS total scores, PANSS positive, negative and general psychopathology subscale scores, CGI-S and Clinical Global Impression-Improvement (CGI—I) scores (Guy, 1976a), the overall response rate (defined as the percentage of patients who achieved a $\geq$ 30% decrease from baseline in PANSS total score or a CGI-I score of at least 2 [much improved]), and the relapse rate (defined as either a $\geq$ 30% increase from baseline in PANSS total score, rehospitalization for psychotic symptoms or use of adjunctive antipsychotic medication after stabilization).

Safety and tolerability were evaluated by assessment of treatment-emergent adverse events (TEAEs), discontinuations due to TEAEs and treatment-related TEAEs, vital signs, laboratory tests, electrocardiograms (ECG), physical examinations, injection site reactions (IRS, i.e., redness, swelling, and induration), and injection site pain, which was rated by patients using a visual analog scale (VAS) ranging from 0 (no pain) to 10 (worst possible pain). Extrapyramidal symptoms (EPS) were evaluated using the Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976b), Barnes Akathisia Rating Scale (BARS) (Barnes, 1989) and the Simpson-Angus Scale (SAS) (Simpson and Angus, 1970), and suicidality was assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS) (Posner et al., 2007).

Information regarding concomitant medications, including new medications and changes to existing medications were also recorded.

2.4. Statistical analyses

All analyses were undertaken on the population of patients who received at least one dose of study drug during the OLE study. For unstable and stabilized patients (i.e., "rollover" patients), the baseline of the OLE study was study day 85 of the DB phase. For all patients, study day 365 or the last post-baseline assessment was defined as the endpoint for efficacy assessment. Efficacy variables were summarized according to the OLE study subgroup, but no formal between-group testing was conducted. Temporal threshold when PANSS and/or CGI-I total scores in the unstable and stabilized patients were similar to the baseline scores of stable patients was evaluated post-hoc.

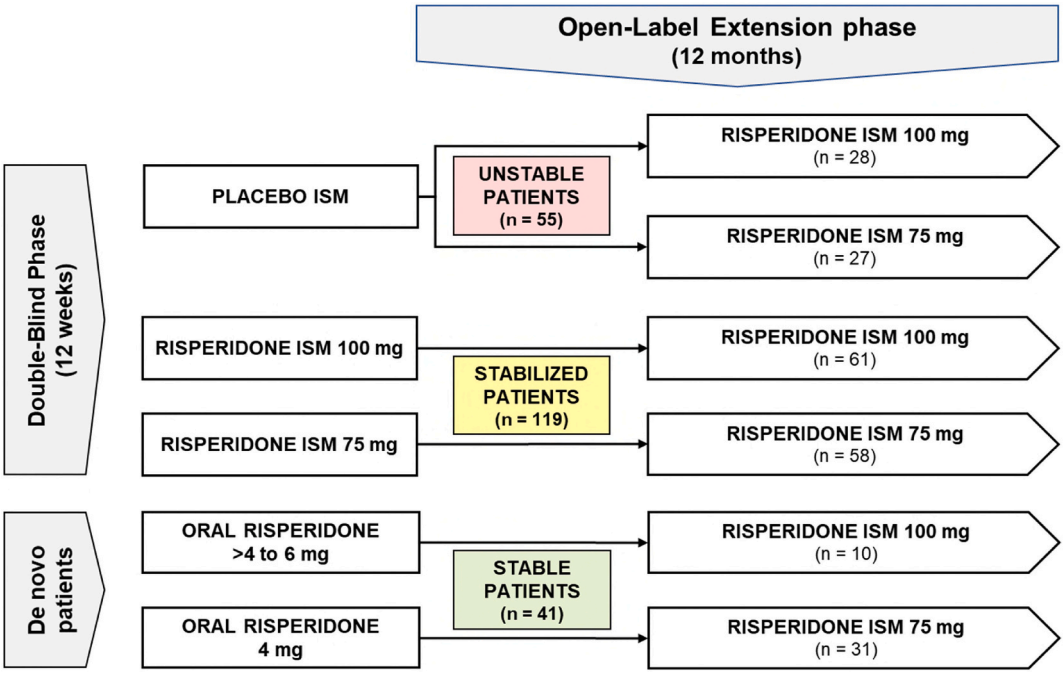

Fig. 1. Study design. ISM®, in situ microimplant.

3. Results

Altogether, 215 patients (55 unstable, 119 stabilized and 41 stable) received at least one dose of Risperidone ISM®; 116 received the 75 mg dose and 99 the 100 mg dose (Fig. 1, Supplementary Fig. 1). Overall median duration of the OLE study was 365 days. Most patients (76.3%) received 13 doses of Risperidone ISM®, and of these patients, 92 were administered the 75 mg dose and 72 the 100 mg dose. The total number of Risperidone ISM® doses administered was 2358 (Risperidone ISM® 75 mg: 1303 doses, Risperidone ISM® 100 mg: 1055 doses), of these, 2355 IM injections of Risperidone ISM® were assessed for ISR.

Most patients (74.9%) completed the OLE study. Among the 54 patients (25.1%) who did not complete the OLE study, the most commonly reported primary reason for discontinuation was withdrawal of consent (26 patients; 12.1%). Discontinuation rates were broadly similar across the study subgroups (Supplementary Fig. 1).

Baseline characteristics were comparable across study groups, except for the PANSS and CGI-S scores as expected (Table 1). Most patients were male (60.9%), white (84.7%), not Hispanic/Latino (96.3%); the mean (SD) age of patients was 39.3 (10.8) years.

Table 1
Patient baseline characteristics.

Baseline characteristics	Unstable patients (N = 55)	Stabilized patients (N = 119)	Stable patients (N = 41)
Age, mean (SD), years	38.5 (9.79)	40.6 (11.46)	36.7 (9.95)
Sex, n (%)			
Male	31 (56.4)	76 (63.9)	24 (58.5)
Female	24 (43.6)	43 (36.1)	17 (41.5)
Race, n (%)			
White	44 (80.0)	97 (81.5)	41 (100)
Black or African American	11 (20.0)	21 (17.6)	0
Asian	0	1 (0.8)	0
Ethnicity, n (%)			
Hispanic or Latino	3 (5.5)	5 (4.2)	0
Not Hispanic or Latino	52 (94.5)	114 (95.8)	41 (100)
BMI, mean (SD), kg/m^2	27.59 (4.69)	27.04 (4.91)	25.47 (3.72)
Time since schizophrenia diagnosis, mean (SD), years	10.5 (7.19)	11.8 (8.55)	8.8 (7.60)
PANSS total score, mean (SD)	82.3 (12.19)	70.0 (14.29)	60.3 (8.22)
CGI-S score, mean (SD)	4.1 (0.87)	3.4 (0.88)	2.8 (0.52)

BMI = body mass index; SD = standard deviation.

3.1. Efficacy

The mean PANSS total score decreased from baseline to study endpoint in all study groups (Fig. 2A), reporting at Study Day 365 a mean (SD) PANSS total score of 58.7 (10.68), 57.6 (10.87) and 57.0 (8.13) in the unstable, stabilized, and stable patient groups, respectively (Supplementary Table 1). The largest decreases were observed in the unstable and stabilized patients, in whom mean (SD) changes from baseline to endpoint were − 20.9 (14.40) and − 9.8 (13.88), respectively (Table 2, Supplementary Figs. 2 and 4). At approximately 6 months (Day 169), the mean (SD) PANSS total scores in the unstable and stabilized patients were similar (60.6 [12.58] and 61.6 [13.78], respectively) to the score of stable patients at entry into the OLE study (60.3 [8.22]) (Fig. 2A; Supplementary Table 1). Furthermore, a slight mean (SD) decrease from baseline to endpoint in PANSS total score was observed in stable patients (Table 2, Supplementary Fig. 6).

PANSS subscale (Positive, Negative and General Psychopathology) scores decreased from baseline to endpoint in all study groups, with the largest decreases observed in unstable patients (Table 2).

CGI-S scores also improved in the unstable and stabilized patients (Fig. 2B and Supplementary Figs. 3 and 5) and were maintained for the stable patients throughout the study (Table 2 and Supplementary Fig. 7). At approximately 4 months (Day 113), the mean CGI-S score in both unstable and stabilized patients reached mean (SD) values (2.9 [0.71] and 2.9 [0,67], respectively) similar to those shown at baseline by the stable patients prior to entering the OLE study (2.8 [0.52]) (Fig. 2B; Supplementary Table 2).

At the end of the OLE study, those patients who completed 1 year of treatment with monthly Risperidone ISM® 75 or 100 mg (N = 161) exhibited mean PANSS total and CGI-S scores similar to the mean values recorded in the de novo patients clinically stable on oral risperidone

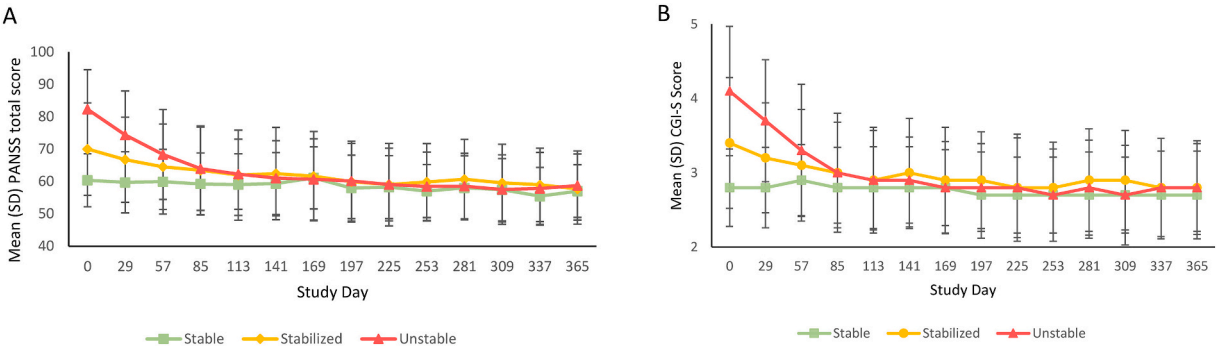

Fig. 2. Mean (SD) PANSS total score (A) and CGI-S score (B) at each time point in Unstable, Stabilized and Stable patients treated with monthly Risperidone ISM® (pooled 75 and 100 mg). CGI—S, Clinical Global Impression-Severity; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.

Table 2
Efficacy assessments at endpoint.

Efficacy Assessments	Unstable Patients (N = 55)	Stabilized Patients (*N* = 114)	Stable Patients (*N* = 40)
PANSS, change from baseline to endpoint, mean (SD)			
PANSS total score	−20.9 (14.40)	−9.8 (13.88)	−1.8 (8.60)
PANSS positive subscale	−6.3 (5.05)	−3.0 (5.10)	−0.9 (3.16)
PANSS negative subscale score	−3.7 (4.58)	−2.2 (3.62)	−0.4 (3.43)
PANSS general psychopathology subscale score	−10.9 (7.95)	−4.6 (7.37)	−0.5 (5.26)
CGI-S total score, change from baseline to endpoint, mean (SD)	−1.1 (0.96)	−0.4 (0.87)	0.0 (0.48)
CGI-I total score at endpoint, mean (SD)	2.4 (1.05)	2.9 (1.19)	3.6 (1.11)
Responders, % patients (95% CI)[a]	69.1 (55.2–80.9)	45.4 (36.2–54.8)	12.2 (4.1–26.2)

CGI-I, Clinical Global Impression-Improvement Scale; CGI—S, Clinical Global Impression-Severity of Illness Scale; PANSS, Positive and Negative Syndrome Scale; SD, Standard Deviation.

[a] Percentage of patients achieving overall response at endpoint; responders are those patients who achieved a decrease from baseline in PANSS Total Score ≥ 30% or CGI-I score of at least 2 (much improved).

before entering the OLE study (Fig. 2A and B; Supplementary Tables 1 and 2).

Both the unstable and stabilized groups showed a mean improvement at endpoint of between 2 (much improved) and 3 (minimally improved) points on the CGI—I, while in stable patients the CGI-I score was maintained at an almost constant mean value (Table 2), ranging from 4 (no change) to 3.4 points throughout the study.

An overall response was achieved by 69.1% of patients in the unstable group (Table 2).

The overall relapse rate was 10.7% (95% CI, 6.9% to 15.6%). Relapse rates for all study groups are summarized in Supplementary Table 3. Specifically, 9 patients (4.2%) overall were re-hospitalized for psychotic symptoms during the OLE study.

3.2. Safety and tolerability

Altogether, 84 (39.1%) patients reported at least one treatment-related TEAE, 43 (37.1%) of whom were receiving Risperidone ISM® 75 mg and 41 (41.4%) were receiving Risperidone ISM® 100 mg (Supplementary Table 4). Most treatment-related TEAEs were of mild (26.0%) or moderate (12.1%) in severity. The most common treatment-related TEAEs were headache (12.1%), hyperprolactinemia (9.8%), asthenia (5.1%), weight increased (4.2%), insomnia (4.2%), and akathisia (3.7%) (Supplementary Table 4).

Serious TEAEs were reported in 11 (5.1%) patients, and one was considered related to the study drug (one patient was hospitalized due to insomnia). One patient receiving Risperidone ISM® 75 mg died during the study because of an intentional overdose of perindopril; this completed suicide was considered not related to the study drug.

Fifteen patients (7.0%) reported at least one TEAE leading to treatment discontinuation. This was considered related to study treatment in 7 (3.2%) of them: four patients receiving the Risperidone ISM® 75 mg dose and three receiving the Risperidone ISM® 100 mg dose (Table 3).

EPS-related TEAEs (i.e. akathisia, extrapyramidal disorder, restlessness, tremor) were reported in 9 patients (4.2%), and led to treatment discontinuation in two of these patients, one (0.5%) due to akathisia and the other one (0.5%) due to extrapyramidal disorder (Table 3). In addition, 5 patients (2.3%) received anticholinergic medication and 9 (4.2%) beta-blocking agents during the OLE study.

Two patients (0.9%) stopped treatment with Risperidone ISM® because of treatment-related hyperprolactinemia (one libido decreased and one gynecomastia) (Table 3). Overall, the mean (SD) and median change from baseline to end of treatment in prolactin levels was +167.7 (770.5) (Supplementary Table 5) and + 36.1 mIU/L, respectively. In contrast, prolactin levels decreased in patients who had received Risperidone ISM® during the previous DB study of the study (stabilized patients), with the mean (SD) change from baseline to end of treatment of −130.7 (530.8) mIU/L.

At the end of the study, the mean (SD) increase from baseline in bodyweight was 1.0 (4.4) kg (Supplementary Table 5). Twelve (5.6%) patients reported bodyweight increase as a TEAE (treatment-related in 9 [4.2%] patients), and one (0.5%) of them discontinued treatment (Table 3).

No noticeable differences were observed in other clinical laboratory assessments, vital signs, or physical examination findings between treatment dose groups.

Seventeen (7.9%) patients received benzodiazepines. Prohibited antipsychotic and antidepressant medication was used in 3 (1.4%) patients and 1 (0.5%) patient, respectively.

Eight (0.3%) cases of ISR were reported across all 2355 Risperidone ISM® IM injections assessed for a reaction (Fig. 3): 5 redness, 2 swelling and 1 induration. The mean injection site pain score (VAS = 0 to 10) after IM administration was always below 2 points at each study visit (Fig. 3).

No numerical differences between treatment dose groups were noted for C-SSRS scores. Treatment-emergent suicidal behavior or ideation and suicidal behavior or ideation worsening from baseline were reported for 3 (4.9%) patients who had received Risperidone ISM® 100 mg in both the DB and OLE studies. One unstable patient and one stabilized patient, both treated with Risperidone ISM® 75 mg, had treatment-emergent suicidal behavior or ideation and suicidal behavior or ideation that worsened from baseline. However, other than the

Table 3
Summary of treatment-related TEAEs leading to study drug discontinuation and their overall incidence.

	Risperidone ISM® 75 mg ($N = 116$)		Risperidone ISM® 100 mg ($N = 99$)		All Risperidone ISM® ($N = 215$)	
	Overall incidence	Leading to discontinuation	Overall incidence	Leading to discontinuation	Overall incidence	Leading to discontinuation
Akathisia	4 (3.4)	0	4 (4.0)	1 (1.0)	8 (3.7)	1 (0.5)
Diabetes mellitus	1 (0.9)	1 (0.9)	0	0	1 (0.5)	1 (0.5)
Extrapyramidal disorder	1 (0.9)	1 (0.9)	0	0	1 (0.5)	1 (0.5)
Gynecomastia	0	0	1 (1.0)	1 (1.0)	1 (0.5)	1 (0.5)
Hepatic steatosis	0	0	1 (1.0)	1 (1.0)	1 (0.5)	1 (0.5)[a]
Hepatocellular injury	0	0	1 (1.0)	1 (1.0)	1 (0.5)	1 (0.5)[a]
Libido decreased	3 (2.6)	1 (0.9)	0	0	3 (1.4)	1 (0.5)
Bodyweight increased	6 (5.2)	1 (0.9)	3 (3.0)	0	9 (4.2)	1 (0.5)
Total	15 (12.9)	4 (3.4)	9 (9.0)	3 (3.0)	24 (19.2)	7 (3.2)

Data are presented as n (%). Description of TEAEs is coded using MedDRA version 22.1.
NA, not applicable; TEAEs, treatment-emergent adverse event.
[a] The same patient had 2 treatment-related TEAEs.

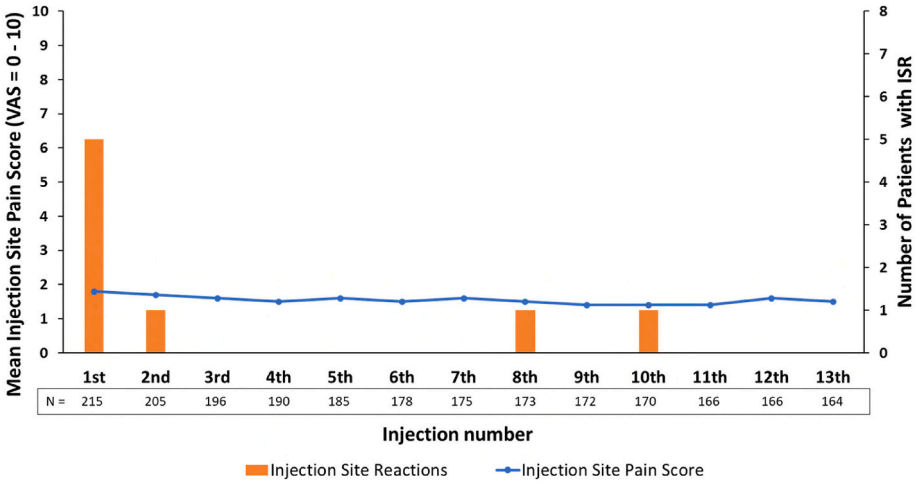

Fig. 3. Evaluation of injection site pain and reactions in patients treated with monthly Risperidone ISM® (pooled 75 and 100 mg). Total number of administered IM injections of Risperidone ISM® assessed for ISR was 2355. The VAS ranged from 0 (no pain) to 10 (worst possible pain). ISR, injection site reaction; VAS, Visual analogical scale.

completed suicide described above, there were no suicide attempts, aborted, or interrupted attempts, during the study.

Extrapyramidal symptom scale (AIMS, BARs and SAS) scores were comparable between treatment dose groups, with no clinically relevant changes from baseline to end of treatment with either treatment dose (Supplementary Table 5).

There were no notable differences between treatment dose groups regarding ECG data, nor clinically relevant changes from baseline in the corrected QT interval (Supplementary Table 5).

4. Discussion

The results of the efficacy parameters evaluated in the present study show clinically meaningful responses in patients treated with Risperidone ISM® and confirm the long-term effectiveness of both doses of Risperidone ISM® (75 mg and 100 mg), as well as its safety and tolerability over 12 months of treatment.

Patients entered this long-term OLE study of PRISMA-3 either as roll over from the preceding DB phase (i.e., the unstable and stabilized patient groups) or as newly enrolled patients from outpatient settings (i.e., the de novo stable patient group). This study design should be carefully considered when interpreting the efficacy and safety outcomes because the three study groups had a different severity of schizophrenia at the initiation of this OLE study.

A decrease from baseline in scores from efficacy scales was shown in all study groups, and as expected, the largest effect was observed in unstable patients who had a more severe clinical condition at baseline (baseline mean PANSS total score = 82.3, and CGI-S score = 4.1). During the DB phase, patients treated with monthly Risperidone ISM® 75 or 100 mg for 12 weeks showed a marked and clinically meaningful mean reduction from baseline of 25 points in PANSS total score and 1.3 points in CGI-S score (Correll et al., 2020), and thereafter, those who rolled over to the OLE study (stabilized patients) obtained a further mean reduction of 9.8 and 0.4 points, respectively. Furthermore, it should be noted that unstable and stabilized patients reached a mean CGI-S score (2.9) at month 4 similar to that shown at baseline in stable patients (2.8); likewise, the mean PANSS total scores in both groups of rollover patients (unstable = 60.6; stabilized = 61.6) at approximately 6 months were already similar to the mean baseline value (60.3) of the de novo stable patients.

On the other hand, the stable group showed mild decreases, or unchanged scores in efficacy scales throughout the OLE, although the number of these “de novo” patients (who had previously been receiving oral risperidone) was small and therefore additional data would be desirable to explore this effect further. However, these results on PANSS and CGI-S scores, along with the known pharmacokinetic profile of both tested doses of Risperidone ISM® (Anta et al., 2018; Llaudó et al., 2016b), as well as the results obtained in a bioavailability study comparing Risperidone ISM versus oral risperidone at steady state (Walling et al., in press) could support for the therapeutic strategy of switching patients with stable schizophrenia from maintenance oral risperidone to maintenance Risperidone ISM®.

As expected, the highest overall response rate (69%) at endpoint (i.e., patients achieving a decrease from baseline in PANSS Total Score of ≥30% or a CGI-I score of at least 'much improved') was seen in the group of unstable patients. Notably, during the DB study, 50% of acutely exacerbated patients had already achieved an overall response after 12 weeks' treatment with monthly Risperidone ISM® 75 or 100 mg (Correll et al., 2020), and 45% of the patients who rolled over to the OLE study (stabilized patients) showed further treatment response. Remarkably, in the stable group, an additional 12% of patients showed an overall response at the end of the OLE study.

Although the criteria for defining a relapse of schizophrenia vary in the literature, the global relapse rate in this OLE (10.7%) was lower than the rates (24%) reported in a recent meta-analysis of several maintenance treatment trials with antipsychotic drugs for schizophrenia in preventing relapse at 7 to 12 months (Ceraso et al., 2020). These outcomes indirectly confirm the long-term effectiveness of Risperidone ISM® in the treatment of schizophrenia, demonstrating its extended effect in controlling symptoms.

Generally, this OLE study also confirmed the favorable safety and tolerability profile of Risperidone ISM® shown in previous studies and in the DB study. Indeed, the proportion of patients who completed the OLE study was high (75%) compared with the completion rate obtained, for instance, with bi-weekly risperidone (50%) and monthly paliperidone palmitate (41%) in a 53-week clinical trial (Fleischhacker et al., 2012), or with subcutaneous LAI risperidone (47%) or aripiprazole lauroxil (68%) in similar 52-week OLE studies (Andorn et al., 2019; Nasrallah et al., 2019). The pharmacokinetic profile of this novel risperidone injectable formulation may be contributing to increased tolerability and consequently to the high completion rate observed in this study.

The results from this OLE study also showed that both doses of Risperidone ISM® were well tolerated. TEAEs were mainly mild or moderate, and 15 (7%) out of the 215 enrolled patients discontinued treatment because of TEAEs, which is a lower rate than that reported for oral risperidone in two 12-month clinical trials (14.4% (Citrome et al., 2012) and 11.9% (Naber et al., 2013), and matches the 7% reported for paliperidone palmitate in the aforementioned 53-week study (Fleischhacker et al., 2012). Moreover, TEAEs resulting in treatment discontinuation were considered related to Risperidone ISM® only in 7 (3.2%) patients.

Another point of interest is that only 4.2% of patients reported EPS-related TEAEs (i.e. akathisia, extrapyramidal disorder, tremor, or restlessness) after 1 year of treatment with Risperidone ISM®. Although indirect comparisons between studies should be interpreted with caution, this rate was slightly lower than that reported (6%) by Gopal et al. (2011) in a 52-week study with paliperidone palmitate, and much lower than rates were reported by Naber et al. (2013) and Citrome et al. (2012) for oral risperidone in 1-year studies (20.6% and 15.8%, respectively) or by Kane et al. (2012) for LAI-aripiprazole in another 52-week trial (14.9%). Of the 8 patients (3.7%) with treatment-related akathisia, only one patient (0.5%) discontinued the study because of this adverse event. These findings are also underpinned by a very low percentage (2.3%) of patients using anticholinergic medications during the 12-month OLE study, as opposed to other 1-year studies, evaluating LAI-aripiprazole or paliperidone palmitate, where 16.7% (Kane et al., 2012) and 8.5–18% (Fleischhacker et al., 2012; Gopal et al., 2011) of patients, respectively, received anticholinergic agents for alleviation of EPS.

It should be noted that, despite the expected increase in prolactin levels, interestingly only two patients (0.9%) developed a hyperprolactinemia-related adverse event that led to treatment discontinuation (one libido decreased and one gynecomastia), which also confirms the good tolerability profile of Risperidone ISM®.

Furthermore, it should be mentioned that only 12 patients (5.6%) reported an increase in body weight as a TEAE (4.2% treatment-related). In this regard, Risperidone ISM® may compare favorably with the 9.7% of patients receiving a LAI formulation of aripiprazole in the trial by Kane et al. (2012) and the 6% of patients in the Gopal et al. (2011) trial receiving paliperidone palmitate.

While second-generation antipsychotics have been associated with metabolic disorders such as type 2 diabetes mellitus, dyslipidemia, hypertension, and metabolic syndrome (De Hert et al., 2012; Firth et al., 2019; Hirsch et al., 2017; Shymko et al., 2021), there is no significant difference in the incidence of these events between oral and long-acting antipsychotics (Misawa et al., 2016; Vermeulen et al., 2007). Diabetes and metabolic syndrome are of particular concern due to their high prevalence in patients with schizophrenia (Vancampfort et al., 2016; Vancampfort et al., 2014; Ward and Druss, 2015). The incidence of metabolic disorders in the current OLE study was low, and only one patient discontinued treatment because of type 2 diabetes mellitus. Given the increased morbidity and mortality associated with metabolic disorders in patients with schizophrenia (Correll et al., 2017; Hirsch et al., 2017; Shymko et al., 2021; Vermeulen et al., 2007), the low rate of metabolic disorders observed with Risperidone ISM® (albeit potentially also being related to the varying degrees of weight gain and metabolic effects of prior treatments), may represent an important benefit for the maintenance treatment of patients with schizophrenia. This may be especially relevant for patients with coexisting metabolic disorders or risk factors, associated with anti-psychotic treatments (Correll et al., 2011; De Hert et al., 2012).

Overall, there were no notable differences between treatment groups regarding ECG data, and the QT interval mean (SD) change showed negligible variations at the end of the treatment regarding baseline values (0.2 [25.79]).

Local tolerability, injection site pain scores (below 2 points at each study visits) and frequency of ISR (0.3%) were low, reinforcing results obtained in the DB phase of the study (Correll et al., 2020). These results provide further reassurance on the local tolerability of Risperidone ISM®, facilitating long-term treatment adherence.

The pharmacokinetic profile of Risperidone ISM® is characterized by rapid absorption and slow elimination (terminal half-life of 9–11 days) (Llaudó et al., 2016b), which allows not only a once-monthly posology, but also permitted treatment initiation without requiring any loading dose or supplementation with oral risperidone in the unstable and stable patient groups. Interestingly, a monthly dose of 75 or 100 mg corresponds to an estimated average daily dose of 2.5 or 3.3 mg, respectively, which is almost one-half that of the recommended daily oral dose of risperidone (4–6 mg) used for the treatment of schizophrenia in adults (European Medicines Agency, 2021; U.S. Food and Drug Administration, 2021).

A kinetic hypothesis has been proposed to explain the safety profile of atypical antipsychotics in which both association and dissociation rates of the drug for dopamine (D2) receptors are considered, as well as the potential for dissociated ligands to rebind to dopamine receptors leading to increased competition with the local dopamine at receptors on the synapse (Sykes et al., 2017). Using this model, the incidence of EPS with atypical antipsychotics could be correlated with the reversal rate of D2 receptor blockade (Sykes et al., 2017).Thus, the favorable tolerability profile observed in the maintenance treatment of adult patients with schizophrenia may be explained by the unique pharmacokinetic profile of Risperidone ISM®, which could be linked to its optimized binding kinetics at the D2 receptor (Llaudó et al., 2016a).

The main limitation of this study was the study design. As patients from the DB phase of the study were invited to participate, this might have introduced bias by excluding patients who did not respond to the treatment or had previously developed adverse events. However, this limitation was addressed by also including de novo patients, which allowed for the evaluation of Risperidone ISM® in a cohort of patients starting treatment with this formulation for the first time. The open-label nature of this study was another potential source of bias, but OLE studies of LAI antipsychotics are often carried out after completion of preceding DB phases (Andorn et al., 2019; Gopal et al., 2011;

Nasrallah et al., 2019). Besides, this study provides very useful information for clinicians on the long-term tolerability and durability of the antipsychotic effect of this novel monthly injectable formulation of risperidone.

5. Conclusions

The findings of the OLE of this clinical trial furnish evidence to support Risperidone ISM® 75 or 100 mg as an effective, safe, and well tolerated monthly antipsychotic for the long-term treatment of schizophrenia in adults, regardless of the initial disease severity or whether patients were previously treated with Risperidone ISM® during an acute exacerbation or switched from oral risperidone in a stable disease setting.

Twitter

Intramuscular risperidone once monthly was an effective well tolerated antipsychotic in a year-long open-label study of 215 adults with schizophrenia.

Role of the funding source

This study was funded by Laboratorios Farmacéuticos Rovi, S.A. Madrid, Spain. The sponsor has participated in the study design, data interpretation, writing of the report; and has been an active member in the decision to submit the article for publication.

CRediT authorship contribution statement

All the authors have made substantial contributions and have revised, edited, and approved the manuscript.

Yuriy Filts was involved in the design and interpretation, as well as in the recruitment of the patients.

Robert E. Litman was involved in the design and interpretation, as well as in the recruitment of the patients.

Javier Martínez was involved in the data analysis, in the design and interpretation, as well as in the manuscript development.

Lourdes Anta was involved in the data analysis, interpretation as well as the in the manuscript development.

Dieter Naber was involved in the data analysis.

Christoph U. Correll was involved in the data analysis, interpretation as well as in the manuscript development.

Declaration of competing interest

Javier Martínez and Lourdes Anta are employees of Laboratorios Farmacéuticos Rovi, S.A., the sole developer of Risperidone ISM®

Christoph U. Correll has been a consultant and/or advisor to or have received honoraria from: AbbVie, Acadia, Alkermes, Allergan, Angelini, Aristo, Axsome, Damitsa, Gedeon Richter, Hikma, IntraCellular Therapies, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedAvante-ProPhase, MedInCell, Medscape, Merck, Mitsubishi Tanabe Pharma, Mylan, Neurocrine, Noven, Otsuka, Pfizer, Recordati, Rovi, Servier, SK Life Science, Sumitomo Dainippon, Sunovion, Supernus, Takeda, Teva, and Viatris. He provided expert testimony for Janssen and Otsuka. He served on a Data Safety Monitoring Board for Lundbeck, Rovi, Supernus, and Teva. He has received grant support from Janssen and Takeda. He is also a stock option holder of LB Pharma.

Robert E. Litman, is a Member, Speakers Bureau, for JNJ and for Allergan, Member, Scientific Advisory Board, Terran BioSciences. He participated as Investigator Coordinator in The United States of America and as Principal Investigator in the study PRISMA-3.

Yuriy Filts has participated as Investigator Coordinator in Ukraine and Principal Investigator in the study PRISMA-3. He received fees from the sponsor for his advice in some previous tasks related to this study.

Dieter Naber, has received consulting fees from Laboratorios Farmacéuticos Rovi, S.A. He served on the Data Monitoring Committee for Rovi at the present study.

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Appendix A. Supplementary data

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Yuriy Filts, MD, is a psychiatrist and the Head of Department at the Communal Non-commercial Enterprise of Lviv Regional Council-Lviv Regional Clinical Psychiatric Hospital in Ukraine. He completed his residency in Psychiatry at the National Medical University of Danylo Halytsky, where he also completed a number of postgraduate courses including Psychotherapy and Child Psychiatry. Since 2010 he has worked in 51 clinical trials of which, 36 were core studies and 15 were extension studies. He has been the Principal Investigator in 20 of them. These clinical trials were focused on schizophrenia, depressive and bipolar disorders, and Alzheimer's disease.

Robert Litman, MD, is the Medical Director and Principal Investigator at CBH Health. Following his residency at Massachusetts General Hospital he became a Senior Staff Fellow at the Experimental Therapeutics Branch of the National Institute of Mental Health (NIH), where he focused on the effects of atypical neuroleptics on biologic and genetic markers in schizophrenia, and on combination therapies with idazoxan. He has conducted over 300 clinical trials and has over 30 academic publications. He is currently an Associate Professor of Psychiatry at Georgetown University Medical School, and Fellow and Diplomate of the American Board of Psychiatry and Neurology.

Javier Martínez is the Director of the Medical Department at Laboratorios Farmacéutios Rovi, S.A. His academic background includes a Medicine and Surgery Degree and postgraduate degrees in Pharmaceutical Medicine and in Biostatistics and Business, all from the Universidad Complutense de Madrid. He has extensive experience in pharmaceutical medicine, especially in the preclinical and clinical development of drugs in several therapeutic areas. He has more than 30 years of experience in the pharmaceutical industry, is a professor in several master courses, and has authored/co-authored over 50 journal articles.

Lourdes Anta, MD, PhD, has a Degree in Biology, a PhD in Clinical Microbiology and a Masters on AIDS and Viral Hepatitis, all from the Universidad Complutense de Madrid. Since 2015 she has been a clinical scientist at the Medical Department of Laboratorios Farmacéuticos Rovi, S.A., where she is responsible for the scientific and medical aspects of clinical study protocols, and other scientific aspects related to the management of clinical trials, including for clinical trials of Risperidone ISM®. She has over 25 published academic articles and has been a peer reviewer for peer-reviewed journals.

Dieter Naber, MD, is Professor and Chairman of the Department of Psychiatry and Psychotherapy at the University Medical Center Hamburg-Eppendorf in Germany. He attended medical school at the University of Göttingen and the University of Bonn, followed by an internship in Internal Medicine, Surgery, and Biochemistry. Professor Naber is a member of several professional organisations, including the Collegium Internationale Psychopharmacologicum and the European College of Neuropsychopharmacology. He has published over 315 articles, 28 books and 140 chapters. His research interests include long-term effects of neuroleptic treatment, subjective effects of neuroleptics, the quality of life in psychiatric patients, and the therapeutic alliance.

Christoph Correll is a Professor of Psychiatry at The Zucker School of Medicine at Hofstra/Northwell in New York, the Head of Department of Child and Adolescent Psychiatry at the Charité University in Berlin, and is board-certified in General Psychiatry, and Child and Adolescent Psychiatry. His work focuses on the characterization and treatment of adults and youth with psychiatric disorders, clinical trials, psychopharmacology, comparative effectiveness and the risk–benefit evaluation of psychotropic medications. He has published over 700 academic articles and has been listed by Web of Science/Clarivate annually since 2014 as one of the most influential minds in psychiatry.

LONG-TERM EFFICACY AND SAFETY OF ONCE-MONTHLY RISPERIDONE ISM® IN THE TREATMENT OF SCHIZOPHRENIA: RESULTS FROM A 12-MONTH OPEN-LABEL EXTENSION STUDY

Yuriy Filts, Robert E. Litman, Javier Martínez, Lourdes Anta, Dieter Naber, Christoph U. Correll

SUPPLEMENTARY TABLES AND FIGURES

Supplementary Table 1. PANSS Total scores.

Visit Day Statistic	Unstable patients	Stabilized patients	Stable patients
Baseline			
n	55	119	41
Mean (SD)	82.3 (12.19)	70.0 (14.29)	60.3 (8.22)
Day 29			
n	55	113	40
Mean (SD)	74.3 (13.61)	66.7 (13.17)	59.7 (9.41)
Day 57			
n	54	107	40
Mean (SD)	68.3 (13.92)	64.5 (13.24)	59.9 (10.03)
Day 85			
n	50	104	38
Mean (SD)	63.9 (12.88)	63.4 (13.79)	59.2 (9.59)
Day 113			
n	49	102	37
Mean (SD)	62.2 (10.86)	61.9 (13.94)	59.0 (9.56)
Day 141			
n	48	101	36
Mean (SD)	61.0 (11.61)	62.4 (14.29)	59.3 (9.56)
Day 169			
n	44	98	35
Mean (SD)	60.6 (12.58)	61.6 (13.78)	61.1 (9.61)
Day 197			
n	43	95	35
Mean (SD)	60.1 (11.63)	59.9 (12.51)	57.9 (10.17)
Day 225			
n	43	95	35
Mean (SD)	59.0 (11.23)	59.0 (12.77)	58.2 (9.74)
Day 253			
n	43	94	35
Mean (SD)	58.4 (10.69)	59.8 (11.90)	57.0 (8.23)
Day 281			
n	43	93	34
Mean (SD)	58.5 (10.13)	60.6 (12.37)	58.0 (9.90)
Day 309			
n	42	90	34
Mean (SD)	57.5 (10.73)	59.5 (12.02)	57.4 (9.68)
Day 337			
n	42	89	33
Mean (SD)	57.8 (11.13)	58.9 (11.33)	55.4 (8.93)
Day 365			
n	41	87	33
Mean (SD)	58.7 (10.68)	57.6 (10.87)	57.0 (8.13)

PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.

Supplementary Table 2. CGI-S scores.

Visit Day Statistic	Unstable patients	Stabilized patients	Stable patients
Baseline			
n	55	119	41
Mean (SD)	4.1 (0.87)	3.4 (0.88)	2.8 (0.52)
Day 29			
n	55	113	40
Mean (SD)	3.7 (0.82)	3.2 (0.74)	2.8 (0.54)
Day 57			
n	54	107	40
Mean (SD)	3.3 (0.89)	3.1 (0.75)	2.9 (0.48)
Day 85			
n	50	104	38
Mean (SD)	3.0 (0.80)	3.0 (0.68)	2.8 (0.54)
Day 113			
n	49	102	37
Mean (SD)	2.9 (0.71)	2.9 (0.67)	2.8 (0.55)
Day 141			
n	48	101	36
Mean (SD)	2.9 (0.58)	3.0 (0.73)	2.8 (0.55)
Day 169			
n	44	98	35
Mean (SD)	2.8 (0.62)	2.9 (0.71)	2.8 (0.51)
Day 197			
n	43	95	35
Mean (SD)	2.8 (0.59)	2.9 (0.65)	2.7 (0.58)
Day 225			
n	43	95	35
Mean (SD)	2.8 (0.67)	2.8 (0.72)	2.7 (0.51)
Day 253			
n	43	94	35
Mean (SD)	2.7 (0.62)	2.8 (0.61)	2.7 (0.51)
Day 281			
n	43	93	34
Mean (SD)	2.8 (0.64)	2.9 (0.69)	2.7 (0.58)
Day 309			
n	42	90	34
Mean (SD)	2.7 (0.67)	2.9 (0.67)	2.7 (0.51)
Day 337			
n	42	89	33
Mean (SD)	2.8 (0.66)	2.8 (0.66)	2.7 (0.59)
Day 365			
n	41	87	33
Mean (SD)	2.8 (0.59)	2.8 (0.63)	2.7 (0.59)

CGI-S, Clinical Global Impression-Severity; SD, standard deviation.

Supplementary Table 3. Relapse rates.

	Unstable patients (N=55)	Stabilized patients (N=119)	Stable patients (N=41)	All patients (N=215)
Relapse, n (%), 95% CI*	3 (5.5) 1.1 to 15.1	14 (11.8) 6.6 to 19.0	6 (14.6) 5.6 to 29.2	23 (10.7) 6.9 to 15.6
Increase from baseline in PANSS, n (%)	0	10 (8.4)	4 (9.8)	14 (6.5)
Re-hospitalization for psychotic symptoms, n (%)	2 (3.6)	4 (3.4)	3 (7.3)	9 (4.2)
Use of adjunctive antipsychotics after stabilization, n (%)	1 (1.8)	5 (4.2)	3 (7.3)	9 (4.2)

* Clopper Pearson Exact CI.

PANSS, Positive and Negative Syndrome Scale; CI, confidence interval.

Supplementary Table 4. Summary of treatment-related TEAEs occurring in ≥ 2% of Risperidone ISM® patients.

Preferred Term	Risperidone ISM 75 mg (N=116)	Risperidone ISM 100 mg (N=99)	All Risperidone ISM (N=215)
	n (%)	n (%)	n (%)
Patients with at least one treatment-related TEAE	43 (37.1)	41 (41.4)	84 (39.1)
Akathisia	4 (3.4)	4 (4.0)	8 (3.7)
Asthenia	7 (6.0)	4 (4.0)	11 (5.1)
Dizziness	3 (2.6)	3 (3.0)	6 (2.8)
Headache	16 (13.8)	10 (10.1)	26 (12.1)
Hyperprolactinemia[a]	11 (9.5)	10 (10.1)	21 (9.8)
Insomnia	6 (5.2)	3 (3.0)	9 (4.2)
Weight increased	6 (5.2)	3 (3.0)	9 (4.2)

TEAE, Treatment-emergent Adverse Event.

Description of TEAEs is coded using MedDRA version 22.1.

[a] An increase in prolactin plasma levels was considered as an adverse event when any of the following criteria were present: Values above 1000 mIU/L for three consecutive determinations after randomization, although no clinical symptoms are present or Values above 530 mIU/L if clinical symptoms of hyperprolactinemia are present (e.g., headache, decreased libido, oligoamenorrhea).

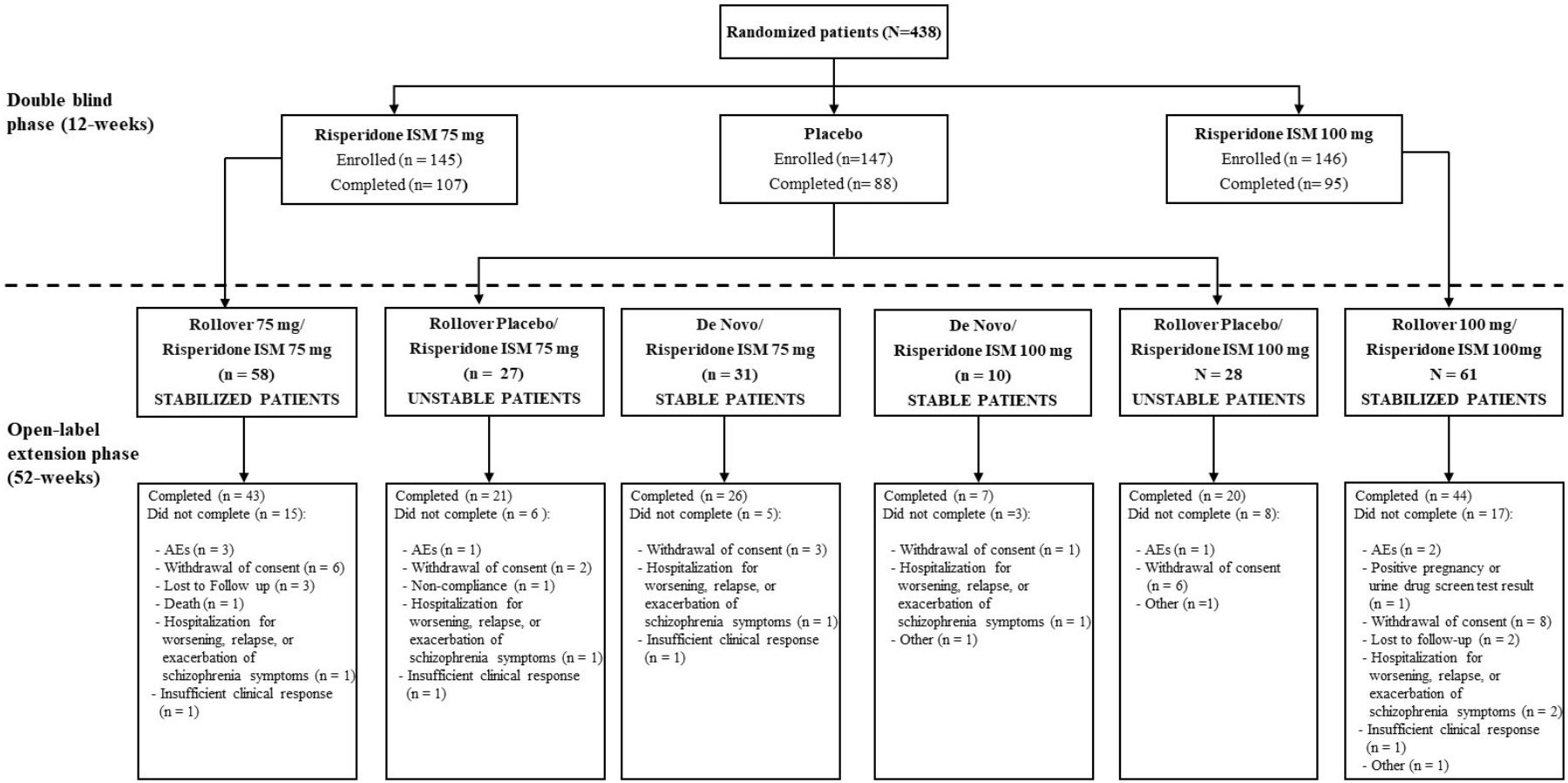
Supplementary Table 5. Additional safety outcomes: mean change from baseline to end of treatment.

Parameter	Risperidone ISM® 75 mg (N=116)	Risperidone ISM® 100 mg (N=99)	All Risperidone ISM® (N=215)
Glucose, mmol/L			
Baseline	5.25 (0.98)	5.31 (0.89)	5.28 (0.94)
Mean change (SD)	0.42 (1.98)	0.36 (1.96)	0.39 (1.97)
Cholesterol, mmol/L			
Baseline	4.67 (1.08)	4.67 (1.06)	4.67 (1.07)
Mean change (SD)	0.14 (0.96)	0.13 (0.94)	0.13 (0.95)
Bodyweight, Kg			
Baseline	79.6 (14.81)	79.4 (16.09)	79.5 (15.37)
Mean change (SD)	0.9 (5.14)	1.2 (3.09)	1.0 (4.35)
Prolactin, mIU/L			
Baseline	531.21 (645.44)	645.84 (645.66)	583.99 (646.57)
Mean change (SD)	110.33 (674.58)	235.11 (869.00)	167.71 (770.48)
Extrapyramidal symptoms scales			
AIMS, Mean (SD)	0.3 (1.73)	0.2 (1.07)	0.3 (1.47)
BARS, Mean (SD)	0.1 (0.38)	0.2 (0.64)	0.1 (0.52)
SAS, Mean (SD)	0.3 (1.06)	0.3 (0.76)	0.3 (0.93)
QT interval			
Baseline	380.4 (27.14)	377.3 (27.03)	379.0 (27.07)
Mean change (SD)	−1.1 (27.94)	1.8 (22.99)	0.2 (25.79)

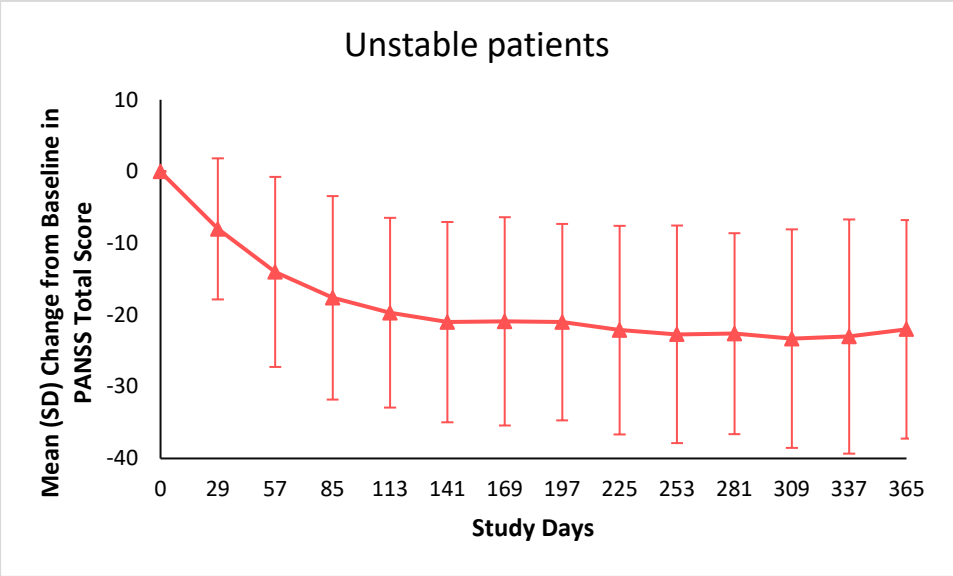
AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; SAS, Simpson-Angus Scale; SD, Standard Deviation.

SUPPLEMENTARY FIGURES

Supplementary Figure 1. Patient disposition

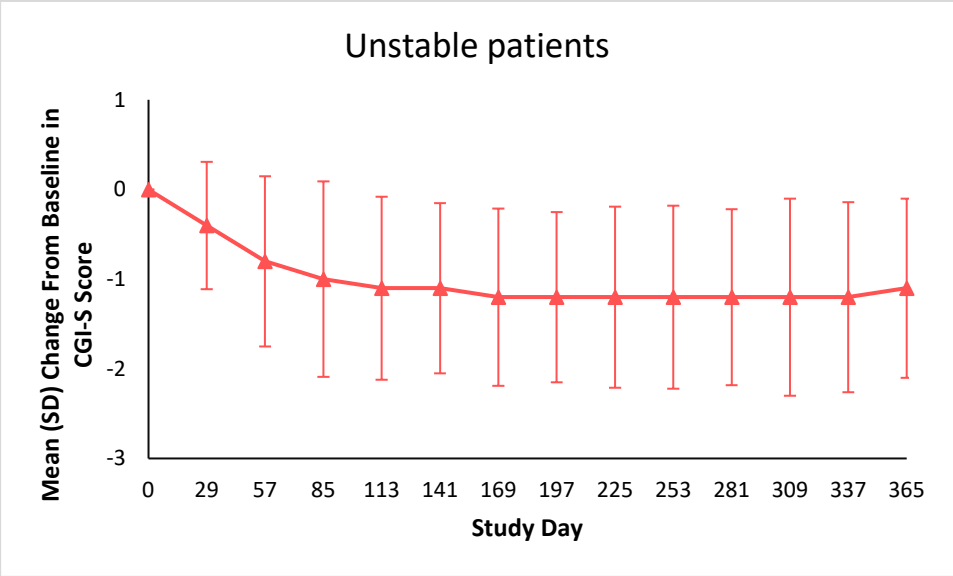


Supplementary Figure 2. Mean (SD) change from baseline in PANSS total score at each timepoint in unstable patients treated with Risperidone ISM® (pooled 75 and 100 mg).



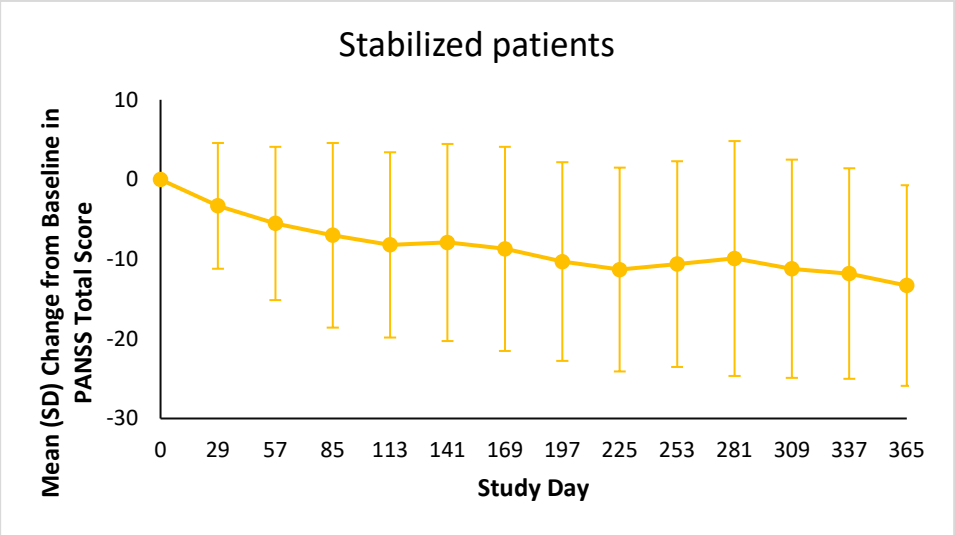
PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.

Supplementary Figure 3. Mean (SD) change from baseline in CGI-S score at each timepoint in unstable patients treated with Risperidone ISM® (pooled 75 and 100 mg).



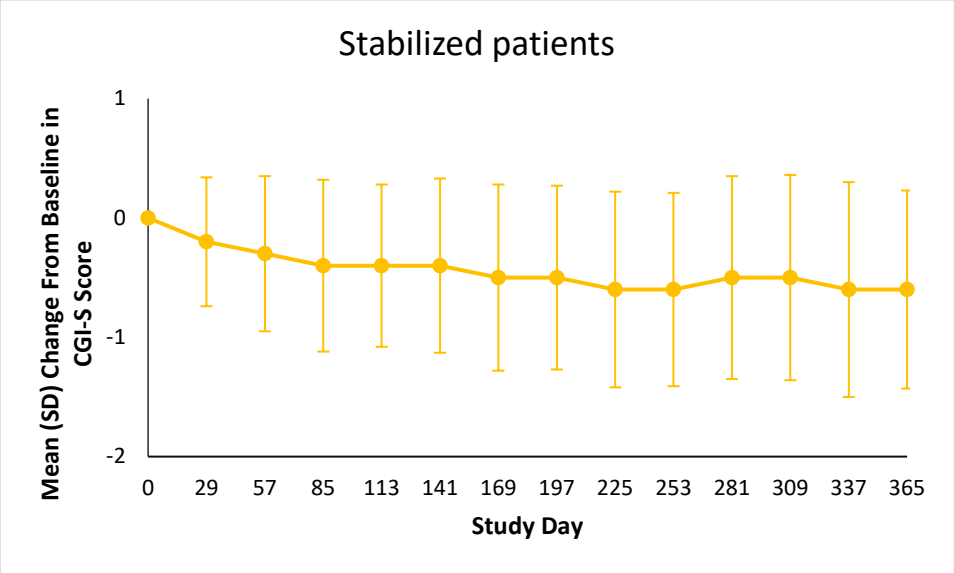
CGI-S, Clinical Global Impression-Severity; SD, standard deviation.

Supplementary Figure 4. Mean (SD) change from baseline in PANSS total score at each timepoint in stabilized patients treated with Risperidone ISM® (pooled 75 and 100 mg).



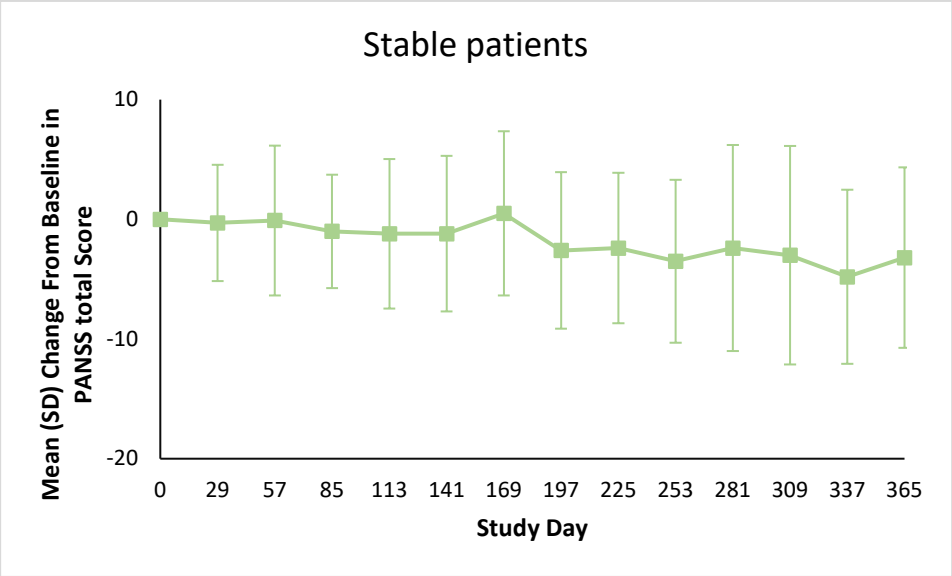
PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.

Supplementary Figure 5. Mean (SD) change from baseline in CGI-S at each timepoint in stabilized patients treated with Risperidone ISM® (pooled 75 and 100 mg).



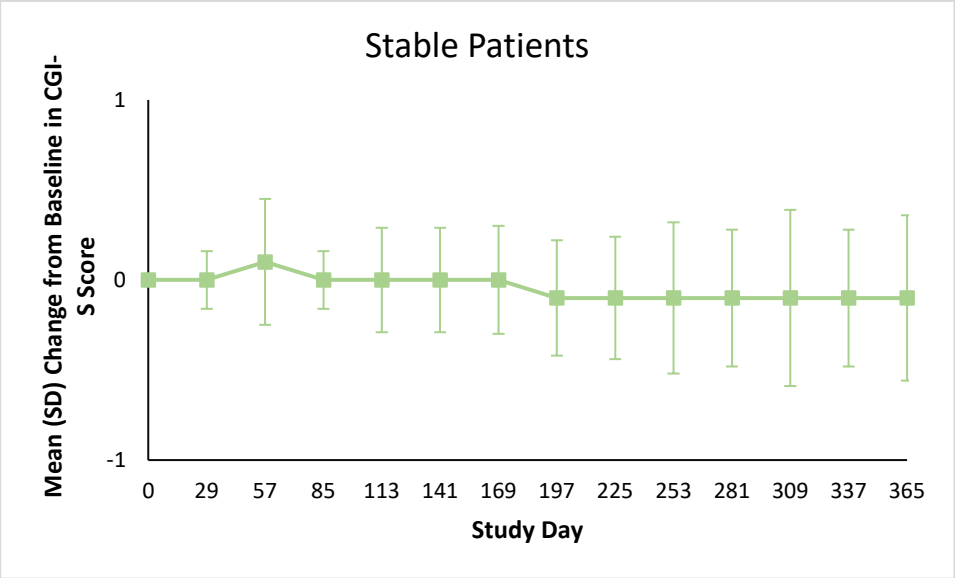
CGI-S, Clinical Global Impression-Severity; SD, standard deviation.

Supplementary Figure 6. Mean (SD) change from baseline in PANSS total score at each timepoint in stable patients treated with Risperidone ISM® (pooled 75 and 100 mg).



PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.

Supplementary Figure 7. Mean (SD) change from baseline in CGI-S at each timepoint in stable patients treated with Risperidone ISM® (pooled 75 and 100 mg).



CGI-S, Clinical Global Impression-Severity; SD, standard deviation.