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Risperidone-ISM® effectiveness and tolerability in acute schizophrenia patients hospitalised due to a relapse: results from an international, prospective, non-interventional evaluation (RESHAPE study)

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ORIGINAL INVESTIGATION

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Risperidone-ISM® effectiveness and tolerability in acute schizophrenia patients hospitalised due to a relapse: results from an international, prospective, non-interventional evaluation (RESHAPE study)

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ABSTRACT

Objective: To evaluate the effectiveness, time to discharge, functioning, and tolerability of Risperidone-ISM® in hospitalised patients with schizophrenia relapse.

Methods: Non-interventional, multicentre, prospective study of adults admitted for acute exacerbation of schizophrenia and treated with Risperidone-ISM®. Effectiveness was assessed using the Clinical Global Impression-Severity scale (CGI-S) and 6-item Positive and Negative Syndrome Scale (PANSS-6) at days 8 (FU1), 28 (FU2), and 56 (FV). Functioning was evaluated with the Personal and Social Performance scale (PSP), patient satisfaction with the Medication Satisfaction Questionnaire (MSQ). Admission/discharge data and adverse events were recorded.

Results: In 275 patients, significant reductions from baseline in CGI-S and PANSS-6 scores occurred as early as day 8, with continued improvement through day 56 (CGI-S: −1.4 and PANSS-6: −7.6; $p < 0.0001$), regardless of use of concomitant antipsychotics. Median discharge occurred 8 days after first Risperidone-ISM® injection. PSP improved by 17.6 points at day 28. No new/unexpected

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safety information was reported; 4% discontinued due to related adverse events. At final visit, 78% reported satisfaction with treatment, and therapeutic alliance improved in 89.4% of participants.
Conclusions: Risperidone-ISM® demonstrated rapid and sustained effectiveness, functional improvement, and favourable tolerability, enabling early stabilisation and discharge. Adding another antipsychotic provided no additional benefits. Results support Risperidone-ISM® for treating acute schizophrenia relapse in real-world settings.

Introduction

Non-adherence to antipsychotics is a significant problem for many patients with schizophrenia (Marcus et al. 2015). Rates of poor adherence reported in many studies are as high as 50% (García et al. 2016; Greene et al. 2018), and patient characteristics, including younger age, substance abuse, low level of education, poor therapeutic alliance, etc., have been associated with non-adherence (García et al. 2016). Antipsychotic discontinuation after an acute episode or intermittent use during maintenance treatment is also associated with an increased risk of symptom worsening or relapse (Takeuchi et al. 2012) and increased suicide risk (Pompili 2019), which is the major cause of premature death in people living with schizophrenia (Pompili et al. 2005). Indeed, poor adherence has been associated with relapses and worsening of long-term functional and mental health outcomes (Keith and Kane 2003; Ascher-Svanum et al. 2006; Kane et al. 2013b), as well as mortality (Correll et al. 2025). Therefore, treatments delivering effectiveness and good tolerability as well as adherence are essential to ensure robust patient functioning and reduce the risk of recurrent relapses and hospitalisations (Correll et al. 2025a).

Long-acting injectable antipsychotics (LAIs) are recommended by most evidence-based clinical guidelines for patients who need maintenance treatment and explicitly prefer them over oral antipsychotics, and in patients with multiple relapses who have a known history of non-adherence (Heres et al. 2014; Correll et al. 2022). However, LAIs are likely to provide benefits beyond patients with a history of poor treatment adherence (Correll et al. 2016, 2025b). In fact, LAI use has been associated with an ~30% lower risk of mortality compared with oral antipsychotic agents (Taipale et al. 2018). LAIs have further demonstrated an important role in symptom reduction and relapse prevention in randomised clinical trials (RCTs) (Kishimoto et al. 2021), although there are several limitations inherent to RCTs and their clinical effectiveness should also be evaluated in real-world clinical practice to maximise external validity of the results (Kane et al. 2013a; Kishimoto et al. 2014). In real-world settings, LAIs have been associated with a 20–30% lower risk of readmission during treatment than the equivalent oral formulation (Kishimoto et al. 2014; Kim et al. 2020). Nonetheless, despite currently available second-generation LAIs, some unmet clinical needs remain, e.g. the need for loading doses, booster injections, or oral co-treatment for 2–3 weeks to achieve therapeutic drug levels when starting treatment with a LAI (Correll et al. 2021; Højlund and Correll 2023).

In the case of patients with an acute exacerbation of schizophrenia, it is commonly accepted in usual clinical practice, as treatment guidelines recommend, that pharmacological treatment must be promptly initiated with rapid titration to reach the target therapeutic dose as soon as possible and to ensure tolerability, especially if a LAI is planned (Hasan et al. 2013; Vadiei et al. 2020). Furthermore, an important issue in schizophrenia care is the gap between in-hospital treatment for an acute episode and the transition to outpatients after discharge, which represents a time of particularly high vulnerability for non-adherence (Tiihonen et al. 2011). The observation that LAIs reduce symptom severity but thereafter also relapse risk in acutely ill patients suggests that these agents provide an important strategy to help bridge this gap and ensure that patients leave the hospital with effective antipsychotic coverage (Correll et al. 2016).

Since long-term maintenance antipsychotic treatment is the goal in patients with schizophrenia (Correll et al. 2018, 2022), it is important to take into account the long-term safety profile of the chosen antipsychotic and to build a therapeutic alliance with the patient and their family or caregivers as an important element that should be included in the management. (Thomas et al. 2009).

Risperidone-ISM® is an intramuscular (IM) LAI formulation of risperidone (Schoretsanitis and Correll 2025) which obtained marketing authorisation in the EU after completing a comprehensive clinical program (Llaudó et al. 2016; Anta et al. 2018; Correll et al. 2020; Walling et al. 2021; Filts et al. 2022). This formulation uses the ISM (*in situ* microparticles) technology, which is based on a solid and stable polymeric matrix system

that *in situ* entraps risperidone after the intramuscular (IM) injection. Accordingly, Risperidone-ISM® is reconstituted to an injectable suspension that precipitates *in situ* (inside the body) after IM injection, resulting in the formation of a small matrix, by solvent diffusion to body fluids. This matrix biodegrades slowly, providing a sustained and controlled release of drug for up to 28 days.

Risperidone-ISM® has a distinctive pharmacological profile (Schoretsanitis and Correll 2025) providing a rapid onset of action, allowing once monthly (every 28 days) injection that provides immediate and sustained plasma levels without the need for oral antipsychotic supplementation and/or loading doses or a booster injection (Correll et al. 2020; Álamo 2022; Laveille et al. 2024). This unique pharmacokinetics and dose used also allows Risperidone-ISM® to achieve an optimal D2 receptor occupancy between 65 and 80% from day 1, which is related with adequate efficacy and minimal adverse events (Snoeck et al. 2025). In addition, Risperidone-ISM® demonstrated an improvement in quality of life and functioning in schizophrenia patients, both in the short term, when an acute exacerbation had recently occurred, and during long-term maintenance treatment (Litman et al. 2023).

Results from RCTs are the gold standard for demonstrating efficacy and safety of new antipsychotics, but it is also important to study the effectiveness and tolerability in the real-world hospital setting, and to evaluate the way patients with schizophrenia are managed by clinicians under usual clinical practice conditions. Thus, the aim of this study was to assess the effectiveness of Risperidone-ISM® in routine clinical practice in acute patients hospitalised due to a schizophrenia relapse, evaluate the time to discharge, as well as to analyse social functioning and tolerability. We hypothesised that Risperidone-ISM® would overall perform similarly in patients with less restrictive in- and exclusion criteria compared to those agreeing to be part of a double-blind, placebo-controlled trial that formed the basis for regulatory approval of Risperidone-ISM® for schizophrenia.

Materials and methods

Design

RESHAPE was a non-interventional, multicentre, prospective study conducted between 10/2022 and 03/2025 at 76 sites from five European countries in adult patients diagnosed with schizophrenia who were admitted to a psychiatric inpatient unit (public or private institution) after suffering an acute exacerbation and who were subsequently treated with Risperidone-ISM®, according to routine clinical practice. The study was scheduled across 5 visits (Supplementary Figure 1): Baseline Visit (BV), was conducted within the first 48 h after administration of the first Risperidone-ISM® injection, while the patient was hospitalised. During this visit written Informed Consent was obtained, and eligibility was confirmed by assessment of inclusion and exclusion criteria. The BV marked the start of the prospective observation period. Three follow-up visits were scheduled at day 8 (FU1), 28 days after the first Risperidone-ISM® injection (FU2), and a final visit 28 days after the second injection (FV). In addition, another visit was scheduled at the time of the patient's discharge from the hospital (DV).

Patients

Eligible participants were 18 years or older with a clinical diagnosis of schizophrenia and admitted to a psychiatric inpatient unit due to an acute exacerbation. Participants had started treatment with Risperidone-ISM® within the previous 48 h before consent to participation in the RESHAPE study. Exclusion criteria were pregnancy or breast-feeding, or a diagnosis of schizoaffective or bipolar disorder, mental retardation or other cognitive and neurodevelopmental disorders. Participants with substance-induced psychosis or psychosis during intoxication (patients with comorbid substance abuse/dependence were allowed) and those with a serious and unstable medical condition, forensic, or with any contraindication mentioned in the Summary of Product Characteristics (SmPC) of Risperidone were also excluded, as well as participants unable to answer the study questionnaires and those on current treatment with clozapine or any LAI antipsychotic.

Treatment

Risperidone-ISM® 75 or 100 mg was administered intramuscularly (gluteal or deltoid) on a monthly basis (every 28 days) under routine clinical practice conditions, according to the terms of the marketing authorisation and the approved SmPC.

Study assessments

The effectiveness of Risperidone-ISM® was assessed by two validated instruments over the follow-up study period: the Clinical Global Impression-Severity of Illness scale (CGI-S) (Guy 1976), and the 6-item Positive and

Negative Syndrome Scale (PANSS-6) (Østergaard et al. 2016).

Additional assessments were performed through the follow-up study period, including the Personal and Social Performance scale (PSP) (Morosini et al. 2000) for patient functioning; duration of hospitalisation (time from admission to discharge [a predefined list of clinical discharge criteria was provided to enhance consistency across sites]; Time from admission to first Risperidone-ISM® administration and time from first Risperidone-ISM® administration to discharge were also analysed); presence of comorbidities with the *Charlson Comorbidity Index* (CCI) (Charlson et al. 1987); patient satisfaction with treatment with the Medication Satisfaction Questionnaire (MSQ) (Kalali 1999; Vernon et al. 2010); contribution of the treatment to therapeutic alliance (through the study-specific structured question: 'Has the treatment with a long-acting injectable antipsychotic without the need for initial oral cotreatment, loading dose or a booster injection, like Risperidone ISM®, contributed to build/improve the therapeutic alliance with your patient? Yes/no'; and the use of concomitant medications.

Finally, safety and tolerability were assessed by recording spontaneously reported adverse events (AEs), treatment-related AEs (TRAEs), and AEs/TRAEs leading to treatment discontinuation. Tolerability domains such as metabolic parameters, extrapyramidal symptoms, and prolactin-related effects were not systematically assessed beyond reported adverse events, in line with the observational nature of the study.

Statistical analysis

All analyses were performed using SAS® Guide Enterprise 7.15 or higher (SAS Institute, Inc., Cary, North Carolina) or using R version 4.1.1 or higher and R studio version 1.4.1717 or higher.

The initial sample size calculation aimed to detect a mean reduction from baseline in CGI-S of 0.1 ± 1.0, assuming a power of 0.80 and a significance level of 0.05. Accounting for an anticipated 20% dropout rate, the planned sample size was 1,198 patients. However, this estimate was based on an extremely small effect size compared to previous results with Risperidone-ISM®, which showed a CGI-S reduction of 0.5 ± 0.7 within the first 8 days of treatment. Given the longer-than-expected recruitment period (mainly due to administrative delays) and preliminary data indicating a mean change of 1.2 ± 1.3, the sponsor re-evaluated the required sample size. The revised calculation considered the need to analyse primary and secondary effectiveness variables in the overall population as well as in pre-specified subgroups, adjusting for their estimated proportions and an increased expected dropout rate of 35%. The final sample size was set at ~272 patients, ensuring sufficient power (nearly 100%) for these analyses (unadjusted for multiple comparisons).

Changes from baseline (CFB) to endpoint in CGI-S scores as the primary outcome were assessed using the Wilcoxon-signed rank test. All statistical tests were two-tailed with alpha = 0.05. The same approach applied to the subgroup analysis of patients 'markedly ill' (CGI-S = 5) or higher, as well as those with CGI-S scores ≤4 (moderately ill).

CFB in PANSS-6 and PSP were also analysed using Student *t*-test for paired data or Wilcoxon-signed rank test, depending on whether the data were normally distributed.

The duration of hospitalisation, measured as time from admission/first Risperidone-ISM® dose to discharge, was analysed using Kaplan–Meier survival curve estimates, describing median and interquartile range (IQR).

To determine whether the use of concomitant antipsychotics had a statistically significant effect on the differences observed between baseline and endpoint values in each period, a mixed regression adjusted model was built with CGI-S scores as the dependent variable, and time point (start or end of period), use of concomitant antipsychotics, and the interaction between the last two as independent variables.

Continuous variables were reported as mean ± standard deviation (*SD*), or median and IQR values. Categorical variables were summarised as number and proportion of the total study population, and by subgroups. The number of valid and missing values were reported for all variables. Medical history and all AE verbatim terms were recorded and coded using the Medical Dictionary for Regulatory Activities (MedDRA v27.1).

The full analysis set contained all enrolled participants who meet all selection criteria. The Outcome analysis set was defined as all subjects who had provided written Informed Consent, had at least one post-baseline visit and who received at least one injection of Risperidone-ISM® in the inpatient unit.

Ethical and regulatory aspects

The study followed the applicable European and local regulations and the Good Pharmacoepidemiology Practices (GPP) guidelines (Epstein and International Society of Pharmacoepidemiology 2005) for non-interventional studies, as well as the Declaration of

Helsinki and its amendments. Accordingly, the clinical decision to start treatment with Risperidone-ISM® was part of routine clinical practice, independent of deliberations regarding the possibility of participating in this study and before the participant provided the informed consent. The protocol, amendments, and informed consent were approved by the corresponding Ethics Committees, and written informed consent was obtained from all subjects before study participation.

From each participating country, a National Steering Committee (SC) was established to ensure the scientific validity of the study, provide expert advice to the site investigators and the sponsor, and participate in the dissemination and publication of the study results.

This study was registered at ClinicalTrials.gov [NCT05480046].

Results

Altogether, 275 participants were enrolled in the study. Demographic and baseline characteristics are summarised in Table 1. Most of the patients were men (70%), with a mean age of 42 years, mean BMI of 26 kg/m^2, and predominantly White race (79%) who had experienced a mean of 2.4 (2.7) relapses within the last 2 years. Thirty-four percent of patients presented with dual diagnosis (comorbid abuse/dependence of substances), and the mean Charlson Comorbidity Index (CCI) at baseline was 0.64 ± 0.99. The mean (*SD*) CGI-S, PANSS-6, and PSP scores at baseline were 4.7 (1.1), 21.9 (6.4), and 37.6 (18.3), respectively (Table 1). The median time from the first dose of Risperidone ISM® to BV was 1 (IQR = 0; 1) day.

Seventy percent of participants completed all the study visits. The reasons for early termination were lost to follow-up (79%), patient's withdrawal of consent (7%), switch to another antipsychotic treatment (6%), physician decision (5%), and other reasons, such as worsening of schizophrenia, death, or unknown (3%). A descriptive analysis of baseline demographic characteristics, clinical characteristics, and clinical outcomes comparing study completers and non-completers showed that the two groups had similar profiles across all analysed variables (Supplementary Table 1).

At baseline, the majority of participants, 189 (69.2%), had a prior history of treatment with risperidone, while 84 (30.8%) were risperidone-naïve.

Poor adherence to treatment was the main trigger of the psychotic relapse, noted in 65.9% of the included patients (Supplementary Table 2), with poor or absent insight (59.8%) and poor therapeutic alliance (56.3%) being the most frequent potential reasons for poor adherence (Supplementary Table 3). The leading cause for hospitalisation was severe positive symptoms (80.7%) (Supplementary Table 4).

Table 1. Baseline demographic and illness characteristics.

Baseline parameters	*N* = 275
Age (years)	
N	275
Mean (*SD*)	41.9 (12.8)
Sex, *N* (%)	
Male	192 (69.8)
Female	83 (30.2)
Race, *N* (%)	
White Caucasian and/or European Descent	217 (78.9)
Middle Eastern and/or North African Descent	20 (7.3)
Black and/or Sub-Saharan African Descent	14 (5.1)
Central and/or South American Descent	13 (4.7)
Central, South, and/or East Asian Descent	6 (2.2)
Other	5 (1.8)
Country, *N* (%)	
Germany	118 (43.0)
Spain	93 (33.8)
Italy	47 (17.0)
Portugal	16 (5.8)
UK	1 (0.4)
BMI (kg/m^2)	
N	225
Mean (*SD*)	26.4 (6.0)
Time since schizophrenia diagnosis (years)	
N	211
Mean (*SD*)	11.2 (11.0)
Relapses (within the last 2 years)	
Mean (*SD*)	2.4 (2.7)
Relapses requiring hospitalisation (within the last 2 years)	
Mean (*SD*)	1.9 (2.2)
Patients with dual diagnosis*	
N (%)	92 (34.0)
CGI-S score	
N	275
Mean (*SD*)	4.7 (1.1)
PANSS-6 total score	
N	275
Mean (*SD*)	21.9 (6.4)
PSP score	
N	261
Mean (*SD*)	37.6 (18.3)

Abbreviations: BMI, body mass index; CGI-S, Clinical Global Impression-Severity of Illness scale; CI, confidence interval; PANSS, Positive and Negative Syndrome Scale; PSP, Personal and Social Performance scale; *SD*, standard deviation.
Note: *Dual diagnosis as defined by heavy-drinking and/or consumption of any recreational drug.

Medication

Eighty-one (29.5%) participants received antipsychotic medication within the month before hospital admission. The most commonly used antipsychotic was oral risperidone (14.5%). In contrast, 232 participants (84.4%) did receive antipsychotic medication between admission and the first dose of Risperidone-ISM®, with oral risperidone being the most frequently used antipsychotic (Table 2), ranging regarding the daily

Table 2. Previous antipsychotic medications.

Prior antipsychotics (within 1 month before admission) *N* (%)	81 (29.5)
Oral risperidone	40 (14.5)
Olanzapine	22 (8)
Aripiprazole	7 (2.6)
Quetiapine fumarate	6 (2.2)
Other antipsychotics*	32 (11.6)
Prior antipsychotics (between admission and first injection of Risperidone ISM) *N* (%)	232 (84.4)
Oral risperidone	207 (75.3)
Olanzapine	56 (20.4)
Quetiapine fumarate	20 (7.3)
Quetiapine	19 (6.9)
Aripiprazole	17 (6.2)
Haloperidol	15 (5.5)
Other antipsychotics*	71 (25.8)

Note: *<5% use reported.

Table 3. Concomitant antipsychotic medications.

Antipsychotic	From first Risperidone ISM dose to discharge *N* (%)	After discharge *N* (%)
Total antipsychotics	198 (72.0)	102 (41.6)
Oral risperidone	129 (46.9)	28 (10.2)
Olanzapine	54 (19.6)	28 (10.2)
Quetiapine	22 (8.0)	20 (7.3)
Quetiapine fumarate	19 (6.9)	8 (2.9)
Aripiprazole	15 (5.5)	14 (5.1)
Other antipsychotics*	81 (29.4)	50 (18.1)

Notes: 207 (75.3%) patients received antipsychotics concomitantly along the study; *<5% use reported.

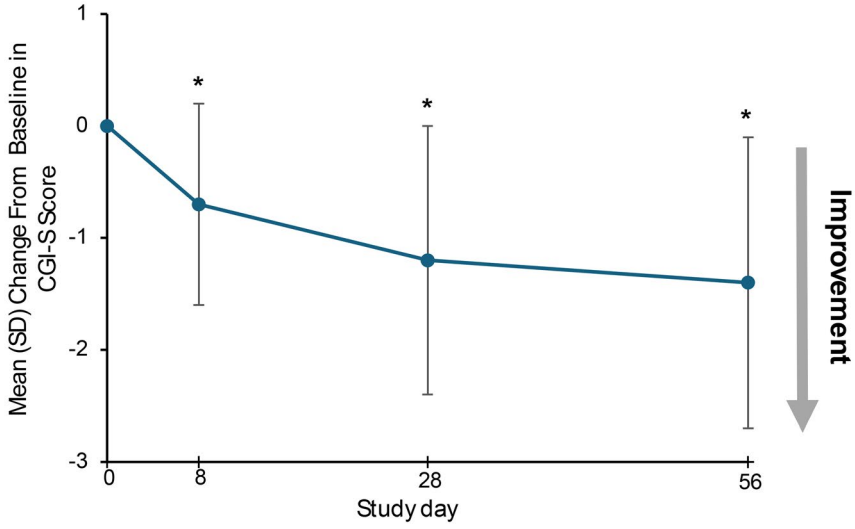
doses from 1 mg up to 12 mg before initiation of Risperidone-ISM®.

Altogether, 207 (75.3%) patients received oral antipsychotics concomitantly with Risperidone-ISM® during the study period. Specifically, before the discharge visit, 198 (72.0%) patients received concomitant antipsychotic medications, with oral risperidone being the most common (46.9%). After the discharge visit, 102 (41.6%) patients were also receiving antipsychotics, with 28 (10.2%) of them being on oral risperidone (Table 3). Besides this, 163 (59.3%) patients were treated with other psychotropic medications during the study, with lorazepam being the most common one (21.5%).

Additionally, 7 patients (2.5%) received concomitantly anticholinergic agents, and 1 (0.4%) beta-blocking agents.

CGI-S

The mean CGI-S score decreased from baseline to all the study visits, reporting a mean (SD) CGI-S score of 3.2 (1.2) on the final visit (Figure 1). Furthermore, the mean CFB was statistically significant ($p < 0.0001$) at all the study visits, starting as early as 8 days after the first injection of Risperidone-ISM® with a reduction of



	BV N = 275	FU1 (Day 8) N = 256	FU2 (Day 28) N = 218	FV (Day 56) N = 185
Mean (SD) CGI-S score	4.7 (1.1)	4.0 (1.1)	3.5 (1.1)	3.2 (1.2)
Mean (SD) CFB [%] in CGI-S score	-	-0.7 (0.9) [14.9 %]	-1.2 (1.2) [25.5%]	-1.4 (1.3) [31.9%]

Figure 1. Mean change from baseline in CGI-S score.
Notes: The error bars represent standard deviation (*SD*). *p*-Values are calculated for the difference between each visit and the baseline visit (*$p < 0.0001$). Abbreviations: CFB, change from baseline; CGI-S, Clinical Global Impression-Severity scale (scale range: 1–7); BV, baseline visit; FU1, follow-up visit 1 (day 8); FU2, follow-up visit 2 (day 28); FV, final visit (day 56).

14.9% and decreasing up to 31.9% at the end of the study (Figure 1).

In the subgroup analysis of most severely ill patients (CGI-S ≥ 5), CGI-S scores significantly improved ($p < 0.0001$) from first injection onwards. The proportion of these most severely ill patients decreased from 58.2% at baseline to approximately half after 8 days and to 11.3% at final visit (Supplementary Figure 2 and Supplementary Table 5). Conversely, in the less severely ill patients (CGI-S ≤ 4), CGI-S scores also significantly improved ($p < 0.0001$) from first injection onwards, and the proportion of patients not more than moderately ill increased significantly from 41.9 to 88.7%.

There were no statistically significant differences in CGI-S mean change from baseline at each visit between patients receiving Risperidone-ISM® as monotherapy and those who received other oral antipsychotics concomitantly during the study (Supplementary Figure 3).

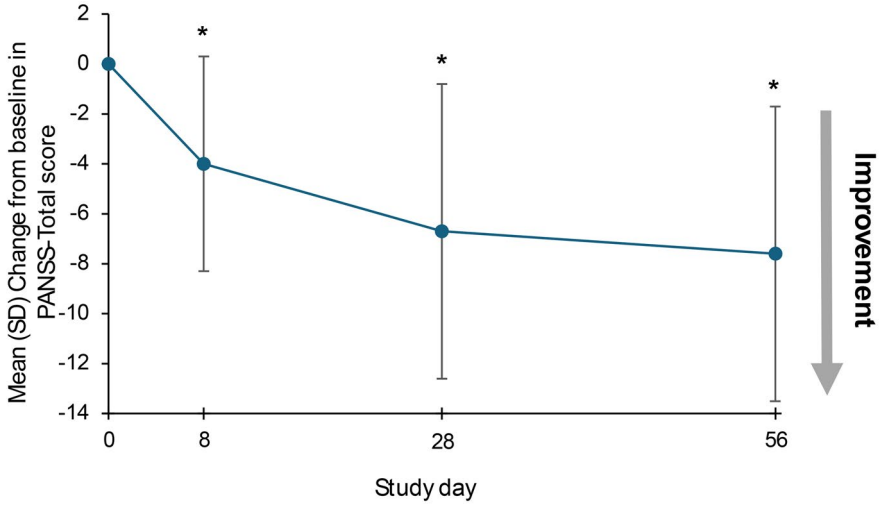
PANSS-6

The mean PANSS-6 total score also decreased from baseline to all the study visits. At final visit, the mean (SD) PANSS-6 total score was 14.0 (5.6). In addition, there was a statistically significant reduction on mean CFB at all the study visits (Figure 2), also seen as early as 8 days after starting Risperidone-ISM® with a decrease of 17.4% and increasing to 36.1% decrease from baseline at the final visit. A progressive decrease was also observed in both positive and negative subscale scores of the PANSS-6, with statistically significant reductions ($p < 0.0001$) at each visit (Supplementary Figure 4).

There were no statistically significant differences in PANSS-6 mean CFB at each visit between patients receiving Risperidone-ISM® as monotherapy compared to those who were receiving other oral antipsychotics concomitantly (Supplementary Figure 5).

Duration of hospitalisation

The median time from admission to discharge was 22 (IQR = 14.0; 35.0) days, being 19 (IQR = 12.0; 31.0) days for patients receiving Risperidone-ISM® as monotherapy and 23 (IQR = 14.0; 36.5) days for those receiving concomitantly other antipsychotics. Specifically,



	BV N = 275	FU1 (Day 8) N = 256	FU2 (Day 28) N = 218	FV (Day 56) N = 185
Mean (SD) PANSS-6 score	21.9 (6.4)	18.1 (5.7)	15.3 (5.5)	14.0 (5.6)
Mean (SD) CFB [%] in PANSS-6 score	-	-4.0 (4.3) [17.4%]	-6.7 (5.9) [30.1%]	-7.6 (5.9) [36.1%]

Figure 2. PANSS-6 mean change from baseline at each study visit.
Notes: The error bars represent standard deviation (*SD*). *p*-Values are calculated for the difference between each visit and the baseline visit (*$p < 0.0001$). Abbreviations: CFB, change from baseline; BV, baseline visit; FU1, follow-up visit 1 (day 8); FU2, follow-up visit 2 (day 28); FV, final visit (day 56). PANSS-6, Positive and Negative Syndrome Scale of 6 items (scale range: 6–42).

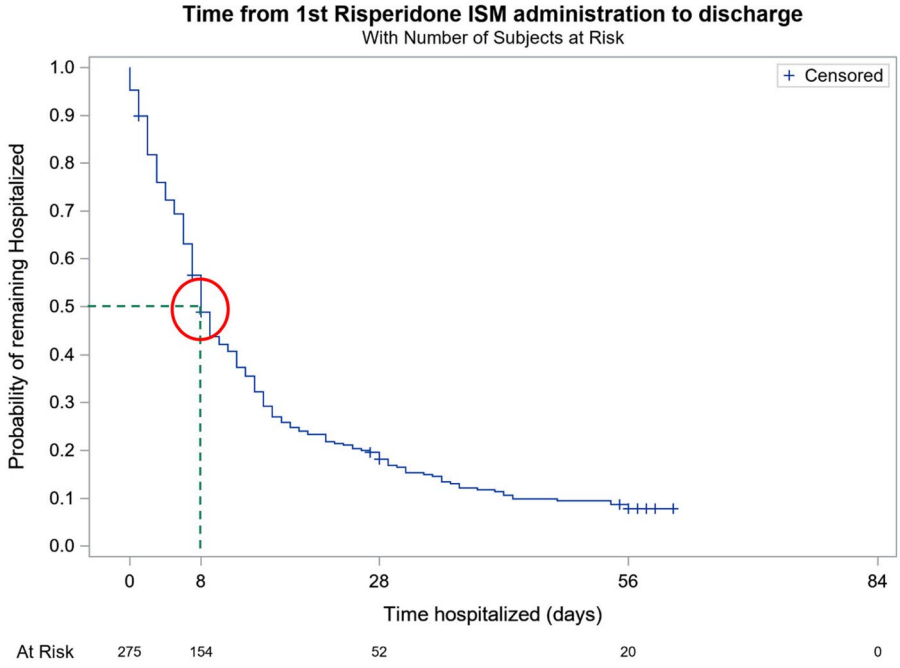


Figure 3. Time from first Risperidone ISM administration to discharge.
Notes: At risk indicates the number of subjects still hospitalised at each time point. Y axis indicates the proportion of patients who have not been discharged; Median time to discharge is 8 days (interquartile range: 3.0; 15.0).
Abbreviations: 1st, first.

the median time from first Risperidone-ISM® administration to discharge was 8 (IQR = 3.0; 15.0) days (Figure 3), being 6 (IQR = 2.0; 12.0) days for patients receiving Risperidone-ISM® as monotherapy and 8 (IQR = 4.0; 15.0) days for those receiving concomitant antipsychotic medication.

The main reason for discharge was 'the patient no longer has delusions and hallucinations, or they do but do not significantly interfere with functioning' (Supplementary Table 6).

PSP

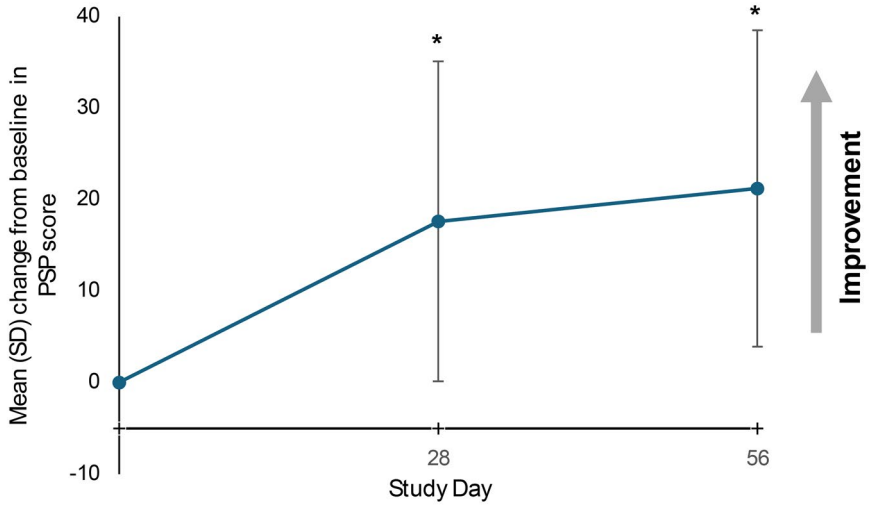
At baseline, the mean (*SD*) PSP total score was 37.6 (18.3) (Table 1). Throughout the study, participants showed improvements in the PSP total score. From baseline, a statistically significant improvement ($p < 0.0001$) in functioning of 17.6 points (48.4%) was observed after 28 days of the first injection and improved further statistically ($p < 0.0001$) up to 21.2 points (59.0%) at the last study visit (Figure 4).

Improvement from baseline was also observed in all domains of the PSP based on clinicians' assessment. In addition, according to the severity classification for each PSP domain at the final visit compared to baseline, patients treated with Risperidone-ISM® showed a decrease in the 'marked', 'severe', and 'very severe' rating in all domains. Moreover, the proportion of patients with 'absent' impairment rating in all domains increased from baseline to final visit (Supplementary Figures 6–9). Specifically, the proportion of patients with 'absent' impairment rating in 'self-care' and 'disturbing and aggressive behaviours' increased from baseline visit (10.8 and 30.1%, respectively) to final visit (41.9 and 69.4%, respectively), while the proportion of patients with a 'very severe' rating in both domains decreased from baseline visit (3.5 and 6.6%, respectively) to final visit (0.6 and 0%, respectively) (Supplementary Figures 7 and 9).

Likewise, as observed for both effectiveness endpoints, there were no statistically significant differences in the PSP mean CFB at each visit between patients receiving Risperidone-ISM® as antipsychotic monotherapy *versus* those who were receiving other antipsychotics concomitantly (Supplementary Figure 10).

MSQ (patient's treatment satisfaction)

Patient treatment satisfaction measured by the MSQ increased from first injection onwards. The proportion of patients who were 'extremely satisfied', 'very satisfied', or 'somewhat satisfied' increased from 45% (referring to their prior antipsychotic medication) to 78% after the second injection of Risperidone-ISM®. Conversely, the number of patients who were 'somewhat dissatisfied', 'very dissatisfied', or 'extremely dissatisfied' decreased from 31 to 12% (Figure 5).



	BV N = 275	FU2 (Day 28) N = 218	FV (Day 56) N = 185
Mean (SD) PSP score	37.6 (18.3)	55.8 (18.7)	59.8 (18.3)
Mean (SD) CFB [%] in PSP score	-	17.6 (17.5) [48.4 %]	21.2 (17.3) [59.0 %]

Figure 4. Mean change from baseline in PSP score.
Notes: The error bars represent standard deviation (*SD*). *p*-Values are calculated for the difference between each visit and the baseline visit (*$p < 0.0001$). Mean (*SD*) PSP score at baseline was 37.6 (18.3). Higher PSP scores indicate a better social functioning.
Abbreviations: BV, baseline visit; FU2, Follow-up visit 2 (day 28); FV, Final visit (day 56); PSP, Personal and Social Performance scale (scale range: 1–100).

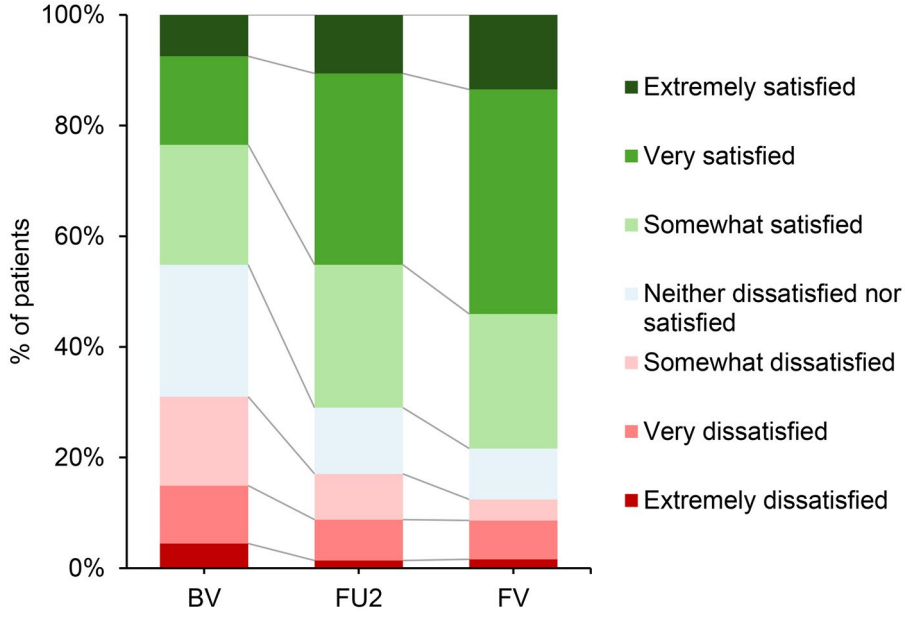


Figure 5. Patient satisfaction with treatment at each study visit.
Notes: Distribution of MSQ scores for each visit. BV data refer to satisfaction with previous medication. Numbers indicate the percentage of patients in each category.
Abbreviations: BV, baseline visit; FU2, Follow-up visit 2 (day 28); FV, Final visit (day 56); MSQ, Medication Satisfaction Questionnaire.

Contribution to therapeutic alliance

According to clinician assessment, treatment with Risperidone-ISM® contributed to improving the therapeutic alliance in 89.4% of participants (Supplementary Figure 11).

Safety and tolerability

Overall, 71 (25.8%) participants experienced at least one AE. Among these AEs, 46 (16.7%) were considered related to the study treatment (Supplementary Table 7). Most of the reported TRAEs were mild (45.8%) or moderate (47.2%), and the most frequent individual TRAEs were weight increase (2.6%) and injection site pain (2.2%).

Serious AEs were reported in 20 (7.3%) patients, and 6 (2.2%) were considered related to the study drug (one exacerbation of schizophrenia, one torticollis, two psychosis relapses, one QT prolongation, one galactorrhoea, and one hyperprolactinaemia—one patient suffered two serious TRAEs). In addition, one patient died before the final visit of the study for unknown reasons and the investigator considered it not related to the study drug.

Fourteen (5.1%) patients reported at least one AE leading to treatment discontinuation, with 11 (4.0%) being rated as related to study treatment. No treatment discontinuations due to increased body weight were reported (Table 4). Fewer patients experienced AEs among patients receiving Risperidone-ISM® as monotherapy (16.2%) compared to those receiving other antipsychotics concomitantly (29.0%) (Supplementary Table 8).

Table 4. Summary of treatment-related adverse events: overall incidence and leading to study drug discontinuation.

TRAEs, preferred term	Overall incidence *N* (%)	Leading to discontinuation *N* (%)
Patients with at least one TRAE	–	11 (4.0)
Akathisia	2 (0.7)	1 (0.4)
Bradykinesia	1 (0.4)	1 (0.4)
Dyskinesia	1 (0.4)	1 (0.4)
Fatigue	5 (1.8)	1 (0.4)
Headache	1 (0.4)	1 (0.4)
Injection site swelling	1 (0.4)	1 (0.4)
Psychotic disorder	2 (0.7)	1 (0.4)
Restlessness	1 (0.4)	1 (0.4)
Salivary hypersecretion	3 (1.1)	1 (0.4)
Schizophrenia	1 (0.4)	1 (0.4)
Sedation	3 (1.1)	1 (0.4)
Sexual dysfunction	3 (1.1)	2 (0.7)

Abbreviation: TRAE, treatment-related adverse event.
Notes: $N = 275$. There was one participant in which the investigator mentioned two adverse events as the reason for discontinuation and another participant with two reported adverse events without the investigator determining the main event that led to discontinuation. Description of TRAEs is coded using MedDRA version 27.1.

Discussion

The results from the present study provide real-life data that confirm the effectiveness of Risperidone-ISM® in acute patients hospitalised due to a schizophrenia relapse seen in the phase 3, placebo-controlled trial (Correll et al. 2020). Although RCTs are the gold standard for assessing the efficacy and safety of new medications, they often fall short in representing the full spectrum of patients treated in clinical practice (Taipale et al. 2022). RCTs typically exclude patients with comorbidities, substance use, or poor response to antipsychotics. However, these are precisely the patients that clinicians treat. Real-world studies further allow to observe how treatments perform in naturalistic settings, with all the related variability and complexity. Thus, the clinical effectiveness of LAIs should also be evaluated under routine care conditions in real-world clinical practice to maximise external validity (Kishimoto et al. 2014). Furthermore, LAIs should be studied not only in the maintenance treatment of schizophrenia, but also in the hospital setting during a relapse, with the goal of helping patients to bridge the gap from early treatment to long-term care (Correll et al. 2016; Wang et al. 2024). In this sense, Risperidone-ISM® was designed for allowing the treatment of acute patients with schizophrenia (Correll et al. 2020; Messer et al. 2024; Snoeck et al. 2025).

The characteristics of the participants in the present study reflect the kind of patients who are often seen in real-world inpatient psychiatric care. The patient population was predominantly male, with a mean age of 42 years and a mean of 2.4 relapses within the last two years. Among those who received oral risperidone from admission until the first administration of Risperidone-ISM®, daily doses ranged between 1 and 12 mg.

Clearly defined symptoms reduction remains the main measurement of treatment success. PANSS-6 includes the core symptoms of schizophrenia and is a psychometrically valid measure of these symptoms, being sensitive to symptom improvement following pharmacological treatment and it can be used to define short-term symptom improvement, response, and cross-sectional remission in schizophrenia (Østergaard et al. 2016, 2018; Hieronymus et al. 2021). Against this background, it is noteworthy that interestingly, a statistically significant improvement on both effectiveness scales was observed for the patients treated with Risperidone-ISM® as early as 8 days after the first injection (14.9% in CGI-S and 17.4% in PANSS-6), indicating rapid symptom improvement and reduction in the severity of the disease. These results are consistent

with those shown in a previous published clinical trial in acute schizophrenia (Correll et al. 2020), where Risperidone-ISM® also provided significant improvement of the symptomatology and disease severity in acutely exacerbated patients, being already statistically significant 8 days after the first injection.

Specifically, the most severe patients (markedly to extremely ill) significantly improved in symptoms and, thereby, their global illness from first injection onwards, and the proportion of patients with such ratings was reduced from 58.2 to 11.4% after 2 injections with Risperidone-ISM®. Notably, these most severely ill patients had a mean PANSS-6 score >20 points, which approximately corresponds to a PANSS-30 total score >90 points, indicative of severe symptomatology (Hieronymus et al. 2021). Indeed, in severely ill patients, there is a particular need for rapid titration to achieve adequate therapeutic plasma concentrations. According to a recent publication, Risperidone-ISM® achieves sustained therapeutic plasma levels and optimal D2 receptor occupancy (65–80%) since Day 1, contributing to adequate efficacy, with rapid symptom reduction and minimal adverse events since injection and throughout the whole administration period in adult patients with an acute relapse of schizophrenia (Snoeck et al. 2025).

Additionally, it should be emphasised that the treatment strategy applied in this study (early initiation of a long-acting injectable with rapid and sustained onset of action and without the need for additional oral supplementation) may also provide economic advantages, such as a potential reduction in hospitalisation duration and associated healthcare costs.

In this regard, results from this study showed that Risperidone-ISM® also had a remarkable median time to discharge of merely 8 (IQR = 3.0, 15.0) days since first injection, unlike the 11 days reported by monthly injectable paliperidone palmitate (PP1M) in a previously published non-interventional study (Parellada et al. 2018). While comparisons between studies should be interpreted cautiously due to differences in clinical practices, patient characteristics, and study methodologies, both studies involved comparable populations of acutely admitted patients experiencing a schizophrenia exacerbation, with similar baseline symptom severity (CGI-S = 4.7).

Risperidone-ISM® showed an outstanding mean improvement of 17.6 points after just one injection in the PSP score in usual clinical practice. This finding is consistent with previously published data from the phase 3 clinical trial of Risperidone-ISM® (Litman et al. 2023). In that study, patients receiving Risperidone-ISM® demonstrated significantly greater improvement on the PSP scale compared to placebo as early as four weeks after treatment initiation. Relatedly, in another non-interventional study with a similar acute setting of schizophrenia patients, a mean CFB of 14.3 points on PSP score was found after 6 weeks of starting antipsychotic treatment with PP1M (Hargarter et al. 2018). Furthermore, in our study, all four PSP individual domains showed improvement over time, with the most remarkable changes in the 'Disturbing and aggressive behaviour' domain. Rapid control of aggressive symptoms is crucial (Correll et al. 2017), not only to prevent potential harm to patients, caregivers, or others, but also to reduce hospital admission length, as patients with these symptoms typically experience prolonged hospitalisation (Greenfield et al. 1989).

No unexpected safety findings were found in this study and the observed TRAEs were those consistent with prior data for risperidone at therapeutic doses (Risperdal Consta Summary of Product Characteristics (SmPC) n.d.; Risperdal Summary of Product Characteristics (SmPC) n.d.) and consistent with those reported in previous studies with Risperidone-ISM® (Llaudó et al. 2016; Anta et al. 2018; Correll et al. 2020; Filts et al. 2022).

Notably, in this study, Risperidone-ISM® was well tolerated, and in fact, most of the TRAEs (>90%) were mild or moderate, and only in 4% of patients led to treatment discontinuation. Additionally, only 3 (1%) patients experienced treatment-related extrapyramidal symptoms (EPS), and 2 (0.7%) prolactin-related TRAEs. No treatment discontinuations due to increased body weight were reported. These data reinforce the favourable safety and tolerability profile of Risperidone-ISM®.

In addition to the improvements obtained in psychotic symptoms, severity of illness, and functioning, nearly twice as many patients were somewhat, very, or extremely satisfied with Risperidone-ISM® after 2 months of treatment compared to their previous medication, collected at baseline. Prior research suggests that treatment satisfaction is associated with improved adherence and psychotic symptoms (Gharabawi et al. 2006), and this enhanced satisfaction may also strengthen the therapeutic alliance, which is essential for reliable monitoring of the patient's progress and treatment adherence (Hasan et al. 2013). The improvement in the therapeutic alliance observed in 89.4% of participants in this study is clinically relevant, especially since this outcome could influence treatment adherence, symptom reduction, and overall functional recovery in schizophrenia (Chang et al. 2019; Browne et al. 2021). A strong collaborative relationship

between patients and clinicians fosters trust, enhances engagement with treatment, and reduces the risk of relapse or treatment discontinuation. Given the chronic nature of schizophrenia, strengthening the therapeutic alliance is important for sustaining long-term stability and optimising clinical outcomes.

As one might expect in a real-life clinical setting, a substantial number of patients received concomitant antipsychotic medication. Actually, antipsychotic polypharmacy, especially with an LAI and oral antipsychotic is a common clinical practice (Degli Esposti et al. 2014; Bergendal et al. 2015). Antipsychotic polypharmacy is particularly common in patients with long-standing schizophrenia (Correll and Gallego 2012), as in those of our study, whose mean time since schizophrenia diagnosis was around 11 years. In fact, the antipsychotic polypharmacy has been also reported in other similar non-interventional studies (Schreiner et al. 2014; Hargarter et al. 2018; Parellada et al. 2018). Nevertheless, antipsychotic polypharmacy has not shown consistent efficacy and effectiveness advantages (Galling et al. 2017; Guinart and Correll 2020; Højlund et al. 2025). Similarly, the improvements observed on effectiveness and functioning in this study appear to be mainly attributed to Risperidone-ISM®, since a subanalysis did not reveal statistically significant differences in these outcomes when comparing patients who received any concomitant antipsychotic medication, apart from Risperidone-ISM®, with those who did not, suggesting that adding another antipsychotic may not provide further clinical benefit. Indeed, in a previously published double-blind RCT, Risperidone-ISM® in monotherapy demonstrated prompt response in reducing psychotic symptoms and the severity of the illness in an acutely exacerbated schizophrenia population (Correll et al. 2020). Consequently, our results underpin the efficacy of Risperidone-ISM® as antipsychotic monotherapy for adults with schizophrenia, i.e. without the need to add other antipsychotics concomitantly, which could even increase the occurrence of adverse events (Gallego et al. 2012; Galling et al. 2017; Højlund et al. 2025).

This study has some limitations that need to be considered when interpreting the results. This was a non-interventional study, and consequently, a certain degree of placebo effect cannot be ruled. Its outcomes might not reflect pivotal clinical trial results, in which patients are assigned to active or control group by chance to reduce errors or bias. However, the results of the present study are confirming those previously observed in clinical trials. Additionally, due to the non-interventional, naturalistic methodology, detailed symptom ratings were not available. Nevertheless, the quantitative data obtained were robust and are clinically meaningful. Furthermore, the study lasted only two months and there was some attrition. Nevertheless, we aimed to collect real-world data to test the robustness of the results obtained in the 3-month RCT (Correll et al. 2020) when using Risperidone-ISM® in real-world clinical settings, which we were able to do. Despite this, caution is required when interpreting results of non-interventional studies because establishing a cause-and-effect relationship may be challenging. Finally, ~30% of participants did not complete all scheduled visits, with loss to follow-up being the most frequent reason (79%). While this level of attrition warrants consideration, it should be interpreted in the context of the observational, real-world design of the study, which inherently includes a broader and more clinically heterogeneous patient population than controlled or highly structured studies. Furthermore, the attrition rate was a key aspect closely monitored throughout the study, and specific measures were implemented to minimise it as much as possible. Despite these efforts, the inherent characteristics of the clinical care process and patient flow within the healthcare system contributed to the observed level of missingness. Taken together, we believe that the observed rate of missing data reflects real-world clinical practice rather than a study limitation that materially compromises the validity of the conclusions. Nevertheless, caution is required when interpreting results of non-interventional studies because establishing a cause-and-effect relationship may be challenging.

However, an important strength of this study, which was conducted in 5 countries, is exactly its naturalistic design. Observational studies are especially helpful for mental health disorders because they can show the complexity of clinical management in a real-world sample and setting. Besides, this study reports the evolution of clinical status by means of well-validated clinical rating scales addressing different aspects of the disease, such as symptoms, social functioning, or patient's satisfaction with the medication. All this information, along with other important clinical data (e.g. hospitalisation stay, discharge criteria, etc.), resulted in a comprehensive study addressing the main clinical effects of Risperidone-ISM® in real-life clinical practice.

Conclusions

Risperidone-ISM® demonstrated rapid and sustained effectiveness in reducing acute symptoms in real-life adult patients diagnosed with schizophrenia who had

been admitted due to a relapse, showing statistically significant improvement in CGI-S and total PANSS-6 scores with significant reductions as early as day 8. This treatment effect achieved without loading dose, booster injections, or oral cotreatment led to a rapid stabilisation of patients, which facilitated discharge in a median time of 8 days after initiating treatment with Risperidone-ISM®. Notably, adding another antipsychotic did not appear to provide further clinical benefits. These findings, along with significant improvement in functioning from first injection onwards and a favourable tolerability profile, with only 4% of patients suffering TRAEs leading to discontinuation contributed even more to an early stabilisation of the patients and confirm the results that had been demonstrated in controlled clinical trials.

Taken together, based on these data, Risperidone-ISM® is an effective antipsychotic option for the rapid stabilisation of hospitalised patients experiencing an acute relapse of schizophrenia.

Statement of interest

C. U. Correll has been a consultant and/or advisor to or has received honoraria from: AbbVie, Alkermes, Allergan, Angelini, Aristo, Autobahn, Axsome, Boehringer-Ingelheim, Bristol-Meyers Squibb, Cardio Diagnostics, Cerevel, CNX Therapeutics, Compass Pathways, Darnitsa, Delpor, Denovo, Draig, Eli Lilly, Eumentis Therapeutics, Gedeon Richter, GH Research, Hetero, Hikma, Holmusk, IntraCellular Therapies, Jamjoom Pharma, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedInCell, MedLink Global, Merck, Mindpax, Mitsubishi Tanabe Pharmaceuticals, Maplight, Mylan, Neumora Therapeutics, Neuraxpharm, Neurocrine, Neurelis, Neurosterix, NeuShen, Neusignal Therapeutics, Newron, Noven, Novo Nordisk, Orion Pharma, Otsuka, PPD Biotech, Recognify Life Science, Recordati, Relmada, Response Pharmaeutical, Reviva, Rovi, Saladax, Sanofi, Seqirus, Servier, Sumitomo Pharma America, Sunovion, Sun Pharma, Supernus, Tabuk, Takeda, Teva, Terran, Tolmar, Vertex, Viatris and Xenon Pharmaceuticals. He provided expert testimony for Janssen, Lundbeck, Neurocrine, and Otsuka. He served on a Data Safety Monitoring Board for Compass Pathways, IntraCellular Therapies, Relmada, Reviva, and Rovi. He has received grant support from Boehringer-Ingelheim, Janssen, and Takeda. He received royalties from UpToDate and is also a stock option or stock holder of Cardio Diagnostics, Kuleon Biosciences, LB Pharmaceuticals, MedLink Global, Mindpax, Quantic, and Terran.

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Steffi Langner-Timm reports there are no competing interests to declare.

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Christopher Landri reports there are no competing interests to declare.

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Montserrat Caballero reports there are no competing interests to declare.

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Data availability statement

Data supporting the results of this study are available from ROVI, but restrictions apply to their availability, which were used under licence for the present study and are therefore not publicly available. However, the data may be provided by corresponding author upon reasonable request and with the permission of ROVI.

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