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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Spravato

esketamine

Procedure no: EMEA/H/C/004535/P46/005

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	11.09.2023	11.09.2023	☐
☐	CHMP Rapporteur Assessment Report	16.10.2023	16.10.2023	☐
☐	CHMP members comments	30.10.2023	30.10.2023	☐
☐	Updated CHMP Rapporteur Assessment Report	06.11.2023	06.11.2023	☐
☒	CHMP adoption of conclusions:	09.11.2023	09.11.2023	☐

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ANCOVA	analysis of covariance
BPRS	Brief Psychiatric Rating Scale
BPRS+	Brief Psychiatric Rating Scale, positive symptom subscale
CADSS	Clinician Administered Dissociative States Scale
CBT	cognitive behavioral therapy
C-CASA	Columbia Classification Algorithm for Suicide Assessment
CDI 2:SR[S]	Children's Depression Inventory 2: Self-Report (Short) version
CDRS-R	Children's Depression Rating Scale, Revised
CGI-SR-I	Clinical Global Impression – Imminent Suicide Risk
CGI-SR-LT	Clinical Global Impression – Long-term Suicide Risk
CGI-SS-R	Clinical Global Impression – Severity of Suicidality - Revised
CSR	clinical study report
DBP	diastolic blood pressure
ECG	electrocardiogram
ER	Emergency Room
EU	European Union
FoST	frequency of suicidal thinking
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LOCF	last observation carried forward
LS	least squares
MADRS	Montgomery Asberg Depression Rating Scale
MDD	major depressive disorder
MDSI	MDD in patients assessed to be at imminent risk for suicide
MedDRA	Medical Dictionary for Regulatory Activities
MINI-KID	Mini International Psychiatric Interview for Children and Adolescents
MMRM	mixed-effects model for repeated measures
MOAA/S	Modified Observer's Assessment of Alertness/Sedation
PCP	phencyclidine
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PWC-20	Physician Withdrawal Checklist
QTcF	QT corrected according to Fridericia's formula
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	standard deviation
SIBAT	Suicide Ideation and Behavior Assessment Tool
SOC	standard of care
TEAE	treatment-emergent adverse event
TLFB	Timeline Follow-Back
Total Esk	combined esketamine treatment groups
TRD	treatment-resistant depression
US	United States
YMRS	Young Mania Rating Scale

1. Introduction

On 29/08/2023 (eCTD: 0049), the MAH submitted a completed paediatric study for Spravato, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measures:

A short critical expert overview together with the full study documentation have also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that "A Double-blind, Randomized, Psychoactive Placebo-controlled, Study to Evaluate the Efficacy and Safety of 3 Fixed Doses (28 mg, 56 mg and 84 mg) of Intranasal Esketamine in Addition to Comprehensive Standard of Care for the Rapid Reduction of the Symptoms of Major Depressive Disorder, Including Suicidal Ideation, in Pediatric Subjects Assessed to be at Imminent Risk for Suicide", Study No. ESKETINSUI2002 is a stand alone study, which will help inform the design of future development of esketamine in MDSI in adolescents.

The Applicant has developed SPRAVATO for 2 populations: patients with treatment-resistant depression (TRD, defined as MDD in adults who have not responded adequately to at least 2 different antidepressants of adequate dose and duration to treat the current depressive episode) and for the rapid reduction of depressive symptoms in adult patients with MDD who have acute suicidal ideation or behaviour.

Studies performed to investigate the efficacy and safety of esketamine for the treatment of adults with TRD and adults with MDD who have acute suicidal ideation or behaviour (MDSI) resulted in a positive benefit/risk assessment and the adult clinical development program in both indications is now completed. A Phase 4 monotherapy trial (54135419TRD4005) and Phase 4 long-term safety trial (54135419TRD4010) in adult patients with TRD are ongoing.

The clinical development program also plans to evaluate esketamine in combination with standard of care (SOC) for adolescent patients with MDSI, including Study ESKETINSUI2002, included in the agreed pediatric plan for SPRAVATO.

The MAH, Janssen Research and Development, presented this submission to fulfill the Company's obligations under Article 46 of the European Community Regulation 1901/2006 as amended ("the pediatric regulation"). This regulation places a requirement on the submission of marketing authorization holder-sponsored studies, which involve the use in the pediatric population within six months of completion of the studies concerned.

2.2. Information on the pharmaceutical formulation used in the study

Spravato (esketamine) has been developed as an intranasal spray using a small volume to deliver the active substance. This is considered as a suitable pharmaceutical form for both children and adolescents. During the study ESKETINSUI2002, esketamine nasal spray was supplied as a solution of esketamine in a nasal spray pump (device), which delivered 16.14 mg esketamine hydrochloride (14 mg esketamine base) per 100-μL spray. Each individual nasal spray device contained a total of 28 mg (ie, 2 sprays).

2.3. Clinical aspects

2.3.1. Introduction

This document and the clinical overview summarizes the efficacy, safety and pharmacokinetics data for SPRAVATO® (esketamine) from Study ESKETINSUI2002, which was conducted in adolescent participants (aged 12 to <18 years) according to an agreed pediatric plan for SPRAVATO.

The MAH submitted a final report for:

- < Study ESKETINSUI2002, A Double-blind, Randomized, Psychoactive Placebo-controlled, Study to Evaluate the Efficacy and Safety of 3 Fixed Doses (28 mg, 56 mg and 84 mg) of Intranasal Esketamine in Addition to Comprehensive Standard of Care for the Rapid Reduction of the Symptoms of Major Depressive Disorder, Including Suicidal Ideation, in Pediatric Subjects Assessed to be at Imminent Risk for Suicide>;

2.3.2. Clinical study ESKETINSUI2002

< Study No. ESKETINSUI2002, A Double-blind, Randomized, Psychoactive Placebo-controlled, Study to Evaluate the Efficacy and Safety of 3 Fixed Doses (28 mg, 56 mg and 84 mg) of Intranasal Esketamine in Addition to Comprehensive Standard of Care for the Rapid Reduction of the Symptoms of Major Depressive Disorder, Including Suicidal Ideation, in Pediatric Subjects Assessed to be at Imminent Risk for Suicide>

EudraCT Number: 2016-004422-42

NCT Number: NCT03185819

Description

This was a randomized, double-blind, double-dummy, psychoactive placebo-controlled, multicenter study conducted at multiple sites in Europe, North America, and South America to evaluate the efficacy and safety of 3 doses of esketamine (28 mg, 56 mg, and 84 mg) in adolescent participants (aged 12 to <18 years) with MDD who were assessed to be at imminent risk for suicide. The planned total sample size was approximately 145 participants.

Methods

Study participants

The study enrolled adolescent participants (aged 12 to <18 years) with a diagnosis of MDD who presented to an ER or other permitted setting and were assessed to be at imminent risk for suicide. Given the vulnerability of the population, this study was conducted in the context of comprehensive SOC treatment. This included initial voluntary hospitalization in an inpatient psychiatric unit or other permitted setting for a recommended duration of 5 days from randomization, with shorter or longer hospitalizations permitted if clinically warranted per local SOC; initiation or optimization of allowed antidepressant treatment (fluoxetine, escitalopram, or sertraline) for at least the duration of the double-blind treatment phase (until Day 25); participation in a specific psychological intervention (individual CBT, interpersonal therapy, family therapy or psychodynamic psychotherapy) at least through the initial 8-week post-treatment follow-up period (Day 81); and close outpatient follow-up. The planned total sample size was approximately 145 participants. A total of 147 participants were randomized and received at least 1 dose of study intervention.

Treatments

Participants were randomized in a 1:1:1:2 ratio to receive one of 3 doses of intranasal esketamine (28, 56, or 84 mg) or oral psychoactive placebo (midazolam 0.125 mg/kg) administered 2 times per week for 4 weeks. A double-dummy design was used; thus, participants randomized to intranasal esketamine also received an oral placebo, and participants randomized to oral midazolam also administered an intranasal placebo. On each dosing day, participants took oral study intervention first, followed closely by intranasal study intervention (3 devices).

The study had a 25-day double-blind treatment phase in which participants received study intervention 2 times per week for 4 weeks. No study intervention was administered during the 6-month post-treatment follow-up phase.

Objectives

The primary objective of this study was to assess the efficacy of a single (first) dose of 3 fixed doses of intranasal esketamine (28 mg, 56 mg, and 84 mg) compared with psychoactive placebo (oral midazolam) in rapidly reducing the symptoms of MDD, including suicidal ideation, in participants 12 to <18 years of age who were assessed to be at imminent risk for suicide. Efficacy was assessed by the change from baseline in Children's Depression Rating Scale-Revised (CDRS-R) total score at 24 hours post first dose (Day 2).

A number of other objectives, such as the evaluation of dose-response, efficacy of single and repeated doses by Clinical Global Impression – Severity of Suicidality – Revised (CGI-SS-R), Montgomery Asberg Depression Rating Scale (MADRS), Clinical Global Impression – Imminent Suicide Risk (CGI-SR-I) and Suicide Ideation and Behavior Assessment Tool (SIBAT) Modules 3 and 5, the characterisation of the pharmacokinetics, the evaluation of safety and tolerability and the evaluation of potential for withdrawal symptoms and abuse, as well as exploring MDD-related biomarkers.

Outcomes/endpoints

The primary efficacy endpoint, change from baseline (Day 1, predose) to 24 hours after the first dose (Day 2) in CDRS-R total score, was analyzed using an ANCOVA model, with factors for treatment and analysis center and baseline CDRS-R total score as a continuous covariate. A pooled sequential multiple testing procedure was implemented to control for type I error. First, the esketamine 56-mg and 84-mg treatment groups were pooled and compared with psychoactive placebo at a 2-sided significance level of 0.05. If this comparison achieved statistical significance in favor of esketamine, the 56-mg dose and the 84-mg dose were each simultaneously tested versus psychoactive placebo at the 2-sided significance level of 0.05 based on the closed testing procedure. Esketamine 28 mg was to be tested at the 2-sided significance level of 0.05 only if both the individual doses of 56 mg and 84 mg were shown to be significant. The treatment effects were estimated using LS means. Point estimates and 95% CIs for the treatment differences, along with the associated p-value were provided.

Sample size

The sample size for this study was calculated assuming an effect size of 0.65 between any dose of esketamine and psychoactive placebo for the change from baseline at 24 hours postdose for the CDRS-R total score and a 2-sided significance level of 0.05. It was planned to randomize a target of 145 participants. Using a 1:1:1:2 randomization ratio (esketamine 28 mg: esketamine 56 mg: esketamine 84 mg: psychoactive placebo), approximately 58 participants would need to be randomized to psychoactive placebo and 29 participants randomized to each esketamine treatment group to achieve 94% power for the comparison of the pooled doses of esketamine 56 mg and esketamine 84 mg

versus psychoactive placebo, and 92% power for at least one of the higher esketamine doses (56 mg and 84 mg) versus psychoactive placebo.

Randomisation and blinding (masking)

A 1:1:1:2 randomization ratio scheme was used (esketamine 28 mg: esketamine 56 mg: esketamine 84 mg: psychoactive placebo) and approximately 58 participants were randomized to psychoactive placebo and 29 participants randomized to each esketamine treatment group.

This study design included investigator and participant blinding. The method used for blinding is further described in sections 3.2.3. Control, Randomization and Blinding and 5. Treatment Allocation and Blinding ~~section~~ of the Protocol.

Administration of esketamine is associated with a number of transient adverse events, including sedation, dissociative symptoms, and elevation of blood pressure. To minimize the risk of unblinding the treatment assignment, a psychoactive placebo, midazolam, was used. Midazolam has been used as a psychoactive placebo in previous studies of ketamine because of its similar onset of action and side effect profile.

A double-dummy design was used in order to preserve the blind since the active study intervention (intranasal esketamine) and the psychoactive placebo (oral midazolam) are administered via different routes. Therefore, 2 matching placebo formulations, intranasal and oral, were included in the treatment regimen. On each dosing day, participants took oral study intervention first, followed closely by intranasal study intervention (3 devices).

Statistical Methods

Efficacy and safety results for the double-blind treatment phase were analyzed using the full efficacy analysis set and safety analysis set, respectively. Results for the follow-up phase were analyzed using the follow-up analysis set.

The primary efficacy analysis was performed on the full efficacy analysis set with LOCF data using an ANCOVA model. As prespecified in the protocol and SAP, a pooled sequential multiple testing procedure was implemented to control for type I error. The esketamine 56-mg and 84-mg treatment groups were pooled and compared with midazolam + SOC at a 2-sided significance level of 0.05. If this comparison achieved statistical significance in favor of esketamine, the 56-mg dose and the 84-mg dose were each simultaneously tested versus midazolam at the 2-sided significance level of 0.05. Esketamine 28 mg was tested only if both the individual doses of 56 mg and 84 mg were shown to be significant.

Results

Participant flow

The study comprised the following phases:

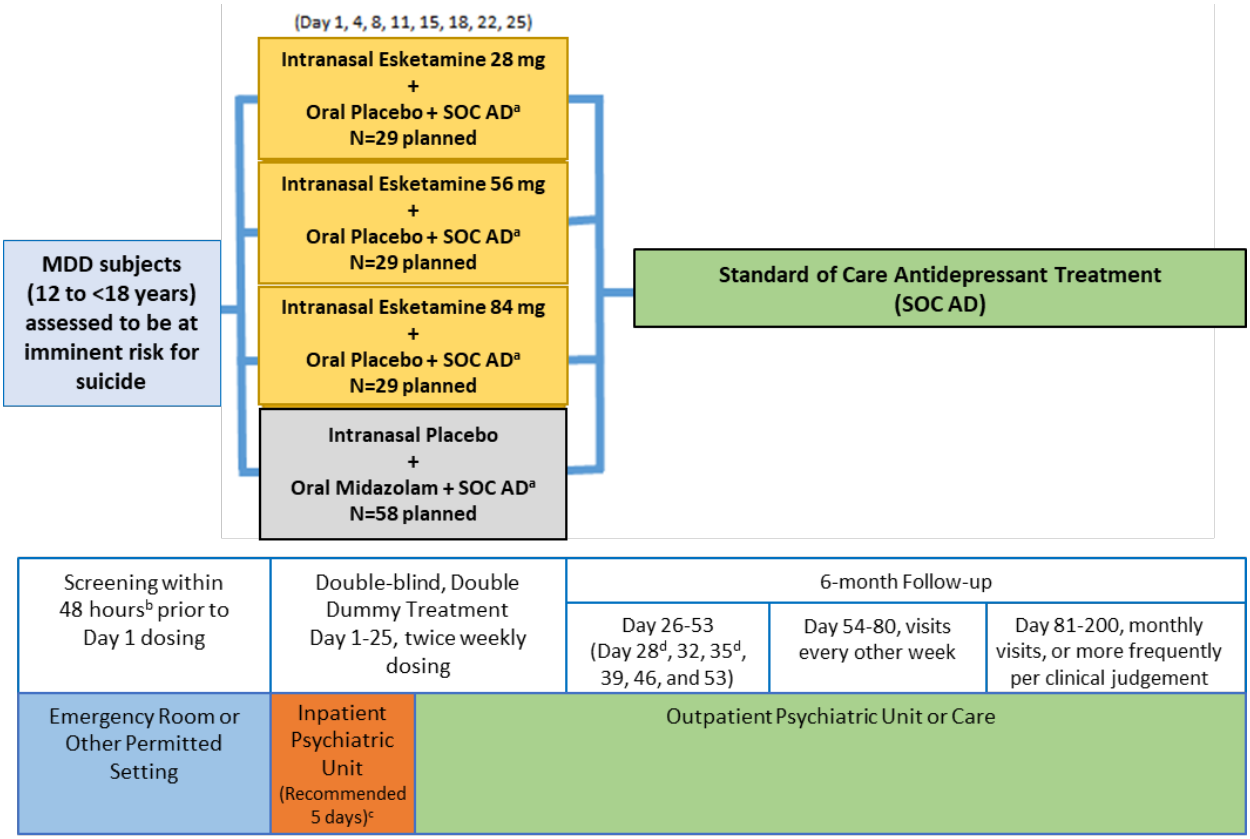
- A screening evaluation performed within 48 hours prior to Day 1 intranasal dose (if possible, screening was to occur within 24 hours prior to the Day 1 intranasal dose);
- A 25-day double-blind treatment phase (Days 1-25), during which study intervention was administered 2 times per week for 4 weeks on Days 1, 4, 8, 11, 15, 18, 22, and 25;
- A 6-month post-treatment follow-up phase, including an 8-week initial post-treatment phase (Days 25-81) and a subsequent phase (Days 82-200). No study intervention was administered

during the post-treatment follow-up phase. The duration of the participant's participation was approximately 29 weeks.

An IDMC, consisting of individuals with appropriate pediatric expertise including pediatric psychiatric expertise, was established to monitor data on an ongoing basis to ensure the continuing safety of the participants enrolled in this study. The committee met periodically to review safety data. After the reviews, the IDMC made recommendations regarding the continuation of the study.

A diagrammatic representation of the study design is presented in Figure 1

Figure 1: Schematic Overview of the Study



a Antidepressant (AD) medication was to be initiated or optimized on Day 1. However, initiating SOC AD medication up to 7 days after the first dose of study intervention (Day 1) was permitted if starting 2 medications simultaneously was inconsistent with local clinical practice.
b If possible, screening was performed within 24 hours prior to Day 1 intranasal dose.
c Hospital discharge before 5 days (from randomization) must have been discussed with and approved by the sponsor's medical monitor. The investigator was required to discuss the need for continued hospitalization beyond 10 days and thereafter on a weekly basis with the sponsor's medical monitor.
d Remote contact.

Recruitment

This study was conducted at 37 centers that enrolled participants in 7 countries/territories (Brazil, France, Hungary, Italy, Poland, Spain, and the United States). The Study Period was from 26 January 2018 (date first participant was screened) to 31 March 2023 (date of last participant last visit).

Baseline data

In general, the treatment groups were similar with respect to baseline characteristics. Of 145 participants in the full efficacy analysis set, 117 (80.7%) were white and 113 (77.9%) were female. The mean (SD) age was 14.9 (1.45) years, with 41.4% of participants aged 12-14 years and 58.6% aged 15-17 years. The mean body weight was 62.9 kg and the mean BMI was 23.5 kg/m^2. Sixty percent of participants were enrolled in the United States; 11.0% were enrolled in Spain, and <10% of participants were enrolled in each of the other countries.

Baseline psychiatric history was similar across the treatment groups. In the full efficacy analysis set, the mean baseline CDRS-R total score was 76.3 and the mean baseline MADRS total score was 38.8, indicating moderate to severe depression.

Prior to the first dose of study intervention on Day 1, approximately 95% of participants were rated by the clinician to be moderately to extremely suicidal as measured by the CGI-SS-R scale. Of note, 80.0% of participants had a prior lifetime suicide attempt per the MINI-KID. Over half (53.8%) of all participants had an attempt within the past month, with a higher proportion of participants with a recent attempt in the Total Esk group versus the midazolam + SOC group (57.3% vs 49.2%).

Number analysed

Participants were classified into the following analysis sets: all randomized, full efficacy, safety and follow-up.

- All Randomized Analysis Set included all participants who were randomized (ie, participants who reported a randomization date and were assigned a randomization number) regardless of whether or not treatment was received. This analysis set was used for summarizing the overall study completion/withdrawal information.
- Full Efficacy Analysis Set was defined as all randomized participants who received at least 1 dose of double-blind study intervention during the double-blind treatment phase and had both a baseline and a post-baseline evaluation for the CDRS-R total score. The efficacy analyses of data in the double-blind treatment phase were based on the full efficacy analysis set.
- Safety Analysis Set was defined as all randomized participants who received at least 1 dose of study intervention in the double-blind treatment phase.
- The follow-up analysis set was defined as all participants who completed the double-blind treatment phase and either entered the follow-up phase or provided AE data after the double-blind treatment phase. This analysis set was used for both efficacy and safety analyses during the follow-up phase.

The number of participants included in each analysis set is presented in Table 1 below:

Table 1: All Randomized Participants

	Midazolam + SOC	Esk 28 mg + SOC	Esk 56 mg + SOC	Esk 84 mg + SOC	Total Esk	Total
Analysis set: All randomized	63	29	31	24	84	147
Safety analysis set	63 (100.0%)	29 (100.0%)	31 (100.0%)	23[a] (95.8%)	83 (98.8%)	146 (99.3%)
Full efficacy analysis set	63 (100.0%)	28[b] (96.6%)	31 (100.0%)	23[a] (95.8%)	82 (97.6%)	145 (98.6%)
Follow-up analysis set	57 (90.5%)	29 (100.0%)	29 (93.5%)	21[a] (87.5%)	79 (94.0%)	136 (92.5%)

	Midazolam + SOC	Esk 28 mg + SOC	Esk 56 mg + SOC	Esk 84 mg + SOC	Total Esk	Total

[a] One randomized participant was excluded from both the full efficacy analysis set, safety analysis set, and follow-up analysis set due to GCP compliance issues at the site.
[b] One participant was excluded from the full efficacy analysis set due to a missing baseline assessment of CDRS-R.

Of 146 participants in the safety analysis set, 138 (94.5%) completed the double-blind treatment phase and 8 (5.5%) participants discontinued study treatment early (2 [6.5%] participants in the esketamine 56 mg + SOC group, 2 [8.7%] in the esketamine 84 mg + SOC group, and 4 [6.3%] in the midazolam + SOC group). The most frequent reason for discontinuation was 'Lack of efficacy', reported for 1 (3.2%) participant in the esketamine 56 mg + SOC group and 2 (3.2%) participants in the midazolam + SOC group.

Table 2: Treatment Disposition; Double-blind Treatment Phase; Safety Analysis Set (Study ESKETINSUI2002) (from ESKETINSUI2002 CSR body)

	Midazolam + SOC Total	Esk 28 mg + SOC Total	Esk 56 mg + SOC Total	Esk 84 mg + SOC Total	Total Esk	Total
Analysis set: Safety	63	29	31	23	83	146
Completed study treatment	59 (93.7%)	29 (100.0%)	29 (93.5%)	21 (91.3%)	79 (95.2%)	138 (94.5%)
Discontinued study treatment	**4** (6.3%)	0	2 (6.5%)	2 (8.7%)	**4** (4.8%)	**8** (5.5%)
Reason for discontinuation						
Adverse event	1 (1.6%)	0	0	0	0	1 (0.7%)
Lack of efficacy	2 (3.2%)	0	1 (3.2%)	0	1 (1.2%)	3 (2.1%)
Subject refused further study						
treatment	0	0	0	1 (4.3%)	1 (1.2%)	1 (0.7%)
Withdrawal by parent/guardian	0	0	0	1 (4.3%)	1 (1.2%)	1 (0.7%)
Other	1 (1.6%)	0	1 (3.2%)	0	1 (1.2%)	2 (1.4%)

Efficacy results

Clinical Pharmacology – Pharmacokinetics

A comprehensive overview of the concentrations of esketamine in plasma following intranasal administration of 28 mg, 56 mg, and 84 mg of esketamine are provided in the CSR (Mod5.3.5.1/CSR/Sec5.3.1). Mean concentrations in samples obtained between 30–50 minutes were the highest, followed by those obtained between 1.5–2.5 hours, while the lowest concentrations were found in samples obtained between 4–12 hours. Mean esketamine concentrations on Day 4 were generally slightly higher than mean concentrations at corresponding timepoints on Day 1, indicating minimal accumulation of esketamine in plasma. Dose proportionality was evident for the 28-mg and 56-mg doses. A slight deviation from dose proportionality (less than dose proportional) was apparent for the 84-mg dose.

A comprehensive overview of the concentrations of noresketamine in plasma following intranasal administration of 28 mg, 56 mg, and 84 mg of esketamine are provided in the CSR (Mod5.3.5.1/CSR/Sec5.3.1). Mean concentrations in samples obtained between 1.5–2.5 hours were

higher than those obtained between 30–50 minutes and 4–12 hours. Mean noresketamine concentrations on Day 4 were generally slightly higher than mean concentrations at corresponding timepoints on Day 1, indicating minimal accumulation of noresketamine in plasma.

Primary Efficacy Analysis

The primary efficacy evaluation was the change from baseline (Day 1, predose) at 24 hours post first dose in depressive symptoms, including suicidal ideation, as measured by the CDRS-R total score.

The mean (SD) changes in CDRS-R total score from baseline to 24 hours post first dose (Day 2) were -29.6 (18.15) for the esketamine 28 mg + SOC group, -31.8 (12.92) for the esketamine 56 mg + SOC group, -30.3 (17.48) for the esketamine 84 mg + SOC group and -31.2 (14.90) for the pooled esketamine doses of 56 mg and 84 mg + SOC, whilst it was -26.2 (16.72) for the midazolam + SOC group. Using an ANCOVA model, the LS mean (95% CI) treatment differences versus the midazolam + SOC group were: -2.4 (-9.08; 4.19), -5.9 (-12.25; 0.53), -5.7 (-12.91; 1.55), and -5.8 (-11.19 ; -0.35) for the esketamine 28 mg, 56 mg, 84 mg, and the pooled 56 mg and 84 mg doses + SOC, respectively.

Based on the ANCOVA analysis, the treatment difference was statistically significant in favor of esketamine for the pooled esketamine doses of 56 mg and 84 mg (2-sided p value=0.037). The esketamine 56 mg + SOC and 84 mg + SOC dose groups were then simultaneously tested versus midazolam + SOC at the 2-sided 0.05 significance level. The improvement in these dose groups did not reach statistical significance (2-sided p values=0.072 for 56 mg and 0.123 for 84 mg) when compared with the midazolam + SOC group. However, numerical differences presented a trend in favour of esketamine. The esketamine 28 mg dose group was not formally tested due to the statistical testing hierarchy.

Results for the change in CDRS-R total score from baseline to 24 hours after the first dose (Day 2) are summarized in Table 3.

Table 3: Children's Depression Rating Scale Revised (CDRS-R) Total Score: Change from Baseline to 24 Hours Post First Dose: ANCOVA LOCF; Double-blind Treatment Phase; Full Efficacy Analysis Set (Study ESKETINSUI2002)

	Midazolam + SOC	Esk 28 mg + SOC	Esk 56 mg + SOC	Esk 84 mg + SOC	Pooled Esk 56 mg + Esk 84 mg
Analysis set: Full Efficacy	63	28	31	23	54
Baseline(DB)					
N	63	28	31	23	54
Mean (SD)	76.1 (10.65)	77.6 (8.08)	76.4 (9.08)	75.3 (11.78)	75.9 (10.23)
Median	76.0	76.5	79.0	74.0	76.5
Range	(58; 101)	(60; 93)	(60; 95)	(58; 98)	(58; 98)
Day 2(DB) LOCF [a]					
N	63	28	31	23	54
Mean (SD)	49.9 (16.24)	48.0 (18.32)	44.5 (13.94)	45.0 (15.05)	44.7 (14.28)
Median	48.0	47.5	44.0	46.0	44.0
Range	(22; 84)	(17; 81)	(19; 71)	(21; 79)	(19; 79)
Change from baseline					
N	63	28	31	23	54
Mean (SD)	-26.2 (16.72)	-29.6 18.15)	-31.8 (12.92)	-30.3 (17.48)	-31.2 (14.90)
Median	-28.0	-32.5	-33.0	-34.0	-33.5
Range	(-57; 8)	(-64; 6)	(-57; -10)	(-67; 4)	(-67; 4)

Table 3: Children's Depression Rating Scale Revised (CDRS-R) Total Score: Change from Baseline to 24 Hours Post First Dose: ANCOVA LOCF; Double-blind Treatment Phase; Full Efficacy Analysis Set (Study ESKETINSUI2002)

	Midazolam + SOC	Esk 28 mg + SOC	Esk 56 mg + SOC	Esk 84 mg + SOC	Pooled Esk 56 mg + Esk 84 mg
2-sided p-value (minus Placebo) [b]			0.072	0.123	**0.037**
Diff. of LS Means (SE)		-2.4 (3.35)	-5.9 (3.23)	-5.7 (3.65)	**-5.8** (2.74)
95% CI		(-9.08; 4.19)	(-12.25; 0.53)	(-12.91; 1.55)	(-11.19; -0.35)

[a] Day 2(DB) is 24 hours post first dose.
[b] Based on analysis of covariance (ANCOVA) model with treatment (midazolam, esketamine 28 mg, 56 mg and 84 mg), analysis center as factors and baseline value as a covariate.
Note, the esketamine 56-mg and 84-mg treatment groups were pooled and compared with midazolam at a 2-sided significance level of 0.05. If this comparison achieved statistical significance in favor of esketamine, the 56-mg dose and the 84-mg dose would be each simultaneously tested versus midazolam at the 2-sided significance level of 0.05 based on the closed testing procedure. Esketamine 28 mg was tested at the 2-sided significance level of 0.05 only when both the individual doses of 56 mg and 84 mg were shown to be significant.
Note: CDRS-R total score ranges from 17 to 113; a higher score indicates a more severe condition. Negative change in score indicates improvement.
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Other Efficacy Evaluations

CDRS-R

Dose response for CDRS-R on Day 2

According to the MAH, a significant dose-response relationship was observed for the change from baseline in CDRS-R total score at Day 2 (one-sided p value=0.030 [ANCOVA multiple trend test]).

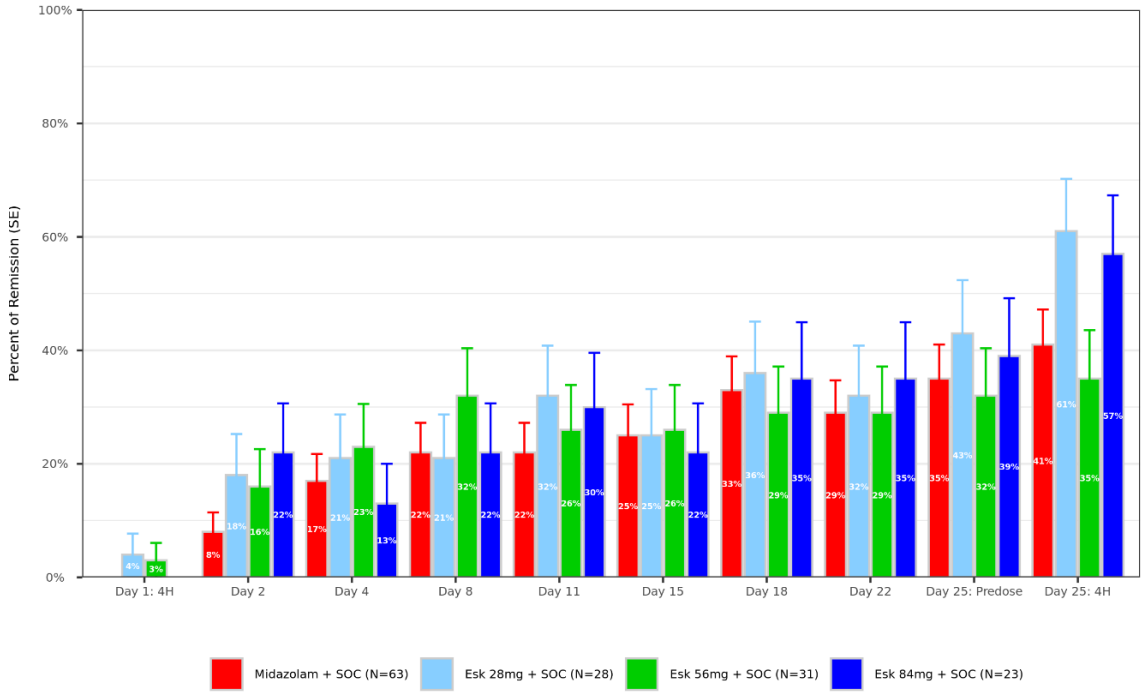
Change in CDRS-R total score (Day 1 to Day 25)

The LS mean treatment differences based on ANCOVA LOCF data numerically favored the esketamine + SOC groups over the midazolam + SOC group at most time-points during the double-blind treatment phase. At the last assessment of the double-blind phase (Day 25, 4 hours post dose) [LOCF], the LS mean (95% CI) treatment differences were -7.0 (-12.85; -1.06), -1.0 (-6.72; 4.63), and -6.5 (-12.94; -0.10) in the esketamine 28 mg, 56 mg, and 84 mg + SOC groups, respectively. Results of an MMRM analysis of CDRS-R total scores over time using observed case data were generally consistent with results of the ANCOVA.

Remission based on CDRS-R total score

The percentage of participants who achieved remission at each timepoint during the double-blind treatment phase is presented in Figure 2.

Figure 2: Children's Depression Rating Scale Revised (CDRS-R) Total Score: Frequency Distribution of Subjects Who Achieved Remission Over Time; Double-blind Treatment Phase; Full Efficacy Analysis Set (Study ESKETINSUI2002)



Note: Remission is based on a CDRS-R Total Score of <=28. Subjects who do not meet such criterion or discontinue prior to the time point for any reason are not considered to be in remission.
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The percentage of participants who met criteria for remission (CDRS-R total score ≤28) on Day 2 was 17.9% in the esketamine 28 mg + SOC group, 16.1% in the esketamine 56 mg + SOC group, 21.7% in the esketamine 84 mg + SOC group, and 7.9% in the midazolam + SOC group. At the last assessment of the double-blind phase (Day 25, 4 hours postdose), these percentages were 60.7%, 35.5%, 56.5%, and 41.3%, respectively.

Response based on CDRS-R total score

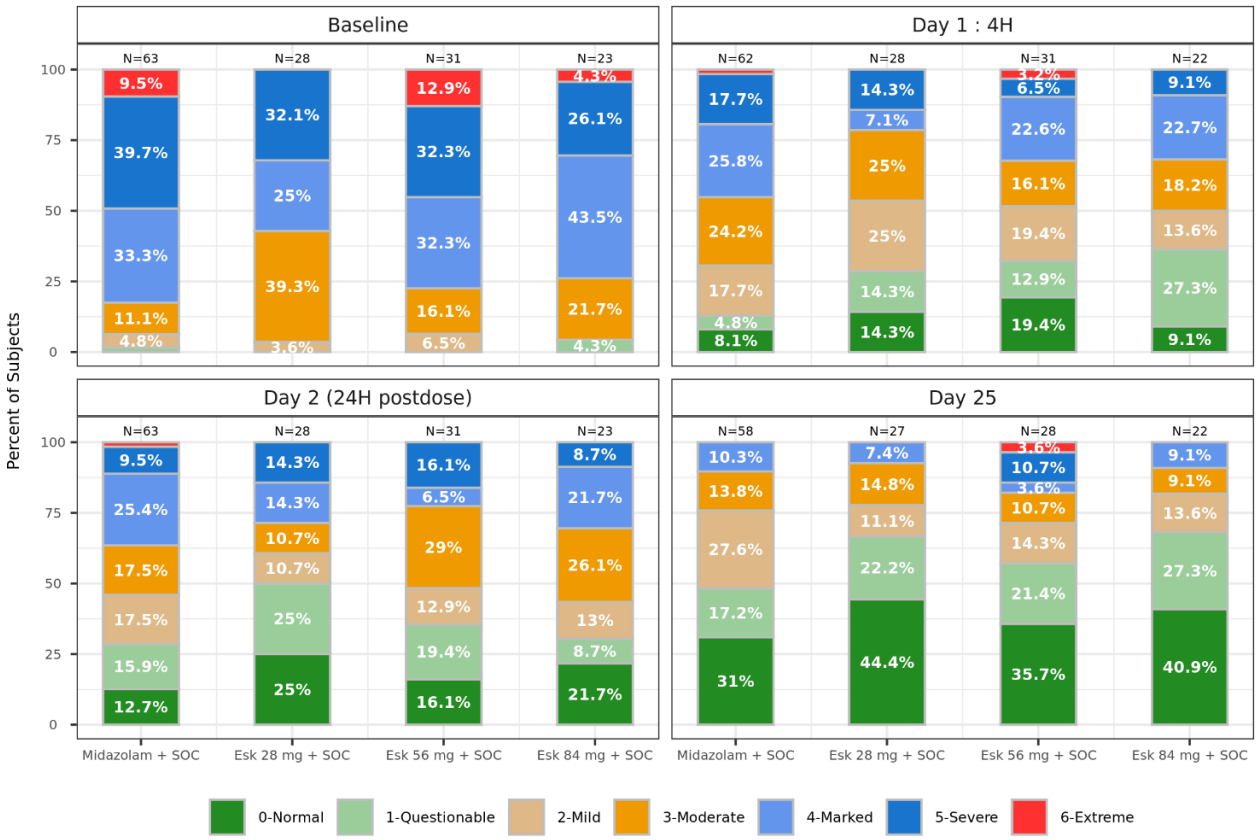
The percentage of participants who met criteria for response based on CDRS-R total score (≥50% improvement from baseline) on Day 2 was 53.6% in the esketamine 28 mg + SOC group, 61.3% in the esketamine 56 mg + SOC group, 56.5% in the esketamine 84 mg + SOC group, and 49.2% in the midazolam + SOC group. At the last assessment of the double-blind phase (Day 25, 4 hours postdose), the response rates were 96.4%, 71.0%, 73.9%, and 77.8%, respectively.

Change in CGI-SS-R Score

The CGI-SS-R summarizes the clinician's overall impression of severity of suicidality. The CGI-SS-R rating is scored on a 7-point scale from 0 (normal, not at all suicidal) to 6 (among the most extremely suicidal patients) and a reduction in score indicates improvement (ie, lower severity of suicidality).

The frequency distributions of CGI-SS-R scores at baseline, 4 hours after the first dose, 24 hours after the first dose (Day 2), and at Day 25 (predose) are displayed below in Figure 3 (observed cases) and in the CSR. CGI-SS-R scores improved from baseline to the end of the double-blind treatment phase (Day 25, predose) in all treatment groups.

Figure 3: Clinical Global Impression – Severity of Suicidality - Revised (CGI-SS-R) Score: Frequency Distribution at Baseline, 4 Hours Post First Dose, 24 Hours Post First Dose and Day 25; Observed Case; Double-blind Treatment Phase; Full Efficacy Analysis Set (Study ESKETINSUI2002)



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The changes from baseline in CGI-SS-R score were similar for all treatment groups at all time-points during the double-blind treatment phase. On Day 2 (24 hours post first dose), the median (range) changes in CGI-SS-R score from baseline were -2.0 (-5; 1), -2.0 (-5; 2), and -1.0 (-5; 0) for the esketamine 28 mg, 56 mg, and 84 mg + SOC groups, respectively, and -2.0 (-6; 0) for the midazolam + SOC group. The Hodges-Lehmann estimate of the differences versus midazolam + SOC was 0.0 for all 3 esketamine dose groups.

Based on observed case data, the Hodges-Lehmann estimate of the treatment difference (95% CI) versus midazolam + SOC for the esketamine 28 mg, 56 mg, and 84 mg + SOC dose groups, respectively, were:

- (-1.00; 0.00), -1.0 (-1.00; 0.00), and 0.0 (-1.00; 0.00), respectively, at 4 hours after the first dose.
- (-1.00; 1.00) for all 3 groups at the end of the double-blind treatment phase (Day 25, predose).

An analysis of change in CGI-SS-R score was also performed using an ANCOVA model with LOCF data; the LS mean differences (95% CI) versus midazolam + SOC for the esketamine 28 mg, 56 mg, and 84 mg + SOC dose groups, respectively, were:

- -0.5 (-1.06; 0.08), -0.8 (-1.36; -0.28), and -0.5 (-1.10; 0.15), respectively, at 4 hours after the first dose.
- -0.2 (-0.87; 0.38), 0.2 (-0.41; 0.77), and -0.2 (-0.92; 0.42), respectively, at the end of the double-blind treatment phase (Endpoint [DB]).

Resolution of Suicidality

The percentage of participants who met criteria for resolution of suicidality (ie, CGI-SS-R total score of 0 [normal, not at all suicidal] or 1 [questionably suicidal]) on Day 1 (4 hours post first dose) was 28.6% in the esketamine 28 mg + SOC group, 32.3% in the esketamine 56 mg + SOC group, 34.8% in the esketamine 84 mg + SOC group, and 12.7% in the midazolam + SOC group. On Day 2 (24 hours post first dose), these percentages were 50.0%, 35.5%, 30.4%, and 28.6%, respectively. On Day 25 (predose), these percentages were 64.3%, 51.6%, 65.2%, and 44.4%, respectively.

Change in Other SIBAT Modules/Items

Analyses of the other SIBAT modules (including Module 7 Clinician-rated FoST; Module 7 CGI-SR-LT; Module 8 Clinical Judgment of Optimal Suicide Management; Module 3 My Current Thinking; and Module 5 Patient-reported FoST) showed an overall improvement in these indices during the double-blind treatment phase in all treatment groups.

The CGI-SR-I summarizes the clinician's best assessment of the likelihood that the participant will attempt suicide in the next 7 days. The CGI-SR-I rating is scored on a 7-point scale from 0 (no imminent suicide risk) to 6 (extreme imminent suicide risk).

All treatment groups showed an improvement in CGI-SR-I score during the double-blind treatment phase. The changes from baseline in CGI-SR-I score on Day 2 (24 hours post first dose) and all other time points during the double-blind phase were similar in all treatment groups.

MAH's Efficacy Conclusions

Results from the primary efficacy analysis in this study in adolescent participants (aged 12 to <18 years) with MDD who were assessed to be at imminent risk of suicide showed a rapid reduction in the symptoms of depression in participants treated with esketamine, with a clinically meaningful and statistically significant treatment benefit observed for the pooled esketamine 56 mg and 84 mg doses + SOC compared with midazolam + SOC on the change from baseline in CDRS-R total score at 24 hours after the first dose. Although the treatment differences versus midazolam + SOC in the individual esketamine 56 mg and 84 mg dose groups did not achieve statistical significance, the magnitude of the mean differences were clinically significant in both groups and consistent with that observed in the pooled dose analysis.

A significant dose-response relationship for the change in CDRS-R total score at 24 hours was observed.

At Day 25, all treatment groups showed an improvement in CDRS-R total score.

While all treatment groups showed an improvement in the severity of suicidality, there were no differences between the esketamine + SOC and midazolam + SOC groups for the change in CGI-SS-R score at 24 hours post first dose or at the end of the double-blind treatment period (Day 25), but there appeared to be some improvement in the esketamine + SOC treatment groups versus the midazolam + SOC group at 4 hours after the first dose.

Safety results

Deaths

There were no TEAEs leading to death during the double-blind treatment phase. One participant (in the midazolam + SOC group) died during the follow-up phase due to completed suicide on Day 193, over 5 months after the last dose of study intervention. No other AEs resulting in death were reported.

Serious Adverse Events

Serious TEAEs were reported in 4 (13.8%) participants in the esketamine 28 mg + SOC group, 7 (22.6%) participants in the esketamine 56 mg + SOC group, 1 (4.3%) participant in the esketamine 84 mg + SOC group, and 9 (14.3%) participants in the midazolam + SOC group during the double-blind treatment phase. The only serious TEAEs (preferred terms) reported by more than 1 participant were suicide attempt (7 [8.4%] in the Total Esk group and 5 [7.9%] participants in the midazolam + SOC group) and suicidal ideation (5 [6.0%] and 3 [4.8%] participants, respectively). No serious TEAEs were considered by the investigator to be possibly, probably, or very likely related to study intervention.

During the 6-month post-treatment follow-up phase, serious AEs were reported in 25 (31.6%) participants in the Total Esk group and 19 (32.2%) participants in the midazolam + SOC group, the most common of which were suicide attempt (12 [15.2%] and 9 [15.3%] participants, respectively) and suicidal ideation (11 [13.9%] and 4 [6.8%] participants, respectively).

TEAEs

TEAEs were defined as events that were new in onset or increased in severity following treatment initiation. Adverse events were not considered treatment-emergent if they occurred or increased in severity during the follow-up phase. AEs were coded in accordance with the MedDRA, Version 25.0.

TEAEs reported during the double-blind treatment phase and AEs reported during the follow-up phase are discussed separately below. For more information, refer to the CSR (Mod5.3.5.1/CSR/Sec5.2).

<u>Double-blind Treatment Phase</u>

An overall summary of TEAEs reported during the double-blind treatment phase is presented for the safety analysis set in Table 4.

The majority of participants experienced at least 1 TEAE during the double-blind treatment phase: 27 (93.1%) participants in the esketamine 28 mg + SOC group, 30 (96.8%) in the esketamine 56 mg + SOC group, 23 (100.0%) in the esketamine 84 mg + SOC group, and 58 (92.1%) in the midazolam + SOC group. Most TEAEs were mild or moderate in severity. Severe TEAEs were reported in 14 (16.9%) participants in the Total Esk group and 12 (19.0%) in the midazolam + SOC group.

There were no TEAEs leading to death during the double-blind treatment phase. One participant (in the midazolam + SOC group) died during the follow-up phase due to completed suicide on Day 193, over 5 months after the last dose of study intervention. No other AEs resulting in death were reported.

Serious TEAEs were reported in 21 participants during the double-blind treatment phase: 4 (13.8%) participants in the esketamine 28 mg + SOC group, 7 (22.6%) in the esketamine 56 mg + SOC group, 1 (4.3%) in the esketamine 84 mg + SOC group, and 9 (14.3%) in the midazolam + SOC group. None of the serious TEAEs were considered related to intranasal or oral study intervention.

One participant (in the midazolam + SOC group) had a TEAE that led to discontinuation of intranasal study intervention and oral study intervention. No TEAEs leading to discontinuation of study intervention were observed in the esketamine + SOC treatment groups.

During the double-blind treatment phase, AESIs (special interest categories) were observed at the following incidences in the Total Esk and midazolam + SOC groups, respectively: TEAEs suggestive of abuse potential (75.9% vs. 65.1%), increased blood pressure (1.2% vs. 3.2%), increased heart rate (2.4% vs. 1.6%), cardiac safety (preferred term syncope [2.4% vs. 0%]), dizziness/vertigo (60.2% vs. 44.4%), impaired cognition (0% vs. 0%), cystitis related (3.6% vs. 1.6%), anxiety (19.3% vs. 23.8%), and TEAEs potentially related to suicidality (31.3% vs. 27.0%). Most of these TEAEs were mild or moderate in severity. For TEAEs suggestive of abuse potential and dizziness/vertigo, the majority of events occurred on a dosing day (usually starting within 1.5 hours post dosing) and the majority resolved on the same day.

Table 4: Overall Summary of Treatment-emergent Adverse Events; Double-blind Treatment Phase; Safety Analysis Set (Study ESKETINSUI2002)

	Midazolam + SOC	Esk 28 mg + SOC	Esk 56 mg + SOC	Esk 84 mg + SOC	Total Esk
Analysis set: Safety	63	29	31	23	83
Subjects with 1 or more:					
TEAEs	58 (92.1%)	27 (93.1%)	30 (96.8%)	23 (100.0%)	80 (96.4%)
TEAEs related to intranasal study agent [a]	43 (68.3%)	25 (86.2%)	27 (87.1%)	21 (91.3%)	73 (88.0%)
TEAEs related to oral study agent [a]	42 (66.7%)	20 (69.0%)	23 (74.2%)	17 (73.9%)	60 (72.3%)
TEAEs leading to death [b]	0	0	0	0	0
Serious TEAEs	9 (14.3%)	4 (13.8%)	7 (22.6%)	1 (4.3%)	12 (14.5%)
TEAEs related to intranasal study agent [a]	0	0	0	0	0
TEAEs related to oral study agent [a]	0	0	0	0	0
Severe TEAEs	12 (19.0%)	5 (17.2%)	6 (19.4%)	3 (13.0%)	14 (16.9%)
TEAEs related to intranasal study agent [a]	5 (7.9%)	2 (6.9%)	1 (3.2%)	2 (8.7%)	5 (6.0%)
TEAEs related to oral study agent [a]	5 (7.9%)	2 (6.9%)	0	1 (4.3%)	3 (3.6%)
TEAEs leading to discontinuation of intranasal study agent	1 (1.6%)	0	0	0	0
TEAEs leading to discontinuation of oral study agent	1 (1.6%)	0	0	0	0

Key: TEAE = treatment-emergent adverse event
[a] TEAE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to intranasal/oral study agent.
[b] TEAEs leading to death are based on TEAE outcome of Fatal.
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

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In the Total Esk group, the most common TEAEs by preferred term (reported in ≥20% of participants) were: dizziness (57.8%), nausea (43.4%), dissociation (42.2%), headache (36.1%), dysgeusia (32.5%), somnolence (32.5%), vomiting (21.7%), hypoesthesia, oral hypoesthesia, and intentional self-injury (20.5% each). Across the 3 esketamine + SOC dose groups, there was no clear dose-related differences in common TEAEs, although the 84-mg dose group had a higher incidence of dizziness than the other two dose groups, and the 56 and 84-mg dose groups had a higher incidence

of nausea, vomiting, and vision blurred than the 28-mg dose. Incidence rates by dose should be interpreted with caution given the small sample size in each dose group.

In the midazolam + SOC group, the most common TEAEs by preferred term (reported by ≥20% of participants) were: dizziness (42.9%), somnolence (38.1%), headache (28.6%), and dysgeusia (23.8%).

Follow-up Phase

An overall summary of AEs reported during the follow-up phase is presented below in Table 5.

Table 5: Overall Summary of Adverse Events; Follow-up Phase; Follow-up Analysis Set (Study ESKETINSUI2002)

	Midazolam + SOC	Esk 28 mg + SOC	Esk 56 mg + SOC	Esk 84 mg + SOC	Total Esk
Analysis set: Follow-up	59	29	29	21	79
Subjects with 1 or more:					
AEs	53 (89.8%)	23 (79.3%)	25 (86.2%)	18 (85.7%)	66 (83.5%)
AEs related to intranasal study agent [a]	0	1 (3.4%)	1 (3.4%)	0	2 (2.5%)
AEs related to oral study agent [a]	0	0	0	0	0
AEs leading to death [b]	1 (1.7%)	0	0	0	0
Serious AEs	19 (32.2%)	10 (34.5%)	8 (27.6%)	7 (33.3%)	25 (31.6%)
AEs related to intranasal study agent [a]	0	1 (3.4%)	1 (3.4%)	0	2 (2.5%)
AEs related to oral study agent [a]	0	0	0	0	0
Severe AEs	16 (27.1%)	5 (17.2%)	6 (20.7%)	6 (28.6%)	17 (21.5%)
AEs related to intranasal study agent [a]	0	1 (3.4%)	1 (3.4%)	0	2 (2.5%)
AEs related to oral study agent [a]	0	0	0	0	0

Key: AE = adverse event
[a] An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to intranasal/oral study agent.
[b] AEs leading to death are based on AE outcome of Fatal.
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

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The most common AEs in the follow-up phase (reported by ≥20% of participants) in the Total Esk group and in the midazolam + SOC group were headache (25.3% and 20.3%, respectively) and intentional self-injury (24.1% and 37.3%, respectively) (see Mod5.3.5.1/CSR/Sec5.2.2).

Other Key Safety Evaluations

Safety results are summarized briefly below and presented in detail in the CSR (Mod5.3.5.1/CSR/Sec5.2).

Vital Signs and Physical Findings

The means and mean changes from baseline over time in vital signs (pulse rate, SBP, DBP, respiratory rate, temperature, and oxygen saturation), weight, and BMI during the double-blind treatment phase were recorded. Across all intranasal dosing days, mean SBP and mean DBP values in the esketamine + SOC treatment groups increased from baseline at the 40-minute postdose timepoint and subsequently returned close to predose values at the 1.5-hour postdose timepoint.

In the esketamine + SOC groups, the greatest mean maximum increases from predose in SBP on any dosing day were 9.4, 10.7, and 14.8 mmHg in the 28 mg, 56 mg, and 84 mg dose groups, respectively, and the greatest mean maximum increases from predose in DBP on any dosing day were 9.1, 10.7, and 15.0, mmHg, respectively. In the midazolam + SOC treatment group, the greatest mean maximum increases from predose in SBP and DBP was 5.0 mmHg and 2.8 mmHg, respectively.

No clinically significant decreases in respiratory rate were observed during the double-blind treatment phase. Two participants (1 in the esketamine 28 mg + SOC group and 1 in the midazolam + SOC group) had at least 2 consecutive postdose oxygen saturation levels below 93% during a dosing session in the double-blind treatment phase.

MOAA/S

The MOAA/S was used to measure treatment-emergent sedation during the study. The percentage of participants with MOAA/S score ≤3 (corresponding to moderate or greater sedation) at any time during the double-blind treatment phase was 17.2% in the esketamine 28 mg + SOC group, 19.4% in the esketamine 56 mg + SOC group, 26.1% in the esketamine 84 mg + SOC group, and 58.7% in the midazolam + SOC group. No participants in the esketamine + SOC groups had a MOAA/S score of 0 or 1.

CADSS

The CADSS is an instrument for the measurement of present-state dissociative symptoms and was administered in this study to assess treatment-emergent dissociative symptoms.

Mean CADSS total scores in the esketamine + SOC groups peaked at the 40-minute postdose assessment and generally returned close to predose values at the 1.5-hour postdose assessment. In the esketamine + SOC groups, the mean of the highest CADSS total scores postdose was 13.2, 21.3, and 24.5 in the 28 mg, 56 mg, and 84 mg dose groups, respectively, and the mean of the greatest change from predose was 12.7, 18.1, and 23.3, respectively. In the midazolam + SOC group, the mean of the highest CADSS total score postdose was 8.8 and the mean of the greatest change from predose was 7.5.

YMRS

The YMRS was administered during the double-blind phase to assess for potential emergence of manic symptoms.

YMRS total mean scores in all groups were lower at each assessment timepoint compared to baseline, indicative of no treatment emergent mania.

BPRS+

The 4-item positive symptom subscale of the BPRS (BPRS+; assessing suspiciousness, hallucinations, unusual thought content, and conceptual disorganization) was administered in this study to assess potential treatment-emergent psychotic symptoms.

In the esketamine + SOC groups, mean BPRS+ total scores peaked at the 40-minute postdose assessment and generally returned close to predose values at the 1.5-hour postdose assessment. The

percentage of participants with a BPRS+ total score of 3 or higher at any time during the double-blind treatment phase was 24.1%, 32.3%, and 30.4% in the esketamine 28 mg, 56 mg, and 84 mg + SOC groups, respectively, and 14.3% in the midazolam + SOC group.

PWC-20

The PWC-20 was administered at the end of the double-blind phase (Day 25) and during the first 2 weeks of the follow-up phase (Days 28, 32, 35 and 39) to assess potential withdrawal symptoms following cessation of study intervention.

The changes in withdrawal symptoms assessed by the PWC-20 after cessation of treatment with esketamine were consistent with observed changes in symptoms of depression and anxiety. No clear evidence of withdrawal was observed within 2 weeks after cessation of intranasal treatment.

TLFB

The TLFB was administered during the follow-up phase to evaluate the potential for ketamine or PCP abuse. No participant reported ketamine or PCP use during the follow-up phase on the TLFB.

Cognitive Battery

Analyses of the cognitive data collected identified no systematic effects of any dose of esketamine on processing speed, executive function, working memory, or visual or verbal learning and memory.

MAH's Safety Conclusions

Esketamine in the context of comprehensive SOC treatment was safe and tolerated at the dose levels evaluated in this study. The observed safety profile in adolescents was consistent with the established safety profile in adults, and no new safety signals were identified in the adolescent population.

2.3.3. Discussion on clinical aspects

This was a double-blind double dummy, psychoactive placebo controlled trial in adolescents. The study enrolled adolescent participants (aged 12 to <18 years) with MDD and assessed to be at imminent risk for suicide after being presented to an ER or other permitted setting. For the psychiatric emergency, the same inclusion criterion that was used in adult studies was also applied in the adolescent population. Subject must have had current suicidal thinking with intent at the time of screening, confirmed by "Yes" responses to both MINI-KID Question B3 ("Think about hurting yourself with the possibility that you might die. Or did you think about killing yourself?") AND Question B10 ("Expect to go through with a plan to kill yourself?"). The inclusion and exclusion criteria are considered acceptable.

As previously discussed, the transient dissociative and sedative side effects of esketamine can be easily observable for many patients and carers/HCPs right after the inhalation, especially in the paediatric field. The choice of a very low dose of midazolam (Oral midazolam solution, 0.125 mg/kg), a psychoactive substance, instead of only placebo, is considered necessary to mask these obvious effects and to avoid "unblinding". Based on the calculations of the MAH the midazolam dose selected for this study is approximately 25% of that recommended for pre-anesthetic use in pediatric populations. The

double dummy was also necessary due to the different administration routes between intranasal Spravato and oral placebo.

The chosen randomisation ratio corresponds finally to 3:2 esketamine:oral placebo, which is not anticipated to create any expectation bias for active treatment to patients. The safety analysis set included 83 patients in total esketamine group and 63 in placebo and the full efficacy analysis included 83 patients in total esketamine group and 63 in placebo. Only two patients from those who were randomised (N=147) were not included in the analysis. The mean (SD) age was 14.9 (1.45) years. The age groups were balanced with 41.4% of participants aged 12-14 years and 58.6% aged 15-17 years.

The primary endpoint was the change from baseline in Children' s Depression Rating Scale, Revised (CDRS-R) total score at 24 hours post first dose (Day 2). CDRS-R is a scale with good reliability and validity in adolescents with depression. The primary efficacy analysis is not optimal since it was performed with LOCF data using an ANCOVA model. However, only eight patients in total (4 in placebo and 4 in esketamine groups) discontinued the study during the double-blind phase and, as anticipated, the most frequent reason for discontinuation was "Lack of efficacy". The small and balanced number of discontinuations (see Table 2 above) is not expected to have an impact on the outcome of the study. Furthermore, the results of the study will help to inform the design of future development of esketamine in MDSI in adolescents and not as confirmation of efficacy.

The overall study design was appropriate for depressed adolescents with a psychiatry emergency and who responded positively to a questionnaire about their suicidal thinking.

For the primary endpoint, the efficacy results for the 28mg group were not so promising compared to the 56 and 84mg groups, with the most favourable results obtained with the pooled 56mg and 84 mg Esketamine groups. The treatment differences versus midazolam + SOC in the individual esketamine 56 mg and 84 mg dose groups did not achieve statistical significance. However, mean (SD) changes in CDRS-R total score from baseline to 24 hours post first dose (Day 2) were -31.2 (14.90) for the pooled esketamine doses of 56 mg and 84 mg + SOC, and -26.2 (16.72) for the midazolam + SOC group. Using an ANCOVA model, the LS mean (95% CI) treatment differences versus the midazolam + SOC group were -5.8 (-11.19; -0.35) for the pooled 56 mg and 84 mg doses + SOC and this was the only statistically significant result (p=0.037).

With respect to the secondary endpoints, the LS mean treatment differences for the Change in CDRS-R total score (Day 1 to Day 25), based on ANCOVA LOCF data, numerically favored the esketamine + SOC groups over the midazolam + SOC group at most time-points during the double-blind treatment phase. Other efficacy evaluations were supportive of the favourable primary endpoint results and included the following:

- Remission based on CDRS-R total score on Day 2: 17.9% in the esketamine 28 mg + SOC group, 16.1% in the esketamine 56 mg + SOC group, 21.7% in the esketamine 84 mg + SOC group, and 7.9% in the midazolam + SOC group
- Response based on CDRS-R total score on Day 2: 53.6% in the esketamine 28 mg + SOC group, 61.3% in the esketamine 56 mg + SOC group, 56.5% in the esketamine 84 mg + SOC group, and 49.2% in the midazolam + SOC group.
- Change in CGI-SS-R Score on Day 2: the median (range) changes in CGI-SS-R score from baseline on Day were similar for all treatment groups: were -2.0 (-5; 1), -2.0 (-5; 2), and -1.0 (-5; 0) for the esketamine 28 mg, 56 mg, and 84 mg + SOC groups, respectively, and -2.0 (-6; 0) for the midazolam + SOC group.

- Resolution of Suicidality on Day 1 (4 hours post first dose): 28.6% in the esketamine 28 mg + SOC group, 32.3% in the esketamine 56 mg + SOC group, 34.8% in the esketamine 84 mg + SOC group, and 12.7% in the midazolam + SOC group.

At Day 25, all treatment groups showed an improvement in CDRS-R total score. In most of the other efficacy evaluations, the results obtained with the 28mg dose were unexpectedly higher than those with 56 mg and did not fit a pattern of dose-response.

The following MAH's statement is noted and it is considered valid: "*While all treatment groups showed an improvement in the severity of suicidality, there were no differences between the esketamine + SOC and midazolam + SOC groups for the change in CGI-SS-R score at 24 hours post first dose or at the end of the double-blind treatment period (Day 25), but there appeared to be some improvement in the esketamine + SOC treatment groups versus the midazolam + SOC group at 4 hours after the first dose*". A similar situation was observed with adults patients.

Overall, the efficacy results in the primary endpoint and other efficacy evaluations (excluding improvement in suicidality) favoured numerically esketamine groups compared to oral psychoactive placebo.

With respect to safety, the majority of participants experienced at least 1 TEAE during the double-blind treatment phase: 27 (93.1%) of 29 participants in the esketamine 28 mg + SOC group, 30 (96.8%) of 31 participants in the esketamine 56 mg + SOC group, 23 (100.0%) of 23 participants in the esketamine 84 mg + SOC group, and 58 (92.1%) of 63 participants in the midazolam + SOC group. There were no TEAEs leading to death during the double-blind treatment phase. However, one participant (in the midazolam + SOC group) died during the follow-up phase due to completed suicide on Day 193, over 5 months after the last dose of study intervention.

During the double-blind treatment phase, AESIs (special interest categories) were observed at the following incidences in the Total Esk and midazolam + SOC groups, respectively: TEAEs suggestive of abuse potential (75.9% vs. 65.1%), increased blood pressure (1.2% vs. 3.2%), increased heart rate (2.4% vs. 1.6%), cardiac safety (preferred term syncope [2.4% vs. 0%]), dizziness/vertigo (60.2% vs. 44.4%), impaired cognition (0% vs. 0%), cystitis related (3.6% vs. 1.6%), anxiety (19.3% vs. 23.8%), and TEAEs potentially related to suicidality (31.3% vs. 27.0%).

The only serious TEAEs (preferred terms) reported by more than 1 participant were suicide attempt (7 [8.4%] in the Total Esk group and 5 [7.9%] participants in the midazolam + SOC group) and suicidal ideation (5 [6.0%] and 3 [4.8%] participants, respectively). There were no discontinuations for safety reasons.

Despite the number of adolescents who received esketamine in the ESKETINSUI2002 study was small (N=83), several safety evaluations did not identify any new or concerning signals from the esketamine use in these 83 adolescents.

It can be agreed with the MAH that the observed safety profile in adolescents was consistent with the established safety profile in adults (ESKETINSUI2002).

3. Rapporteur's overall conclusion and recommendation

Study ESKETINSUI2002 was a double-blind double dummy, oral psychoactive placebo controlled trial in adolescents (aged 12 to <18 years). The study design was overall acceptable. From the primary efficacy analysis, a rapid reduction in the symptoms of depression in participants was observed numerically in favour of the esketamine groups compared to the placebo. However, only the pooled esketamine 56 mg and 84 mg doses + SOC showed a statistically significant treatment benefit on the

change from baseline in CDRS-R total score at 24 hours after the first dose compared to the placebo group (midazolam + SOC). Other efficacy evaluations favoured numerically esketamine.

From the safety perspective, esketamine was well tolerated and no new signals were identified. The safety profile of esketamine observed in adolescents showed no major differences compared to the one already established for adults.

As this study was a requirement in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, the MAH submitted the documentation for study ESKETINSUI2002, which involved the use of intranasal esketamine in the paediatric population within six months of its completion.

☒ **Fulfilled:**

No regulatory action required.

4. Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

Not Applicable

MAH responses to Request for supplementary information

Not Applicable

5. Comments from Member States

MS1

General comments

We support the Rapporteur's conclusions.
It is accepted that the phase 2 trial data from this application are not included in SPC sections 4.2. and 5.1., as results from a confirmatory study (54135419SUI3003) are still to follow as agreed in the PIP. We do have some comments that may be taken into account in finalising the AR (see Clinical Efficacy and Clinical Safety sections).

Clinical Efficacy

The performed study in adolescents utilized a psychoactive placebo – i.e., low-dose midazolam – for blinding purposes. It is not fully clear from the Rapporteur's report why a different approach differing from the adult studies in the same target population was chosen and is considered necessary and acceptable. The adult studies included a plain placebo with a bittering agent and primary efficacy assessment was done by an independent rater, not involved in patient care otherwise. This was considered sufficient for blinding.

Clinical Safety

The Rapporteur concludes that esketamine was well tolerated, which is agreed in the sense of discontinuations for safety reasons (n=0). However as 96.4% of patients receiving esketamine in the double-blind phase had a treatment-emergent adverse event, perhaps another wording could be considered.

Rapporteur's response to MS comments

The comments from MS1 are acknowledged.

With respect to the use of psychoactive substance instead of only placebo, this issue has been previously dealt with. It is thought that the use of placebo will likely unblind the trial because the esketamine effects will be easily observable for many patients and carers/HCPs right after the inhalation, especially in the paediatric field. The use of a "psychoactive placebo" that masks these obvious effects is recommended. The MAH has included the use of an oral psychoactive substance in their protocol (section 3.2.3 of Phase 2b Protocol for the study ESKETINSUI2002). Administration of esketamine is associated with a number of transient adverse events, including sedation, dissociative symptoms, and elevation of blood pressure. To minimize the risk of unblinding the treatment assignment, a psychoactive placebo, midazolam, will be used. Midazolam has been used as a psychoactive placebo in previous studies of ketamine because of its similar onset of action and side effect profile.

With respect to safety, the wording has been modified. The following has been also added: "the majority of participants experienced at least 1 TEAE during the double-blind treatment phase: 27 (93.1%) of 29 participants in the esketamine 28 mg + SOC group, 30 (96.8%) of 31 participants in the esketamine 56 mg + SOC group, 23 (100.0%) of 23 participants in the esketamine 84 mg + SOC group, and 58 (92.1%) of 63 participants in the midazolam + SOC group". These effects could be also associated with the point about the necessity of using a psychoactive substance instead of placebo only. The sentence for zero discontinuations due to safety reasons was also added.

<Annex. Line listing of all the studies included in the development program>

The studies should be listed by chronological date of completion:

<Non clinical studies>

Product Name: Active substance:

Study title	Study number	Date of completion	Date of submission of final study report

<Clinical studies>

Product Name: Active substance:

Study title	Study number	Date of completion	Date of submission of final study report