Janssen Research & Development

Statistical Analysis Plan
Amendment 3

A Randomized, Double-blind, Multicenter, Placebo-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Esketamine Nasal Spray, Administered as Monotherapy, in Adult Participants with Treatment-resistant Depression

Protocol 54135419TRD4005; Phase 4

JNJ54135419 (esketamine)

Status:	Approved
Date:	16 February 2024
Prepared by:	Janssen Research & Development, LLC
Document No.:	EDMS-RIM-224547

Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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VERSION HISTORY

Table 1: SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	26 Jan 2021	Not Applicable	Initial release
2.0	6 Feb 2023	Removed all 1H time interval for vital signs, updated analysis phases and time intervals in Table 2-4 of Section 5.1.2	Corrected time interval to be consistent with protocol
		Added a footnote in Table 2 for deriving Baseline (DB) of efficacy assessments.	To be consistent with protocol, where baseline assessments were allowed to be performed before randomization
		Updated the definition of double-blind and Open-label end date in Section 5.1.3.	To be consistent with eCRF
		Added additional analyses for exploratory endpoints analysis in Section 5.5.1 and 5.5.2 Added combined active intervention group when summarizing baseline disease characteristics in Appendix 6.3	Finetuned the analyses for the responder, open-label and observation analysis sets and made the analysis plan consistent with the protocol with minor changes.
		Updated the analysis set for safety analyses for follow-up phase	Given there is only one assessment (7 days), safety analyses for follow-up phase will be presently only for safety analysis set regardless of which phase a participant completed/discontinued from.
		Updated summary analyses over time for vital signs to include assessments on dosing days for over DB and OL phases [with the exception of Day 2 (DB) and Day 28(DB)] in Section 5.6.3.1. Updated the definition of clinically important abnormalities in vital signs and analysis for abnormalities in Section 5.6.3.1.	Finetuned the summary analyses for vital sign during DB and OL
		Updated the categorization of C-SSRS score of 11 and analyses performed for C-SSRS in Section 5.6.3.2	Finetuned the definition and analyses of C-SSRS.
		Added pharmacokinetics analyses in Section 5.7.2	Added analyses for pharmacokinetics
		Added QTL analyses in Section 6.4	To comply with new standard that a reference to the QTL must be included in the SAP.
3.0	26 Jun 2023	Added a robust sandwich variance estimator for variance-covariance estimation in case unstructured variance-covariance does not converge in Section 5.3.2.1.1	To address the potential adverse impact of covariance matrix mis-specification on the estimation and testing of treatment effect

SAP Version	Approval Date	Change	Rationale
		Added details of multiple imputation model with SAS procedure and SAS code in Section 5.3.2.1.2	Provided SAS code for imputation model including the random seed to enhance the clarity
		Expanded the last paragraph of 5.3.2.1.2 (Sensitivity Analysis) to Section 5.3.3 Supplementary Estimand	Added more details about treatment policy estimand as supplementary analysis for the primary endpoint
		Updated Table 9 Baseline Disease Characteristics to include screening C-SSRS for both lifetime and past 6/12 months and remove baseline C-SSRS	Including Screening C-SSRS to summarize lifetime C-SSRS information
4.0	16 Feb 2024	Added clarification for endpoints in Randomization List 2, OL/OBS phase	Additional summaries requested
		Updated “Responder Analysis Set’ to “Randomization List 2 Analysis Set” in Section 4. Added “List 1” and List 2” to the definition of full efficacy analysis set	Updated to a more straightforward analysis set name to eliminate any confusion and clarified the definiton of full efficacy analysis set
		Updated “therapies” to “treatment” for intercurrent events in Section 5.3.2	To clarify intercurrent events
		Added “(in case of non-convergence, analysis center will be removed from the following model)” to multiple imputation for non-monotone and monotone missing data in Section 5.3.2.1.2.	Make sure that program can run in case of any non-convergence issues when analysis center is included given the large number of categories with analysis center.
		Added “by Imputation_” in the SAS code for monotone imputation in Section 5.3.2.1.2. Updated the delta adjustment part by adding “for subjects who discontinued DB treatment” to indicate only imputed values for subjects who discontinued DB treatment will be adjusted	Updates made to keep the imputation procedure consistent with TRD3001 study
		Combined “Other Secondary Endpoint(s)” and “Exploratory Endpoints” to “Other Endpoints” in Section 5.4	Updates made to be consistent with the protocol
		Added a new remission criterion in Section 1.1 and Section 5.4.3 based on MADRS ≤12	A new criterion and analyses was added to be consistent with the definition in phase 3 program
		Added stacked bar charts for CGI-S in Section 5.5.4.2	To provide graphical presentation of the CGI-S data for better visualization
		Added a new remission (PHQ-9 <5) and response (≥50% improvement) criteria based on	New criteria and analyses were added to be consistent with the definition in phase 3 program

SAP Version	Approval Date	Change	Rationale
		PHQ-9 in Section 1.1 and Section 5.5.6 and 5.5.8	
		Added remission and response rates plot for the double-blind phase and open-label treatment or observation phase in Section 5.5.10	Provided figures for the existing tables for better visualization
		Added Antidepressant status at screening / entry (On-treatment, Off-treatment) to Table 8	Provided summary statistics for stratification factor
		Added two preferred terms "Self-injurious behaviour" and "Suicidal behaviour" to the AE of special interest category of "Events potentially related to suicidality" in Section 6.7	Provided a more comprehensive list of preferred terms for AEs of special interest categories.
		Remove "Clotiapine" from CM of special interest category of Typical Antipsychotics in Section 6.8	Provided a unique CM of special interest category to eliminate confusion

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for all planned analyses for Study 54135419TRD4005.

1.1. Objectives and Endpoints

Primary Objective

The primary objective of this study is to evaluate the efficacy of each individual dose of esketamine nasal spray, 56 mg and 84 mg, compared with placebo nasal spray in improving depressive symptoms in participants with Treatment Resistant Depression (TRD), as assessed by the change in the Montgomery-Asberg Depression Rating Scale (MADRS) total score from Day 1 (prerandomization) to end of the 4-week double-blind treatment phase (Day 28).

Key Secondary Objective

The key secondary objective of this study is to evaluate the efficacy of esketamine nasal spray, 56 mg and 84 mg, compared with placebo nasal spray in improving depressive symptoms in participants with TRD, as assessed by the change in the MADRS total score from Day 1 (prerandomization) to Day 2 (24 hours post first dose).

Other Objectives

- To evaluate the efficacy of esketamine nasal spray, 56 mg and 84 mg, compared with placebo nasal spray in participants with TRD on:
  - Depression response and remission rates
  - Overall severity of depressive illness
  - Change in MADRS total score over time
  - Change in Patient Health Questionnaire 9-item (PHQ-9) total score over time
- To investigate the safety and tolerability of esketamine nasal spray, 56 mg and 84 mg, compared with placebo nasal spray in participants with TRD, including the following:
  - Treatment-emergent adverse events (TEAEs), including adverse events (AEs) of special interest
  - Effects on heart rate and blood pressure
  - Potential effects on suicidal ideation/behavior
- To assess the pharmacokinetic/pharmacodynamic (PK/PD) relationship of esketamine nasal spray and MADRS total score in participants with TRD
- To assess the relationship of biomarkers with response/nonresponse to esketamine nasal spray in participants with TRD

Primary Endpoint

The primary efficacy endpoint is the change in MADRS total score from (Day 1 (prerandomization) to end of the 4-week double-blind treatment phase (Day 28).

Key Secondary Endpoint

The key secondary efficacy endpoint is the change in MADRS total score from Day 1 (prerandomization) to Day 2 (24 hours post first dose).

Other Endpoints

The other efficacy endpoints are as follows:

- MADRS total score
  - Proportion of responders (≥50% reduction from baseline in MADRS total score) over time to the end of the 4- week double-blind treatment phase (Day 28)
  - Proportion of participants in remission (MADRS ≤10 or MADRS ≤12) over time to the end of the 4-week double-blind treatment phase (Day 28)
  - Change from baseline in MADRS total score over time to the end of the 4-week double-blind treatment phase
- Change from baseline in Clinical Global Impression – Severity (CGI-S) over time to the end of the 4-week, double-blind treatment phase (Day 28)
- PHQ-9 total score
  - Proportion of responders (reduction in PHQ-9 score of ≥6 points or ≥50% reduction from baseline in PHQ-9 total score) over time to the end of the double-blind treatment phase (Day 28)
  - Proportion of participants in remission (PHQ-9 total score <5) over time to the end of the double-blind treatment phase (Day 28)
  - Change from baseline in PHQ-9 total score over time to the end of the 4-week double-blind treatment phase (Day 28)

Additional efficacy endpoints will be described for participants who do not meet nonresponse criteria, and participants in open-label treatment or observation phase (Section 5.5.9 and 5.5.10).

1.2. Study Design

This is a randomized, double-blind, placebo-controlled, multicenter study in male and female participants with TRD to evaluate the efficacy, safety, and tolerability of esketamine nasal spray, 56 mg and 84 mg, administered as monotherapy.

This study has 4 phases: screening, double-blind treatment, open-label treatment/observation, and follow-up.

A target of approximately 446 participants will be randomized in a 2:1:1 ratio to placebo, esketamine 56 mg, or esketamine 84 mg. A minimum of 356 participants meeting predefined nonresponse criteria will be randomized for the primary efficacy analysis set. Two separate randomization lists will be generated, a list for those participants who meet the predefined nonresponse criteria and a list for those participants do not meet the nonresponse criteria. The randomization will be stratified by study site and antidepressant treatment status (on- or off-treatment) at screening entry.

The maximum duration of study participation is 24 weeks.

Screening Phase (up to 7 weeks)

All participants will have a minimum of 2 weeks in the Screening Phase without any antidepressant (AD) medication(s) just prior to randomization.

For participants not taking any AD medication at study entry (screening), the mandatory 2-week antidepressant-free period may start at entry. However, the screening phase will be at least 3 weeks to ensure required procedures are completed.

Participants meeting the inclusion/exclusion criteria are eligible to proceed to the double-blind treatment phase.

Double-blind Treatment Phase (4 weeks)

Eligible participants will be randomly assigned at a 2:1:1 ratio to receive double-blind nasal spray treatment with either placebo, esketamine 56 mg, or esketamine 84 mg, twice a week for 4 weeks.

The participant will self-administer nasal spray treatment (esketamine or placebo) under the direct supervision of a healthcare provider during a treatment session at all treatment visits. A treatment session consists of nasal administration of the study medication and post-administration observation.

Missing data in clinical trials can lead to problems that undermine the scientific credibility of causal conclusions. The most common reason for missing data is participants who discontinue the assigned treatment because of AEs, lack of tolerability, lack of efficacy, or inconvenience. In order to reduce missing data in this study, if a participant discontinues double-blind study medication for reasons other than withdrawal of consent, the participant should complete the remaining scheduled visits (without study medication dosing) through the end of the phase (Day 28). For participants remaining in the double-blind treatment phase without study medication dosing, standard-of-care treatment may be initiated. Participants who complete the double-blind treatment phase (ie, including the Day 28 visit) may be eligible to proceed to the open-label treatment/observation phase.

If a participant discontinues from the study in the double-blind treatment phase (ie, prior to completion of the Day 28 visit), an Early Withdrawal visit should be conducted within 1 week of the date of discontinuation. Participants that discontinue early from the double-blind treatment phase (ie, prior to completion of the Day 28 visit) are not eligible to participate in the open-label treatment/observation phase and will proceed to the follow-up phase.

Open-label Treatment or Observation Phase (up to 3 months)

On Day 28, following completion of the double-blind treatment phase assessments (which includes the Day 28 MADRS assessment), participants may participate in an open-label treatment/observation phase.

During the open-label treatment/observation phase, for a duration of up to 3 months, participants can:

- receive open-label esketamine nasal spray
  - If clinically indicated based on the investigator's judgment, participants receiving open-label esketamine nasal spray treatment can also receive standard-of-care treatment for depression.

The decision to receive open-label esketamine must be made at the start of the open-label treatment/observation phase, participants who chose to not receive esketamine (to be observed only) will not be allowed to start open-label esketamine treatment during this phase.

- choose to be observed only (ie, no nasal spray treatment sessions) and receive standard-of-care treatment for depression. Participants who choose to be observed only will not be allowed to switch to the open-label esketamine nasal spray arm during the open-label treatment/observation phase.

Participants in this phase who have opted to receive open-label esketamine will receive 56 mg on Day 28 regardless of the participant's study drug/dose assignment in the double-blind phase. Subsequent doses can remain the same or be adjusted (56 mg or 84 mg) based on efficacy and tolerability. The recommended dosing frequency is as follows:

- Weeks 5 to 8: twice weekly (maximum)
- Weeks 9 to 12: once weekly
- Weeks 13 to 16: weekly or every other week. Dosing frequency will be based on clinical judgment and should be individualized to the least frequent dosing to maintain remission/response.

The participant will self-administer esketamine nasal spray under the direct supervision of a healthcare provider during a treatment session at all treatment visits. A treatment session consists of nasal administration of the study medication and post-administration observation.

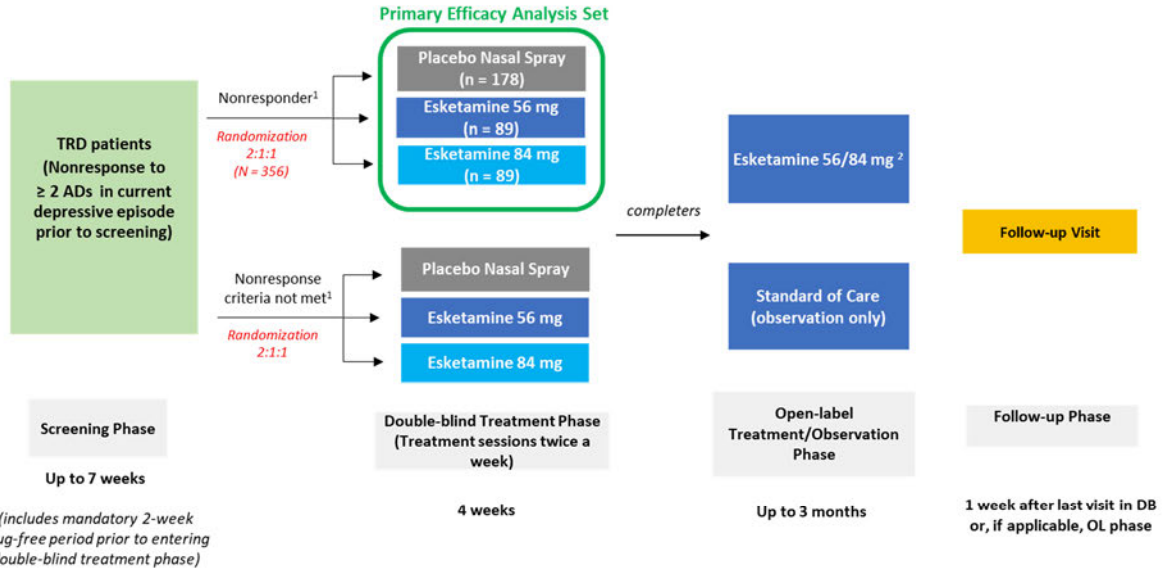
If a participant discontinues the open-label treatment/observation phase for reasons other than withdrawal of consent, the participant will proceed to the follow-up phase.

Follow-up Phase

All participants who have received at least 1 dose of nasal spray medication in the study will complete a follow-up visit in the follow-up phase.

A diagram of the study design is provided in Figure 1.

Figure 1: Schematic Overview of the Study



Abbreviations: AD: antidepressant treatment as specified in ATRQ; DB: double blind; OL: open label; TRD: treatment-resistant depression

1. *Non-response at the end of the screening phase is based on improvement in the Montgomery-Asberg Depression Rating Scale (MADRS) total score from Week 1 to Day 1 and the MADRS total score on select screening MADRS assessments*
2. *With or without standard of care*

2. STATISTICAL HYPOTHESES

The primary efficacy endpoint is the change from baseline in MADRS total score to end of Day 28. The hypothesis of this study is that esketamine nasal spray, 56 mg or 84 mg, when used as monotherapy, is superior to placebo nasal spray in improving depressive symptoms in participants with TRD.

3. SAMPLE SIZE DETERMINATION

The sample size is calculated for the full efficacy analysis set, which includes all randomized patients who meet predefined nonresponse criteria (based on MADRS assessments performed during the screening phase). A standardized treatment effect for the primary endpoint at Day 28 compared to the placebo arm of 0.45 (a treatment difference of 5.4 points for the change from baseline [Day 1 prerandomization] in MADRS total score with a standard deviation of 12) and the Hochberg procedure, with the truncation parameter equal to 1 (which results in the conventional Hochberg method with respect to the primary endpoint) to control the overall familywise error rate of 0.05 (two-sided) were used for the calculation. A 2:1:1 randomization scheme requires 71 participants per active treatment arm and 142 for the placebo arm to complete 4 weeks of treatment to achieve 85% power for each dose and 93% power to correctly reject at least one null hypothesis. Taking into consideration a 20% drop-out rate, 356 patients who meet the predefined nonresponse criteria (based on MADRS assessments performed during the screening phase) will need to be randomized in the study. The treatment discontinuation rate will be closely monitored in a blinded fashion throughout the trial.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

Analysis Sets	Description
Randomized Analysis Set	The randomized analysis set includes all participants who were randomized in the study.
Full Efficacy Analysis Set	The full efficacy analysis set includes all randomized participants who meet nonresponse criteria (List 1) and received at least 1 dose of double-blind study intervention. Four participants meeting nonresponse criteria that were incorrectly randomized to the randomization list for those participants who do not meet the predefined nonresponse criteria (List 2) due to data migration error will be included in the full efficacy analysis set.
Randomization List 2 Analysis Set	The randomization list 2 analysis set includes all randomized participants who do not meet nonresponse criteria during screening and received at least 1 dose of double-blind study intervention. Four participants meeting nonresponse criteria that were incorrectly randomized to the randomization list for those participants who do not meet the predefined nonresponse criteria due to data migration error will be excluded in the randomization list 2 analysis set.
Safety Analysis Set	The safety analysis set includes all randomized participants (both participants who meet and do not meet nonresponse criteria) who received at least 1 dose of double-blind study intervention.
Open-label Analysis Set	The open-label analysis set includes all participants who received at least 1 dose of open-label esketamine study intervention.
Observation Analysis Set	The observation analysis set includes all participants who entered the observation phase but did not receive any open-label esketamine study intervention.

5. STATISTICAL ANALYSES

5.1. General Considerations

5.1.1. Pooling Algorithm for Analysis Centers

Pooling may be conducted for randomized participants who met nonresponse criteria only if a sufficient number of participants are not randomized to a site. If necessary, small study centers with fewer than 4 randomized participants will be combined for the purpose of analysis. These small centers will be ordered according to the total number of participants and then sequentially using the center number. The pooling will be carried out sequentially beginning with the smallest center. The size of any pooled analysis center should be as large as possible and not be larger than the size of the largest center. If the number of small centers is large, and one pooled analysis center cannot include all small centers, then a second (or more) pooled analysis center(s) will be formed after the first one is filled with as many small centers as possible. Pooled sites as described are called analysis centers and will be used in the analyses as center effect.

5.1.2. Visit Windows

As participants do not always adhere to the protocol visit schedule, the following rules are applied to assign actual visits to analysis visits. Listed below are the visit windows and the target days for each visit. The reference day is double-blind start day for the screening and double-blind phases, and the start dates of the respective phases for open-label treatment/observation and follow-up

phases. If a participant has 2 or more actual visits in 1 visit window, the visit closest to the target day will be used as the protocol visit for that visit window. If 2 actual visits are equidistant from the target day within a visit window, the later visit is used.

All assignments will be made in chronological order. Once a visit date is assigned to a visit window, it will no longer be used for a later time point except for the endpoint. Listed below (Table 2-4) are the analysis visit windows and the target days for each visit defined in the protocol.

Table 2: Visit Windows (Screening, Double-blind and Follow-up Phases)

Parameter	Analysis Phase	Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (Day)*
MADRS	Screening	1.1	Week 1 (SC)		
		1.2	Week 2 (SC)		
		1.6	Week 1 (AD free)		
		1.7	Week 2 (AD free)		
	DB	2.1	Baseline (DB)**	≤1	1
		2.2	Day 2 (DB)	2-4	2
		2.4	Day 8 (DB)	5-11	8
		2.6	Day 15 (DB)	12-18	15
		2.8	Day 22 (DB)	19-24	22
		2.10	Day 28 (DB)	25 to end of DB	28
		DB final visit	Endpoint (DB)	2 to End of DB	
	F/U	4.1	Week 1 (F/U)	1 to end of F/U	7
	DB (W/D subjects only)[a]	2.2	Day 2 (DB)	2-4	2
		2.4	Day 8 (DB)	5-11	8
		2.6	Day 15 (DB)	12-18	15
		2.8	Day 22 (DB)	19-24	22
		2.10	Day 28 (DB)	25 to end of DB	28
CGI-S	Screening	1.1	Week 1 (SC)		
	DB	2.1	Baseline (DB)**	≤1	1
		2.2	Day 2 (DB)	2-4	2
		2.4	Day 8 (DB)	5-11	8
		2.6	Day 15 (DB)	12-18	15
		2.8	Day 22 (DB)	19-24	22
		2.10	Day 28 (DB)	25 to end of DB	28
		DB final visit	Endpoint (DB)	2 to end of DB	
	F/U	4.1	Week 1 (F/U)	1 to end of F/U	7
	DB (W/D subjects only)[a]	2.2	Day 2 (DB)	2-4	2
		2.4	Day 8 (DB)	5-11	8
		2.6	Day 15 (DB)	12-18	15
		2.8	Day 22 (DB)	19-24	22
		2.10	Day 28 (DB)	25 to end of DB	28
PHQ-9	Screening	1.6	Week 1 (AD free)		
	DB	2.1	Baseline (DB)**	≤1	1
		2.6	Day 15 (DB)	2-21	15
		2.10	Day 28 (DB)	22 to end of DB	28
		DB final visit	Endpoint (DB)	2 to end of DB	
	DB (W/D subjects only)[a]	2.6	Day 15 (DB)	2-21	15
		2.10	Day 28 (DB	22 to end of DB	28
Vital Signs	Screening	1.1	Week 1 (SC)		
		1.6	Week 1 (AD free)		
		1.7	Week 2 (AD free)		
	DB	2.1	Day 1 (DB): Predose Day 1 (DB): 40M Day 1 (DB): 1.5H	1	1
		2.2	Day 2 (DB)	2	2

Table 2: Visit Windows (Screening, Double-blind and Follow-up Phases)

Parameter	Analysis Phase	Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (Day)*
		2.3	Day 4 (DB): Predose Day 4 (DB): 40M Day 4 (DB): 1.5H	3-6	4
		2.4	Day 8 (DB): Predose Day 8 (DB): 40M Day 8 (DB): 1.5H	7-9	8
		2.5	Day 11 (DB): Predose Day 11 (DB): 40M Day 11 (DB): 1.5H	10-13	11
		2.6	Day 15 (DB): Predose Day 15 (DB): 40M Day 15 (DB): 1.5H	14-16	15
		2.7	Day 18 (DB): Predose Day 18 (DB): 40M Day 18 (DB): 1.5H	17-20	18
		2.8	Day 22 (DB): Predose Day 22 (DB): 40M Day 22 (DB): 1.5H	21-23	22
		2.9	Day 25 (DB): Predose Day 25 (DB): 40M Day 25 (DB): 1.5H	24-26	25
		2.10	Day 28 (DB)	27 to end of DB	28
	F/U	4.1	Week 1 (F/U)	1 to end of F/U	7
	DB (W/D subjects only)[a]	2.2	Day 2 (DB)	2	2
		2.3	Day 4 (DB)	3-6	4
		2.4	Day 8 (DB)	7-9	8
		2.5	Day 11 (DB)	10-13	11
		2.6	Day 15 (DB)	14-16	15
		2.7	Day 18 (DB)	17-20	18
		2.8	Day 22 (DB)	21-23	22
		2.9	Day 25 (DB)	24-26	25
		2.10	Day 28 (DB)	27 to end of DB	28
Weight and BMI	Screening	1.1	Baseline (DB)**	≤1	
	DB	2.10	Day 28 (DB)	2 to end of DB	28
C-SSRS	Screening	1.1	Week 1 (SC)		
		1.2	Week 2 (SC)		
		1.3	Week 3 (SC)		
		1.4	Week 4 (SC)		
		1.5	Week 5 (SC)		
		1.6	Week 1 (AD free)		
		1.7	Week 2 (AD free)		
	DB	2.1	Baseline (DB)**	≤1	1
		2.2	Day 2 (DB)	2	2
		2.3	Day 4 (DB)	3-6	4
		2.4	Day 8 (DB)	7-9	8
		2.5	Day 11 (DB)	10-13	11
		2.6	Day 15 (DB)	14-16	15
		2.7	Day 18 (DB)	17-20	18
		2.8	Day 22 (DB)	21-23	22
		2.9	Day 25 (DB)	24-26	25

Table 2: Visit Windows (Screening, Double-blind and Follow-up Phases)

Parameter	Analysis Phase	Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (Day)*
		2.10	Day 28 (DB)	27 to end of DB	28
	F/U	4.1	Week 1 (F/U)	1 to end of F/U	7
	DB (W/D subjects only)[a]	2.2	Day 2 (DB)	2	2
		2.3	Day 4 (DB)	3-6	4
		2.4	Day 8 (DB)	7-9	8
		2.5	Day 11 (DB)	10-13	11
		2.6	Day 15 (DB)	14-16	15
		2.7	Day 18 (DB)	17-20	18
		2.8	Day 22 (DB)	21-23	22
		2.9	Day 25 (DB)	24-26	25
		2.10	Day 28 (DB)	27 to end of DB	28

*Relative to start date of DB phase for screening and double-blind phases, and relative to the start date of follow-up phase for follow-up phase.
**If a Day 1 value is not available for Baseline (DB), the closest available value prior to randomization with a visit name of "DOUBLE-BLIND DAY 1" will be used for Baseline (DB).
a. DB (W/D subjects only) refers to data collected during the double-blind phase after subjects have discontinued study intervention.

Table 3: Visit Windows for Participants Receiving Esketamine (Open-label Treatment and follow-up phases)

Parameter	Analysis Phase	Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (Day)*
MADRS	Open-label	3.3	Day 35 (OL)	<=11	8
		3.5	Day 42 (OL)	12-18	15
		3.7	Day 49 (OL)	19-25	22
		3.9	Day 56 (OL)	26-32	29
		3.10	Day 63 (OL)	33-39	36
		3.11	Day 70 (OL)	40-46	43
		3.12	Day 77 (OL)	47-53	50
		3.13	Day 84 (OL)	54-60	57
		3.14	Day 91 (OL)	61-67	64
		3.15	Day 98 (OL)	68-74	71
		3.16	Day 105 (OL)	75 to end of OL	78
		OL final visit	Endpoint (OL)	1 to end of OL	
	F/U	4.1	Week 1 (F/U)	1 to end of F/U	7
CGI-S	Open-label	3.2	Day 31 (OL)	<=6	4
		3.3	Day 35 (OL)	7 - 9	8
		3.4	Day 38 (OL)	10 - 12	11
		3.5	Day 42 (OL)	13 - 16	15
		3.6	Day 45 (OL)	17 - 19	18
		3.7	Day 49 (OL)	20 - 23	22
		3.8	Day 52 (OL)	24-26	25
		3.9	Day 56 (OL)	27-32	29
		3.10	Day 63 (OL)	33-39	36
		3.11	Day 70 (OL)	40-46	43
		3.12	Day 77 (OL)	47-53	50
		3.13	Day 84 (OL)	54-60	57
		3.14	Day 91 (OL)	61-67	64
		3.15	Day 98 (OL)	68-74	71
		3.16	Day 105 (OL)	75 to end of OL	78
		OL final visit	Endpoint (OL)	1 to end of OL	
	F/U	4.1	Week 1 (F/U)	1 to end of F/U	7
Vital sign	Open-label	3.1	Day 28 (OL): Predose Day 28 (OL): 40M Day 28 (OL): 1.5H	1	1

Table 3: Visit Windows for Participants Receiving Esketamine (Open-label Treatment and follow-up phases)

Parameter	Analysis Phase	Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (Day)*
		3.2	Day 31 (OL): Predose Day 31 (OL): 40M Day 31 (OL): 1.5H	2-6	4
		3.3	Day 35 (OL): Predose Day 35 (OL): 40M Day 35 (OL): 1.5H	7 - 9	8
		3.4	Day 38 (OL): Predose Day 38 (OL): 40M Day 38 (OL): 1.5H	10 - 12	11
		3.5	Day 42 (OL): Predose Day 42 (OL): 40M Day 42 (OL): 1.5H	13 - 16	15
		3.6	Day 45 (OL): Predose Day 45 (OL): 40M Day 45 (OL): 1.5H	17 - 19	18
		3.7	Day 49 (OL): Predose Day 49 (OL): 40M Day 49 (OL): 1.5H	20 - 23	22
		3.8	Day 52 (OL): Predose Day 52 (OL): 40M Day 52 (OL): 1.5H	24-26	25
		3.9	Day 56 (OL): Predose Day 56 (OL): 40M Day 56 (OL): 1.5H	27-32	29
		3.10	Day 63 (OL): Predose Day 63 (OL): 40M Day 63 (OL): 1.5H	33-39	36
		3.11	Day 70 (OL): Predose Day 70 (OL): 40M Day 70 (OL): 1.5H	40-46	43
		3.12	Day 77 (OL): Predose Day 77 (OL): 40M Day 77 (OL): 1.5H	47-53	50
		3.13	Day 84 (OL): Predose Day 84 (OL): 40M Day 84 (OL): 1.5H	54-60	57
		3.14	Day 91 (OL): Predose Day 91 (OL): 40M Day 91 (OL): 1.5H	61-67	64
		3.15	Day 98 (OL): Predose Day 98 (OL): 40M Day 98 (OL): 1.5H	68-74	71
		3.16	Day 105 (OL): Predose Day 105 (OL): 40M Day 105 (OL): 1.5H	75 to end of OL	78
	F/U	4.1	Week 1 (F/U)	1 to end of F/U	7
C-SSRS	Open-label	3.1	Day 28 (OL) [a]	1	1
		3.2	Day 31 (OL)	2-6	4
		3.3	Day 35 (OL)	7 - 9	8
		3.4	Day 38 (OL)	10 - 12	11
		3.5	Day 42 (OL)	13 - 16	15
		3.6	Day 45 (OL)	17 - 19	18
		3.7	Day 49 (OL)	20 - 23	22
		3.8	Day 52 (OL)	24-26	25
		3.9	Day 56 (OL)	27-32	29
		3.10	Day 63 (OL)	33-39	36
		3.11	Day 70 (OL)	40-46	43

Table 3: Visit Windows for Participants Receiving Esketamine (Open-label Treatment and follow-up phases)

Parameter	Analysis Phase	Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (Day)*
		3.12	Day 77 (OL)	47-53	50
		3.13	Day 84 (OL)	54-60	57
		3.14	Day 91 (OL)	61-67	64
		3.15	Day 98 (OL)	68-74	71
		3.16	Day 105 (OL)	75 to end of OL	78
	F/U	4.1	Week 1 (F/U)	1 to end of F/U	7

*Relative to the first day of open-label treatment phase and relative to the start date of follow-up phase for follow-up phase.
a. If assessment was performed as part of Visit 2.10 (on the same day) in double-blind phase, duplicate predose assessment is not required.

Table 4: Visit Windows for Participants Receiving SOC only: (Observation and follow-up Phases)

Parameter	Analysis Phase	Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (Day)*
MADRS	Observation	3.3	Day 35 (OBS)	<=11	8
		3.5	Day 42 (OBS)	12-18	15
		3.7	Day 49 (OBS)	19-25	22
		3.9	Day 56 (OBS)	26-32	29
		3.10	Day 63 (OBS)	33-39	36
		3.11	Day 70 (OBS)	40-46	43
		3.12	Day 77 (OBS)	47-57	50
		3.14	Day 91 (OBS)	58-71	64
		3.16	Day 105 (OBS)	72 to end of OBS	78
		OBS final visit	Endpoint (OBS)	1 to end of OBS	
	F/U	4.1	Week 1 (F/U)	1 to end of F/U	7
CGI-S, Vital signs, C-SSRS	Observation	3.1	Day 28 (OBS) [a]	1	1
		3.2	Day 31 (OBS)	2-6	4
		3.3	Day 35 (OBS)	7 - 9	8
		3.4	Day 38 (OBS)	10 - 12	11
		3.5	Day 42 (OBS)	13 - 16	15
		3.6	Day 45 (OBS)	17 - 19	18
		3.7	Day 49 (OBS)	20 - 23	22
		3.8	Day 52 (OBS)	24-26	25
		3.9	Day 56 (OBS)	27-32	29
		3.10	Day 63 (OBS)	33-39	36
		3.11	Day 70 (OBS)	40-46	43
		3.12	Day 77 (OBS)	47-57	50
		3.14	Day 91 (OBS)	58-71	64
		3.16	Day 105 (OBS)	72 to end of OBS	78
		OBS final visit[b]	Endpoint(OBS)	1 to end of OBS	
	F/U	4.1	Week 1 (F/U)	1 to end of F/U	7

*Relative to the first day of observation phase and relative to the start date of follow-up phase for follow-up phase.
a. If assessment was performed as part of Visit 2.10 (on the same day) in double-blind phase, duplicate predose assessment is not required.
b. Endpoint (OBS) is only derived for CGI-S.

5.1.3. Analysis Phases

Double-blind Phase

The analysis reference start date of the double-blind analysis phase is the date of the first dose of double-blind study intervention. The analysis reference end date of the double-blind analysis phase is the maximum of the date of the last visit in the double-blind phase and date of early withdrawal

from the double-blind phase. For participants who entered the open-label phase and received first dose of open-label treatment after the date of last visit in double-blind phase, the analysis reference end date of the double-blind analysis phase is the date of first open-label treatment. For randomized participants who did not receive any study intervention in the double-blind phase, both analysis reference start and end dates are missing for the double-blind analysis phase.

Open-label treatment or Observation Phase

Start and end dates for the open-label treatment or observation phase are only defined for participants who participated in the open-label treatment or observation phase. The analysis reference start date of the open-label treatment or observation phase is the reference end date of the double-blind analysis phase. The analysis reference end date of the open-label treatment or observation phase is the maximum of the date of the last visit in the open-label treatment or observation phase and date of early withdrawal from the open-label treatment or observation phase. For randomized participants who did not participate in the open-label treatment or observation phase, both analysis reference start and end dates are missing for the open-label treatment or observation phase.

Follow-up Phase

Start and end dates for the follow-up phase are only defined for participants who continued into the follow-up phase. The analysis reference start date of the follow-up analysis phase is the day after the reference end date for the double-blind analysis phase (for participants who did not continue into open-label treatment or observation phase), or the open-label treatment or observation phase (for participants who participated in the open-label treatment or observation phase). The analysis reference end date of the follow-up analysis phase is the maximum of the last follow-up visit date or the disposition date at follow-up.

5.1.4. Imputation of Efficacy

Imputation method for missing data will include the following methods (Table 5).

Table 5: Imputation of Missing Efficacy Data

Imputation	Text
Multiple Imputation (MI) method	Delta Adjustment

Imputation of total scores will be performed for the following efficacy scales as shown in Table 6 below. If the number of items with missing scores is greater than the maximum number of items presented in the table, the total score will be missing.

For the remaining efficacy assessments which require adding multiple item scores, the total score will be missing if any item score is missing.

Table 6: Imputation of Total Score for Efficacy Scales

Efficacy Scale	Total Number of Items	Maximum Number of Items That Can Be Missing *	Formula for Total Score
MADRS	10	1	Sum of non-missing item scores *

			(10 / number of non-missing items)

5.2. Participant Disposition

The number of participants in the following disposition categories will be summarized throughout the study by intervention group and overall for the all randomized full efficacy, responder, safety, observation and open-label analysis sets as appropriate for the relevant phases:

- Participants randomized
- Participants who received study intervention during each phase
- Participants who completed and discontinued and reasons for discontinuation of study intervention during each phase
- Participants who completed, terminated and reasons for termination from each phase of the study

Listings of participants will be provided for the following categories:

- Participants who discontinued double-blind study intervention
- Participants who discontinued double-blind phase
- Participants who discontinued open-label study intervention
- Participants who discontinued open-label phase
- Participants who terminated study prematurely (trial disposition page)
- Participants who were unblinded during the study period
- Participants who were randomized yet did not receive study intervention.

5.3. Primary Endpoint Analysis

The multiplicity, with regard to testing multiple endpoints (the primary [Day 28] and the key secondary [Day 2]) and multiple doses (esketamine 84 mg vs placebo and esketamine 56 mg vs placebo), will be controlled by a sequential gatekeeping method using the Hochberg procedure, a familywise error rate of 0.05 and a truncation parameter of 1. For the primary hypothesis (Day 28), if the largest p-value of the two dose comparisons of esketamine 84 mg vs placebo and esketamine 56 mg vs placebo is less than two-sided 0.05 level, both esketamine 56 mg and esketamine 84 mg will be declared statistically significantly different from placebo. If the largest p-value of primary endpoint tests is greater than or equal to 0.05, the comparison associated with this p-value will be declared not statistically significant and the smaller p-value will be compared to the 0.025 level. The key secondary hypothesis (Day 2) will be tested using the Hochberg procedure only if the null hypothesis for the primary endpoint is rejected for both doses.

5.3.1. Definition

The primary efficacy endpoint is the change in MADRS total score from Day 1 (prerandomization) to end of the 4-week double-blind treatment phase (Day 28).

The MADRS is a clinician-administered scale designed to measure depression severity and detects changes due to antidepressant intervention. (Montgomery 1979) The scale consists of 10 items, each of which is scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms). Higher scores represent a more severe condition. The MADRS evaluates reported sadness, apparent sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. The test exhibits high inter-rater reliability. The typical recall period for the MADRS is 7 days.

The MADRS total score is the sum of scores from individual question items at a given time point, and ranges from 0 to 60. Higher scores represent a more severe condition. Imputation of total score is presented in section 5.1.4.

Negative changes in MADRS total score indicate improvement.

One estimand is defined for the primary endpoint: Primary Estimand.

5.3.2. Primary Estimand

Primary Trial Objective: To evaluate the efficacy of each individual dose of esketamine nasal spray, 56 mg and 84 mg, compared with placebo nasal spray in improving depressive symptoms in participants with TRD who have met nonresponse criteria, as assessed by the change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) total score from Day 1 (prerandomization) to end of the 4-week double-blind treatment phase (Day 28).

Estimand Scientific Question of Interest: What is the antidepressant benefit from each individual dose (56 mg and 84 mg) of esketamine nasal spray compared with placebo nasal spray in improving depressive symptoms in participants with TRD who have met nonresponse criteria based on the change in the Montgomery-Asberg Depression Rating Scale (MADRS) total score from Day 1 (prerandomization) to end of the 4-week double-blind treatment phase (Day 28) if the participants take study intervention as directed?

The primary estimand is defined by the following 5 components:

Study Intervention:

- Experimental: esketamine 56 mg, esketamine 84 mg
- Control: Placebo

Population: Participants with TRD who have met the inclusion/exclusion criteria and the nonresponse criteria

Variable: Change from baseline to Day 28 in the MADRS total score

Summary Measure: Difference in means between each dose and placebo for the change from baseline in MADRS total score at Day 28.

Intercurrent events and their corresponding strategies:

Intercurrent Events	Name of Strategy for Addressing Intercurrent Events and Its Description
Premature discontinuation of the randomized treatment with or without a switch to alternative antidepressant treatment	Hypothetical strategy: as if the intercurrent event had not occurred

5.3.2.1. Analysis Methods

5.3.2.1.1. Primary Analysis

Descriptive statistics of the actual values and the change from baseline to each postbaseline time point in the double-blind phase will be presented for MADRS total score by intervention group.

MADRS total score will be analyzed by a Mixed-Effect Model for Repeated Measures (MMRM) based on observed case data. The fixed terms included in the model will be intervention group, analysis center, antidepressant treatment status (on- or off-treatment) at screening entry, day, and day-by-intervention interaction, and the baseline MADRS total score as a covariate. The within-subject covariance between visits will be estimated via an unstructured variance-covariance matrix. In case of convergence problems, alternative variance-covariance structures will be tried in the following order, with the first structure that converges being used in the analysis: heterogeneous Toeplitz, standard Toeplitz, and AR(1) with separate subject random effect. In the case that a structured covariance needs to be used, a robust sandwich variance estimator of heterogeneous Toeplitz, standard Toeplitz, and AR(1) will be used to address the potential adverse impact of covariance matrix mis-specification on the estimation and testing of treatment effect. Comparison between each dose of esketamine nasal spray and placebo nasal spray at Day 28 will be performed using the appropriate contrast. Difference in least square means and 2-sided 95% CI will be presented for each dose level.

Means and mean changes from baseline (+/- SE), and least squares mean changes from baseline (+/- SE) over time will be presented graphically.

Model Diagnostics

The normality and equal variance assumptions underlying the primary MMRM model will be assessed graphically for the MADRS total score at Day 28. Residuals from the primary models will be plotted against the predicted values and a QQ plot of the residuals versus the expected quantiles of the standard normal distribution will be presented. If either the equal variance or the normality assumption appears to be grossly violated, other methods including an ANCOVA on ranks model or an appropriate transformation of the primary endpoint might be considered.

5.3.2.1.2. Sensitivity Analysis

To evaluate the robustness of the MMRM analysis to increasing deviations from the MAR assumption, a delta adjustment multiple imputation method will be implemented on the MADRS total score if the results from the primary analysis show a significantly greater improvement in

MADRS total score at Day 28 in each dose of esketamine nasal spray compared to placebo. (National Research Council 2010; Permutt 2015)

This method will employ the following 3 steps:

Step 1 – Multiple Imputation (MI)

Missing at random (MAR) is assumed for intermediate missing data (ie, missing data between non-missing observations). If there are participants with a non-monotone missing data pattern, datasets with only monotone missing data patterns will be created first by imputing the intermediate missing values using methods such as the MCMC (Markov Chain Monte Carlo) method. Five hundred (500) imputations will be performed to create 500 unique datasets which now have monotone missing (ie., missing data after the participant experienced an intercurrent event) data pattern. This will be done using SAS PROC MI and the MCMC statement with the following specifications (in case of non-convergence, analysis center will be removed from the following model):

```
PROC MI DATA=INPUT NIMPUTE=500 SEED=234 OUT=IN  MCMC;
VAR …; (intervention group, analysis center, antidepressant treatment status, and the
preceding non-missing values in the order of clinical visits: baseline, Day 2, Day 8, Day 15,
Day 22 and Day 28)
MCMC CHAIN=SINGLE NBITER=200 NITER=100 IMPUTE=MONOTONE;
RUN;
```

Monotone missing data will first be imputed by MAR-based MI regression, and the imputed scores in the experimental intervention groups will be adjusted to be worse than the other participants in same group with non-missing data as discussed below. The multiple imputation will be performed using SAS PROC MI with the MONOTONE statement and the REGRESSION option with the following specifications (in case of non-convergence, analysis center will be removed from the following model):

```
PROC MI DATA=IN_MCMC NIMPUTE=1 (see note) SEED=234 OUT=OUTPUT;
BY   IMPUTATION  ;
VAR …; (intervention group, analysis center, antidepressant treatment status, and the
preceding non-missing values in the order of clinical visits: baseline, Day 2, Day 8, Day 15,
Day 22 and Day 28)
CLASS …; (intervention group, analysis center, antidepressant treatment status)
MONOTONE REGRESSION;
RUN;
*Note: NIMPUTE=500 if MCMC was NOT applied at the previous step.
```

The imputed values for subjects who discontinued DB treatment [QX[1]will be adjusted by adding δ_C to the imputed values for participants randomized to the control group and adding δ_A to the imputed values for participants randomized to the experimental intervention groups. Delta-adjusted fully imputed datasets will be generated for different combinations of δ_C and δ_A values as defined below:

- $\delta_c = 0$ and $\delta_A = 0$ *to* Δ^* in increments of 1 (experimental group-only adjustment analysis)
  - Adding positive values results in higher (worse) scores. Δ^* represents the adjustments leading to the 'tipping point', so the smallest delta adjustments values at which conclusions change from *favorable* (ie, statistically significant: 2-sided p-values for both doses ≤0.05 in favor of esketamine, or the smaller 2-sided p-value ≤0.025 in favor of esketamine) to *unfavorable* (fail to reject the null hypothesis of no intervention difference).

These methods will be applied to all missing data under hypothetical strategy.

Step 2 – Analysis

Same MMRM analysis as described for the primary efficacy analysis (Section 5.3.2.1.1) will be performed for each set of the adjusted fully imputed datasets.

Step 3 – Pooling

Rubin's methodology will be applied to the MMRM results from the 500 imputed datasets to produce final inferences. (Rubin 1987)

Between-group comparisons to placebo at Day 28 (eg, 2-sided p-values, point estimates for intervention difference) will be displayed for each considered δ_A, up to the 'tipping point' adjustment.

5.3.3. Supplementary Estimand

All components as described under Primary Estimand (Section 5.3.2) apply to the Supplementary Estimand except the strategy for addressing intercurrent events.

Intercurrent events and their corresponding strategies:

Intercurrent Events	Name of Strategy for Addressing Intercurrent Events and Its Description
Premature discontinuation of the randomized treatment with or without a switch to alternative antidepressant treatment	Treatment policy strategy: all observed values of the endpoint are used regardless of whether or not the participant had experienced this intercurrent event

The treatment policy strategy attempts to estimate the treatment effect irrespective of the intercurrent event. Therefore, post-treatment observations will be used in the analysis for those participants who discontinued study intervention.

5.3.3.1. Analysis Methods

This method will employ the following 3 steps:

Step 1 – Multiple Imputation (MI)

Once monotone missing datasets are created after imputing intermediate missing data using the MCMC method as described in Section 5.3.2.1.2, the monotone missing data will be imputed using the Copy Reference (CR) MI method for the primary analysis as a supplementary analysis.

Missing not at random (MNAR) is assumed for monotone missing (i.e., missing data after the occurrence of an intercurrent event under treatment policy) in the experimental intervention group, where efficacy scores are assumed as if participant had always been in the control group. MAR is assumed for missing data in the control group.

The efficacy data that is either missing or not used after the intercurrent event at a given timepoint will be imputed using the imputation model of the control group, i.e., conditional on the data observed or imputed at previous timepoints relative to the mean of the model for the control group.

This approach does not assume a sustained benefit of experimental intervention for the efficacy data that is either missing or not used after the intercurrent event, and uses an imputation method that is based on the control group distribution and the estimated correlations between time points in the control group.

Step 2 – Analysis

Same MMRM analysis as described for the primary efficacy analysis (Section 5.3.2.1.1) will be performed for each set of the adjusted fully imputed datasets.

Step 3 – Pooling

Rubin's methodology will be applied to the MMRM results from the 500 imputed datasets to produce final inferences. (Rubin 1987)

5.4. Secondary Endpoint(s) Analysis

5.4.1. Key Secondary Endpoint

Similar to the primary analysis, analysis of the key secondary endpoint will be based on the full efficacy analysis set using the MADRS total scores collected during the double-blind phase.

5.4.1.1. Definition

The key secondary efficacy endpoint is the change from baseline in MADRS total score from Day 1 (prerandomization) to Day 2.

5.4.1.2. Key Secondary Estimand

All components as described under Primary Estimand (Section 5.3.2) apply to the Key Secondary Estimand except for the variable and summary measure:

Variable: Change from baseline to Day 2 in the MADRS total score

Summary Measure: Difference in means between each dose and placebo for the change from baseline in MADRS total score at Day 2.

5.4.1.3. Analysis Methods

The key secondary efficacy variable, change from baseline in MADRS total score at Day 2 in the double-blind treatment phase, will be analyzed using the same MMRM model as described for the primary endpoint.

5.5. Other Endpoint(s)

Analyses of other endpoints will be based on the full efficacy analysis set unless otherwise specified.

5.5.1. Response (≥50% Improvement) Based on MADRS Total Score

5.5.1.1. Definition

A participant is defined as a responder at a given time point if the percent improvement from baseline in MADRS is ≥50% at that time point (ie, percent change ≤-50%).

5.5.1.2. Analysis

The number and percentage of participants who achieve a response will be summarized at each time point during the double-blind phase by intervention group.

Response rates over time will be plotted for double-blind phase.

5.5.2. Remission (MADRS ⩽10) Based on MADRS Total Score

5.5.2.1. Definition

A participant is defined as a remitter at a given time point if the MADRS total score is ≤10 at that time point.

5.5.2.2. Analysis

The number and percentage of participants who achieve remission (MADRS ≤10) will be summarized at each time point during the double-blind phase by intervention group.

Remission rates will be plotted for double-blind phase.

5.5.3. Remission (MADRS ⩽12) Based on MADRS Total Score

5.5.3.1. Definition

A participant is defined as a remitter at a given time point if the MADRS total score is ≤12 at that time point.

5.5.3.2. Analysis

The number and percentage of participants who achieve remission (MADRS ≤12) will be summarized at each time point during the double-blind phase by intervention group.

Remission rates will be plotted for double-blind phase.

5.5.4. Clinical Global Impression – Severity (CGI-S)

5.5.4.1. Definition

The CGI-S provides an overall clinician-determined summary measure of the severity of the participant's illness that takes into account all available information, including knowledge of the participant's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the participant's ability to function. (Guy 1991) The CGI-S evaluates the severity of psychopathology on a scale of 1 to 7. Considering total clinical experience with the depression population, a participant is assessed on severity of illness at the time of rating according to: 0=not assessed; 1=normal (not at all ill); 2=borderline ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among the most extremely ill patients.

A score of 0 indicates that the participant was not assessed, and will be treated as missing. The score from 1 to 7 will be summarized as recorded.

Negative changes in CGI-S score indicate improvement.

5.5.4.2. Analysis

Descriptive statistics of the actual values and the change from baseline will be presented by intervention group for observed case data.

A frequency distribution over time of the CGI-S scores will be provided by intervention group. The frequency distributions will be presented graphically using stacked bar charts for the baseline, Day 2 and Day 28.

5.5.5. Patient Health Questionnaire - 9 Item (PHQ-9)

5.5.5.1. Definition

The 9-item Patient Health Questionnaire - 9 Item (PHQ-9) scale scores each of the 9 symptom domains of the DSM-5 MDD criteria and it has been used both as a screening tool and a measure of response to intervention for depression. Each item is rated on a 4-point scale (0=not at all, 1=several days, 2=more than half the days, and 3=nearly every day). The participant's item responses are summed to provide a total score (range of 0 to 27), with higher scores indicating greater severity of depressive symptoms. The recall period is 2 weeks.

Negative changes in PHQ-9 total score indicate improvement.

5.5.5.2. Analysis

Descriptive statistics of the actual values and the change from baseline to each postbaseline time point will be presented for PHQ-9 total score by intervention group.

Changes from baseline over time in PHQ-9 total score will be analyzed based on the same MMRM model as described for the primary endpoint with baseline PHQ-9 total score as the covariate.

Least squares mean changes from baseline (+/- SE) over time will be presented graphically.

5.5.6. Response (≥ 6 Points Improvement) Based on PHQ-9 Total Score

5.5.6.1. Definition

A participant is defined as a responder at a given time point if improvement in PHQ-9 total score is ≥6 points at that time point.

5.5.6.2. Analysis

The number and percentage of participants who achieve response (≥ 6 points improvement) will be summarized at each time point during the double-blind phase by intervention group.

Response rates over time will be plotted for the double-blind phase.

5.5.7. Response (≥ 50% Improvement) Based on PHQ-9 Total Score

5.5.7.1. Definition

A participant is defined as a responder at a given time point if the percent improvement from baseline in PHQ-9 total score is ≥50% at that time point (ie, percent change ≤-50%).

5.5.7.2. Analysis

The number and percentage of participants who achieve response (≥ 50% Reduction) will be summarized at each time point during the double-blind phase by intervention group.

Response rates over time will be plotted for the double-blind phase.

5.5.8. Remission (PHQ-9 <5) Based on PHQ-9 Total Score

5.5.8.1. Definition

A participant is defined as a remitter at a given time point if the PHQ-9 total score is <5 at that time point.

5.5.8.2. Analysis

The number and percentage of participants who achieve remission (PHQ-9 <5) will be summarized at each time point during the double-blind phase by intervention group.

Remission rates over time will be plotted for the double-blind phase.

5.5.9. Efficacy Data in the Double-blind Phase for Participants Who Do Not Meet Nonresponse Criteria (Randomization List 2 Analysis Set)

These summaries will be provided for the randomization list 2 analysis set. Descriptive statistics of the actual values and the change from baseline to each post baseline time point in the double-blind phase, will be presented for MADRS total score, CGI-S score and PHQ-9 score by intervention group.

Means and mean changes from baseline (+/- SE) over time will be presented graphically for MADRS total score during double-blind phase.

The number and percentage of participants who achieve remission based on MADRS total score, achieve response based on MARDS total score or achieve response based on PHQ-9 will be summarized at each time point during the double-blind phase by intervention group.

A frequency distribution over time of the CGI-S scores will be provided for the double-blind phase by intervention group.

5.5.10. Efficacy Data in the Open-Label Treatment or Observation Phase

The summaries will be provided for the open-label analysis set and observation analysis set, separately. Descriptive statistics of the actual values and the change from baseline to each post baseline time point in the double-blind and open-label treatment or observation phase, will be presented for MADRS total score and CGI-S score.

Means and mean changes from baseline (+/- SE) over time will be presented graphically for MADRS total score during double-blind phase and open-label treatment or observation phase.

The number and percentage of participants who achieve remission based on MADRS total score, achieve response based on MARDS total score will be summarized at each time point during the double-blind phase and open-label treatment or observation phase by intervention group.

Remission and response rates based on MARDS total score will be plotted for the double-blind phase and open-label treatment or observation phase.

A frequency distribution over time of the CGI-S scores will be provided for the double-blind phase and open-label treatment or observation phase by intervention group.

5.5.11. Subgroup Analyses

Forest plots will be provided displaying analysis results for each subgroup listed in Section 5.7.1. The point estimate of the treatment difference and its 95% confidence interval for each subgroup will be based on an MMRM analysis for the primary endpoint using the appropriate contrast. The model will include factors for treatment, analysis center, antidepressant treatment status at screening entry, day, subgroup, day-by-treatment interaction, treatment-by-subgroup interaction, day-by-treatment-by-subgroup, and baseline MADRS total score as a covariate. The terms in the models will be adjusted for the subgroup of baseline MADRS total score (≤/> median). Baseline MADRS total score (as a continuous covariate) will not be included in the model when the dichotomized baseline MADRS total score is included in the model.

The analyses will be performed for the full efficacy analysis set.

5.6. Safety Analyses

All safety analyses for double-blind phase will be based on the safety analysis set based on actual intervention received, unless otherwise specified. All safety analyses for the open-label treatment/ observation phase will be based on open-label analysis set and observation analysis set based on participants receiving esketamine or SOC only, respectively, in this phase. Safety analyses for the follow-up analysis phase will be based on the safety analysis set.

For all continuous safety variables, descriptive statistics by intervention group will include the N, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by intervention group using frequency counts and percentages.

5.6.1. Extent of Exposure

The number and percentage of participants who receive each study agent within a study intervention will be summarized by phase.

Descriptive statistics for duration of each study agent within a study intervention (N, mean, SD, median, and range [minimum, maximum]) will be summarized by phase.

Duration of intervention will be summarized for the double-blind phase in the following duration categories: ≤7 days, 8-14 days, 15-21 days, 22-25 days, >25 days for each study agent within a study intervention.

Duration of intervention will be summarized for the open-label treatment phase in the following duration categories: ≤28 days, 29-56 days, 57-84, >84 days for participants receiving open-label esketamine study intervention.

Study intervention duration is defined as (date of last dose of study intervention – date of first dose of study intervention) +1.

Total dose days of intervention is defined as the total number of days that study intervention was administered to the participant (excluding days off study intervention). Descriptive statistics for total dose days within a study intervention (N, mean, SD, median, and range [minimum, maximum]) will be summarized. A frequency distribution will also be provided.

The analysis will be performed on safety analysis set and open-label analysis set.

Patients' awareness of study intervention assignment will be summarized for the double-blind phase on the full efficacy analysis set and safety analysis set.

5.6.2. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study intervention through the day of last dose is considered to be treatment emergent. If the event occurs on the day of the initial administration of study intervention, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment emergent unless it is known to be prior to the first administration of study intervention based on partial onset date or resolution date. All reported treatment-emergent adverse events will be included in the analysis. For each adverse event, the number and percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group.

Assignment of adverse events to double-blind, open-label treatment/observation or follow-up phase will be made based on the following rules:

Double-blind phase:

AEs will be assigned to the double-blind analysis phase as detailed below.

- For participants who did not continue to open-label treatment/observation phase or participants who chose to be observed only (receive SOC only) in the observation phase: double-blind phase start date/time ≤AE onset date/time ≤double-blind phase end date.
- For participants who received open-label esketamine nasal spray: double-blind phase start date /time ≤AE onset date/time <double-blind phase end date/time (ie, open-label phase start date/time)
    - AEs that occur on the last day of double-blind phase but AE onset time is missing will be assigned to the double-blind phase.

AEs that are assigned to the double-blind analysis phase as detailed below will be considered as treatment-emergent.

- For participants completed double-blind treatment: all the AEs in the double-blind treatment phase will be considered as treatment-emergent for the double-blind phase.
- For participants who discontinued double-blind treatment and double-blind phase at the same time, all the AEs in the double-blind treatment phase will be considered as treatment-emergent for the double-blind phase.
- For participants who discontinued double-blind treatment but continued to be assessed until the end of double-blind phase (Day 28), AEs will be considered as treatment-emergent for the double-blind phase only if they satisfy the condition: double-blind phase start date /time ≤ AE onset date/time ≤ last day of double-blind treatment.

Open-label treatment phase:

- For participants who received open-label esketamine nasal spray, all AEs that are assigned to the open-label treatment phase will be considered as treatment-emergent if they satisfy the condition: open label treatment phase start date/time≤ AE onset date/time ≤ open label treatment phase end date.
    - AEs that occur on the last day of double-blind phase but AE onset time is after open-label dosing will be considered as treatment-emergent for the open-label treatment phase.

Observation phase:

- For participants who received SOC only in the observation phase, all AEs that are assigned to the observation phase will not be considered as treatment-emergent if they satisfy the condition: double-blind phase end date+1≤ AE onset date ≤ observation phase end date.

Follow-up phase:

- Any AEs that are assigned to the follow-up phase will not be considered as treatment-emergent. AEs during the follow-up phase should satisfy the condition: follow-up phase start date ≤AE onset date ≤follow-up phase end date.

Summary tables will be provided for adverse events by phase:

- AEs
- Serious AEs (SAEs)
- AEs leading to discontinuation of each study agent within a study intervention
- AEs by severity
- AEs by relationship to each study agent within a study intervention
- AEs of special interest

In addition to the summary tables, listings will be provided for participants who had:

- SAEs
- AEs leading to discontinuation of study intervention
- AEs of special interest

Incidence of other treatment-emergent adverse events of special interest will be summarized. See Appendix 7 for list of adverse events in each category.

The proportion of TEAEs occurring on dosing days and the proportion of TEAEs that occur on dosing days with same day resolution will be summarized. Duration and resolution time of severe TEAEs will also be summarized.

A listing of participants who died will be provided.

5.6.3. Additional Safety Assessments

5.6.3.1. Vital Signs and Physical Examination Findings

Descriptive statistics for values and changes from baseline at each scheduled time-point will be presented for temperature, systolic blood pressure, diastolic blood pressure, pulse rate, weight, and BMI by phase. In addition, descriptive statistics of pulse rate and blood pressure (systolic and diastolic) values, changes and percent changes from predose will be provided for each dosing day by phase. These summaries will also be provided by hypertension status (history of hypertension recorded in medical history: Yes/No). For DB and OL phases, summary statistics over time will only be provided on dosing days with the exception of Day 2 (DB) and Day 28(DB). Frequency distributions of maximum percent change increase from predose and time of maximum percent change increase will also be presented by phase. Note that if the maximum value within a phase occurs at multiple time points, the earliest time point is selected.

The proportion of participants who have a treatment-emergent abnormality, as defined in Table 7 below, will be presented over time and by phase. Both the double-blind baseline and the predose assessment will be used to determine abnormal values. A listing of participants meeting any of the criteria will also be provided.

Table 7: Clinically Important Abnormalities in Vital Signs

Vital Sign	Abnormal Category	Criteria
Pulse	Abnormally high	≥100 bpm and with ≥15 bpm increase from baseline/predose
	Abnormally low	≤50 bpm and with ≥15 bpm decrease from baseline/predose
Systolic blood pressure	Abnormally high	≥180 mm Hg and with ≥20 mm Hg increase from baseline/predose
	Abnormally low	≤90 mm Hg and with ≥20 mm Hg decrease from baseline/predose
Diastolic blood pressure	Abnormally high	≥105 mm Hg and with ≥15 mm Hg increase from baseline/predose
	Abnormally low	≤50 mm Hg and with ≥15 mm Hg decrease from baseline/predose

The proportion of participants who experienced acute hypertension (systolic BP≥180 or diastolic BP≥110) at any time during the double-blind phase will be summarized by treatment group and hypertension status.

Mean (+/-SE) values for systolic BP, diastolic BP and heart rate will be presented graphically over the double-blind phase by intervention group and hypertension status. In addition, for participants with hypertension who receive antihypertensive medication, the same graphs will be summarized by medication type (beta-blockers, all other agents).

5.6.3.2. Other Safety Parameters

5.6.3.2.1. Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a low-burden measure of the spectrum of suicidal ideation and behavior that was developed to assess severity and track suicidal events through any intervention (Posner 2007). It is a clinical interview providing a summary of both suicidal ideation and behavior that can be administered during any evaluation or risk assessment to identify the level and type of suicidality present. The C-SSRS has been used frequently in clinical studies, and is a validated, standard measure for suicidal ideation assessment. Using the C-SSRS, the outcomes will be categorized using the scoring for the 11 categories:

Suicidal Ideation (1-5)	
1	Wish to be dead
2	Non-specific active suicidal thoughts
3	Active suicidal ideation with any methods (not plan) without intent to act
4	Active suicidal ideation with some intent to act, without specific plan
5	Active suicidal ideation with specific plan and intent
Suicidal Behavior (6-10)	
6	Preparatory acts or behavior
7	Aborted attempt
8	Interrupted attempt

9	Actual attempt
10	Suicide
Non-suicidal self-injurious behavior (11)	
11	Non-suicidal self-injurious behavior

At each time point, an event of suicidal ideation or behavior will be assigned a score of 1 to 10 based on the maximum response for the C-SSRS at that visit. If there is no event of suicidal ideation or behavior, a score of 0 will be assigned (0="no suicidal ideation or behavior that can be assessed on the basis of C-SSRS"). A participant with an event of non-suicidal self-injurious behavior only will not be considered as having suicidal ideation or behavior, therefore a score of 0 will be assigned. However, an additional score of 11 will be assigned to summarize any participants with an event of non-suicidal self-injurious behavior.

Shifts from the baseline to the maximum postbaseline score pertaining to suicidal ideation or suicidal behavior (i.e., scores 1 to 10) will be summarized by study intervention for each phase.

The maximum score (of scores 0 to 10) assigned to each participant will be grouped into one of three broad categories: No suicidal ideation or behavior (0), Suicidal ideation (1-5), Suicidal behavior (6-10). Shifts from baseline to the maximum postbaseline category will be summarized by study intervention for each phase.

A frequency distribution of the scores for the 11 categories (0 to 10) will be provided by study intervention at each time point for each phase. In addition, the number and proportion of participants with non-suicidal self-injurious behavior (a score of 11) will be provided by study intervention at each time point for each phase.

5.7. Other Analyses

5.7.1. Definition of Subgroups

Subgroup	**Definition**
Sex	Male Female Undifferentiated
Race	White Black Other
Age Group	18-34 years 35-54 years 55-64 years ≥ 65 years
Failed antidepressant intervention history	2 3 or more
Number of major depressive episodes to date, including current episode	1 2 ≥3
Baseline MADRS total score (<=/>median)	Yes No

Subgroup	Definition
Antidepressant status at screening / entry	On-treatment Off-treatment

5.7.2. Pharmacokinetics

PK analyses will be performed on the safety analysis set.

Descriptive statistics (N, mean, SD, median, range, CV (%) and IQ range) will be used to summarize plasma concentrations at each sampling time point for esketamine (and noresketamine if measured)

5.7.3. Quality Tolerance Limit

Quality Tolerance Limit (QTL) parameters and thresholds are defined and will be monitored in this study. QTL parameters will be summarized. More details are described in the Integrated Analytical Risk-Based Monitoring (iARBM) Plan.

5.8. Interim Analyses

Not applicable.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

AD	antidepressant
AE	adverse event
ANCOVA	analysis of covariance
BMI	body mass index
BP	Blood pressure
CGI-S	Clinical Global Impression – Severity
CI	confidence interval
CR	Copy reference
CRF	case report form
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
DB	Double-blind
DSM-5	Diagnostic and Statistical Manual of Mental Disorders (5th edition)
eCRF	electronic case report form
FDA	Food and Drug Administration
F/U	Follow-up
ICH	International Conference on Harmonisation
MADRS	Montgomery-Asberg Depression Rating Scale
MAR	missing at random
MCMC	Markov Chain Monte Carlo
MDD	Major Depressive Disorder
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MMRM	Mixed-Effect Model for Repeated Measures
MNAR	Missing not at random
OBS	Observation
OL	Open-label
PD	pharmacodynamic(s)
PHQ-9	Patient Health Questionnaire - 9 Item
PK	pharmacokinetic(s)
SAE	serious adverse event
QTL	Quality Tolerance Limits
SAP	Statistical Analysis Plan
SD	standard deviation
SE	Standard error
SOC	Standard of care
TEAE	treatment-emergent adverse event
TRD	Treatment Resistant Depression
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

6.2. Appendix 2 Changes to Protocol-Planned Analyses

Not applicable

6.3. Appendix 3 Demographics and Baseline Characteristics

The number of participants in each analysis set will be summarized and listed by intervention group, combined active intervention group, and overall. In addition, the distribution of participants by site ID will be presented.

Table 8 presents a list of the demographic variables that will be summarized by intervention group, combined active intervention group, and overall for the full efficacy analysis set, safety analysis set and randomization list 2 analysis set.

Table 8: Demographic Variables

Continuous Variables	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Weight (kg)	
Height (cm)	
Body Mass Index (BMI) (kg/m^2)	
Categorical Variables	Frequency distribution with the number and percentage of participants in each category.
Age (18-34 years, 35-54 years, 55-64 years, and ≥65 years)	
Sex (male, female, undifferentiated)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	
BMI (underweight <18.5 kg/m^2, normal 18.5-<25 kg/m^2, overweight 25-<30 kg/m^2, obese >=30 kg/m^2)	
Antidepressant status at screening / entry (On-treatment, Off-treatment)	

[a] If multiple race categories are indicated, the Race is recorded as 'Multiple'

A summary of the stratification factors will be provided by intervention arm.

Table 9 presents a list of the baseline disease characteristics variables that will be summarized by intervention group, combined active intervention group, and overall for the full efficacy analysis set, safety analysis set and randomization List 2 analysis set.

Table 9: Baseline Disease Characteristics

Continuous Variables	**Summary Type**
Age (years) when diagnosed with MDD	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Duration (weeks) of current depressive episode	
Baseline MADRS total score	
Baseline CGI-S score	
Baseline PHQ-9 total score	
Screening IDS-C_{30} total score	
Categorical Variables	Frequency distribution with the number and percentage of participants in each category.
Baseline CGI-S score (Normal (not at all ill), Borderline mentally ill, Mildly ill, Moderately ill, Markedly ill, Severely ill, Among the most extremely ill patients)	
Screening C-SSRS lifetime (no event, suicidal ideation, suicidal behavior)	
Screening C-SSRS past 6 or 12-month (no event, suicidal ideation, suicidal behavior)	
Antidepressant treatment history (number of medications taken for at least 6 weeks during the current episode as obtained in the MGH-ATRQ)	
Failed antidepressant intervention history (2, 3 or more)	
Number of major depressive episodes to date, including current episode (1, 2, ≥3)	
Family history of alcohol abuse (Yes, No)	
Family history of anxiety disorder (Yes, No)	
Family history of bipolar disorder (Yes, No)	
Family history of depression (Yes, No)	

Family history of schizophrenia (Yes, No)	
Family history of substance abuse (Yes, No)	

6.4. Appendix 4 Protocol Deviations and Quality Tolerance Limits (QTL)

In general, the following list of major protocol deviations may have the potential to impact participants' rights, safety or well-being, or the integrity and/or result of the clinical study. Participants with major protocol deviations will be identified prior to database lock and the participants with major protocol deviations will be summarized by category for the all randomized analysis set.

- Developed withdrawal criteria but not withdrawn
- Entered but did not satisfy criteria
- Received a disallowed concomitant treatment
- Received wrong treatment or incorrect dose
- Other

Number of participants not meeting inclusion criteria, or meeting exclusion criteria will be summarized by study intervention group for the all randomized analysis set.

Quality Tolerance Limit parameters and thresholds are defined and will be monitored in this study. QTL parameters will be summarized. More details are described in the Integrated Analytical Risk-Based Monitoring (iARBM) Plan.

6.5. Appendix 5 Prior and Concomitant Medications

Prior medications and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study intervention. Concomitant medications are defined as any therapy used on or after the same day as the first dose of study intervention, including those that started before and continue on after the first dose of study intervention.

Summaries of concomitant medications will be presented by base preferred term for the double-blind, open-label treatment/observation and follow-up phases for safety, open-label/observation and safety analysis sets, respectively. The proportion of participants who receive each concomitant medication will be summarized as well as the proportion of participants who receive at least 1 concomitant medication. In addition, concomitant medications of special interest will be summarized. These include antidepressant medications received prior to the first dose of study intervention. See Appendix 8 for list of medications in each category.

Prior medications and prior medications of special interest will be summarized by base preferred term.

6.6. Appendix 6 Medical History

Not applicable

6.7. Appendix 7 Adverse Events of Special Interest

Adverse events of special interest are defined as follows:

AE Special Interest Category	Preferred Term
Drug abuse, dependence and withdrawal	Aggression, Confusional state, Decreased activity, Dependence, Disorientation, Dissociation, Dissociative disorder, Dizziness, Drug use disorder, Drug abuse, Drug abuser, Drug dependence, Drug detoxification, Drug diversion, Drug rehabilitation, Drug tolerance, Drug tolerance increased, Drug withdrawal convulsions, Drug withdrawal headache, Drug withdrawal syndrome, Euphoric mood, Feeling abnormal, Feeling drunk, Feeling of relaxation, Hallucination, Hallucination auditory, Hallucination gustatory, Hallucination olfactory, Hallucination synesthetic, Hallucination tactile, Hallucination visual, Hallucinations mixed, Inappropriate affect, Mental impairment, Product tampering, Psychomotor hyperactivity, Psychotic disorder, Rebound effect, Somatic Hallucination, Somnolence, Substance abuser, Substance dependence, Substance use, Substance use disorder, Substance-induced mood disorder, Substance-induced psychotic disorder, Thinking abnormal, Withdrawal arrhythmia, Withdrawal syndrome
Increased blood pressure	Blood pressure increased, Blood pressure diastolic increased, Blood pressure systolic increased, Hypertensive crisis, Hypertensive emergency, Hypertension
Increased heart rate	Heart rate increased, Tachycardia, Extrasystoles
Transient dizziness/vertigo	Dizziness, Dizziness exertional, Dizziness postural, Dizziness procedural, Procedural dizziness, Vertigo, Vertigo labyrinthine, Vertigo positional, Vertigo CNS origin
Impaired cognition	Cognitive disorder
Cystitis	Allergic cystitis, Chemical cystitis, Cystitis, Cystitis erosive, Cystitis haemorrhagic, Cystitis interstitial, Cystitis noninfective, Cystitis ulcerative, Cystitis-like symptom, Pollakiuria, Dysuria, Micturition urgency, Nocturia
Anxiety	Anticipatory anxiety, Anxiety, Anxiety disorder, Agitation, Fear, Feeling jittery, Irritability, Nervousness, Panic attack, Tension
Anticipated Dosing-related AEs	Anxiety, Anticipatory anxiety, Dissociation, Dizziness, Dizziness postural, Feeling abnormal, Feeling drunk, Nausea, Somnolence, Vertigo, Vomiting
Events potentially related to suicidality	Completed suicide, Depression suicidal, Intentional overdose, Intentional self-injury, Multiple drug overdose intentional, Poisoning deliberate, Self-injurious behavior, Self-injurious behaviour Self-injurious ideation, Suicidal behavior, Suicidal behaviour, Suicidal ideation, Suicide attempt
Hepatic adverse events	Cholecystitis, Cholelithiasis, Hepatic steatosis, Hepatitis, Non-alcoholic steatohepatitis, Primary biliary cholangitis, Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood bilirubin increased, Gamma-glutamyl transferase increased, Hepatic enzyme increased, Liver function test abnormal, Liver function test increased, Transaminases increased, Urine bilirubin increased, Urobilinogen urine increased
Events related to renal disorders	Cystitis, Pyelonephritis, Urethritis, Urinary tract infection, Blood creatinine increased, Blood urea increased, Blood urine present, Creatinine renal clearance increased, Protein urine present, Urine analysis abnormal, Urine leukocyte esterase positive, Bladder discomfort, Bladder irritation, Bladder outlet obstruction, Cystitis noninfective, Dysuria, Haematuria, Hypertonic bladder, Lower urinary tract symptoms, Micturition urgency, Nephrolithiasis, Nocturia, Pollakiuria, Polyuria, Proteinuria, Renal colic, Renal failure, Semenuria, Stress urinary incontinence, Ureterolithiasis, Urge incontinence, Urinary bladder polyp, Urinary hesitation, Urinary incontinence, Urinary retention

AE Special Interest Category	**Preferred Term**
Symptoms of dissociation persisting beyond the typical ≤2 hour post esketamine administration	Dissociation[QX[2]
Delirium	Post-injection delirium sedation syndrome, Postoperative delirium, Delirium, Intensive care unit delirium
Psychosis	Acute psychosis, Affective disorder, Alcoholic psychosis, Bipolar I disorder, Epileptic psychosis, Hysterical psychosis, Mania, Parkinson's disease psychosis, Postictal psychosis, Psychosis postoperative, Psychotic disorder, Psychotic disorder due to a general medical condition, Reactive psychosis, Rebound psychosis, Schizoaffective disorder, Substance-induced psychotic disorder, Transient psychosis
Mania	Hypomania, Mania

6.8. Appendix 8 Medications of Special Interest

Concomitant medications of special interest are defined as follows:

Concomitant Medication Special Interest Category	Standard Medication Name
Antidepressants	Agomelatine
Antidepressants	Amfebutamone
Antidepressants	Amfebutamone Hydrochloride
Antidepressants	Amitriptyline
Antidepressants	Amitriptyline Hydrochloride
Antidepressants	Amixid
Antidepressants	Amoxapine
Antidepressants	Bupropion
Antidepressants	Bupropion Hydrochloride
Antidepressants	Citalopram
Antidepressants	Citalopram Hydrobromide
Antidepressants	Clomipramine
Antidepressants	Clomipramine Hydrochloride
Antidepressants	Desipramine
Antidepressants	Desipramine Hydrochloride
Antidepressants	Desvenlafaxine
Antidepressants	Desvenlafaxine Succinate
Antidepressants	Dibenzepin Hydrochloride
Antidepressants	Dosulepin
Antidepressants	Dosulepine
Antidepressants	Doxepin
Antidepressants	Doxepin Hydrochloride
Antidepressants	Duloxetine
Antidepressants	Duloxetine Hydrochloride
Antidepressants	Escitalopram
Antidepressants	Escitalopram Oxalate
Antidepressants	Fluoxetine
Antidepressants	Fluoxetine Hydrochloride
Antidepressants	Fluvoxamine
Antidepressants	Fluvoxamine Maleate
Antidepressants	Imipramine
Antidepressants	Imipramine Hydrochloride
Antidepressants	Levomilnacipran
Antidepressants	Levomilnacipran Hydrochloride
Antidepressants	Maprotiline
Antidepressants	Maprotiline Hydrochloride
Antidepressants	Mianserin
Antidepressants	Mianserin Hydrochloride

Concomitant Medication Special Interest Category	Standard Medication Name
Antidepressants	Milnacipran
Antidepressants	Milnacipran Hydrochloride
Antidepressants	Mirtazapine
Antidepressants	Moclobemide
Antidepressants	Nefazodone Hydrochloride
Antidepressants	Nortriptyline
Antidepressants	Nortriptyline Hydrochloride
Antidepressants	Paroxetine
Antidepressants	Paroxetine Hydrochloride
Antidepressants	Paroxetine Mesilate
Antidepressants	Phenelzine
Antidepressants	Pipofezine
Antidepressants	Pirlindole
Antidepressants	Reboxetine
Antidepressants	Sertraline
Antidepressants	Sertraline Hydrochloride
Antidepressants	Stangyl
Antidepressants	Symbiax
Antidepressants	Tianeptine
Antidepressants	Tranylcypromine
Antidepressants	Trazodone
Antidepressants	Trazodone Hydrochloride
Antidepressants	Trimipramine Maleate
Antidepressants	Venlafaxine
Antidepressants	Venlafaxine Hydrochloride
Antidepressants	Vilazodone
Antidepressants	Vortioxetine
Antidepressants	Vortioxetine Hydrobromide
Antidepressants	Deanxit
Atypical Antipsychotics	Amisulpride
Atypical Antipsychotics	Aripiprazole
Atypical Antipsychotics	Asenapine
Atypical Antipsychotics	Asenapine Maleate
Atypical Antipsychotics	Brexpiprazole
Atypical Antipsychotics	Cariprazine Hydrochloride
Atypical Antipsychotics	Clotiapine
Atypical Antipsychotics	Clozapine
Atypical Antipsychotics	Lurasidone
Atypical Antipsychotics	Olanzapine
Atypical Antipsychotics	Paliperidone
Atypical Antipsychotics	Prothipendyl

Concomitant Medication Special Interest Category	Standard Medication Name
Atypical Antipsychotics	Quetiapine
Atypical Antipsychotics	Quetiapine Fumarate
Atypical Antipsychotics	Risperidone
Atypical Antipsychotics	Seroquel
Atypical Antipsychotics	Ziprasidone
Atypical Antipsychotics	Ziprasidone Hydrochloride
Atypical Antipsychotics	Melperone
Atypical Antipsychotics	Melperone Hydrochloride
Atypical Antipsychotics	Nemonapride
Atypical Antipsychotics	Rapitry-3
Atypical Antipsychotics	Sertindole
Atypical Antipsychotics	Sulpiride
Typical Antipsychotics	Benperidol
Typical Antipsychotics	Chlorpromazine
Typical Antipsychotics	Chlorpromazine Hydrochloride
Typical Antipsychotics	Chlorpromazine Maleate
Typical Antipsychotics	Chlorprothixene
Typical Antipsychotics	Chlorprothixene Hydrochloride
Typical Antipsychotics	Clopenthixol
Typical Antipsychotics	Clopenthixol Hydrochloride
Typical Antipsychotics	Cyamemazine
Typical Antipsychotics	Droperidol
Typical Antipsychotics	Etrafon-D
Typical Antipsychotics	Flupentixol
Typical Antipsychotics	Flupentixol Dihydrochloride
Typical Antipsychotics	Fluphenazine
Typical Antipsychotics	Fluphenazine Hydrochloride
Typical Antipsychotics	Haloperidol
Typical Antipsychotics	Haloperidol Lactate
Typical Antipsychotics	Levomepromazine
Typical Antipsychotics	Levomepromazine Hydrochloride
Typical Antipsychotics	Levomepromazine Maleate
Typical Antipsychotics	Loxapine
Typical Antipsychotics	Loxapine Succinate
Typical Antipsychotics	Mesoridazine
Typical Antipsychotics	Molindone
Typical Antipsychotics	Penfluridol
Typical Antipsychotics	Perazine
Typical Antipsychotics	Perazine Dimaleate
Typical Antipsychotics	Periciazine
Typical Antipsychotics	Perphenazine

Concomitant Medication Special Interest Category	Standard Medication Name
Typical Antipsychotics	Perphenazine Enantate
Typical Antipsychotics	Pimozide
Typical Antipsychotics	Pipamperone
Typical Antipsychotics	Pipotiazine
Typical Antipsychotics	Prochlorperazine
Typical Antipsychotics	Promazine
Typical Antipsychotics	Promazine Hydrochloride
Typical Antipsychotics	Promethazine
Typical Antipsychotics	Promethazine Hydrochloride
Typical Antipsychotics	Thioproperazine
Typical Antipsychotics	Thioproperazine Dimesilate
Typical Antipsychotics	Thioridazine
Typical Antipsychotics	Thioridazine Hydrochloride
Typical Antipsychotics	Tiapride
Typical Antipsychotics	Tiotixene
Typical Antipsychotics	Trifluoperazine
Typical Antipsychotics	Trifluoperazine Hydrochloride
Typical Antipsychotics	Trinicalm Forte
Typical Antipsychotics	Trinicalm Plus
Typical Antipsychotics	Zotepine
Typical Antipsychotics	Zuclopenthixol
Typical Antipsychotics	Zuclopenthixol Acetate
Typical Antipsychotics	Zuclopenthixol Hydrochloride
Mood Stabilizers And Antiepileptics	Carbamazepine
Mood Stabilizers And Antiepileptics	Ergenyl Chrono
Mood Stabilizers And Antiepileptics	Gabapentin
Mood Stabilizers And Antiepileptics	Lamotrigine
Mood Stabilizers And Antiepileptics	Levetiracetam
Mood Stabilizers And Antiepileptics	Lithium
Mood Stabilizers And Antiepileptics	Lithium Carbonate
Mood Stabilizers And Antiepileptics	Lithium Citrate
Mood Stabilizers And Antiepileptics	Primidone
Mood Stabilizers And Antiepileptics	Topiramate
Mood Stabilizers And Antiepileptics	Valproate Semisodium
Mood Stabilizers And Antiepileptics	Valproate Sodium
Mood Stabilizers And Antiepileptics	Valproic Acid
Mood Stabilizers And Antiepileptics	Zonisamide
Benzodiazepines	Alprazolam
Benzodiazepines	Bromazepam
Benzodiazepines	Brotizolam
Benzodiazepines	Chlordiazepoxide

Concomitant Medication Special Interest Category	Standard Medication Name
Benzodiazepines	Chlordiazepoxide Hydrochloride
Benzodiazepines	Cinolazepam
Benzodiazepines	Clobazam
Benzodiazepines	Clonazepam
Benzodiazepines	Clorazepate
Benzodiazepines	Clorazepate Dipotassium
Benzodiazepines	Clorazepic Acid
Benzodiazepines	Clotiazepam
Benzodiazepines	Cloxazolam
Benzodiazepines	Diazepam
Benzodiazepines	Estazolam
Benzodiazepines	Ethyl Loflazepate
Benzodiazepines	Fludiazepam
Benzodiazepines	Flunitrazepam
Benzodiazepines	Flurazepam
Benzodiazepines	Flurazepam Hydrochloride
Benzodiazepines	Gidazepam
Benzodiazepines	Loprazolam
Benzodiazepines	Loprazolam Mesilate
Benzodiazepines	Lorazepam
Benzodiazepines	Lormetazepam
Benzodiazepines	Medazepam
Benzodiazepines	Midazolam
Benzodiazepines	Midazolam Hydrochloride
Benzodiazepines	Midazolam Maleate
Benzodiazepines	Nimetazepam
Benzodiazepines	Nitrazepam
Benzodiazepines	Noctran
Benzodiazepines	Nordazepam
Benzodiazepines	Oxazepam
Benzodiazepines	Phenazepam
Benzodiazepines	Prazepam
Benzodiazepines	Staurodorm
Benzodiazepines	Temazepam
Benzodiazepines	Tofisopam
Benzodiazepines	Triazolam
Benzodiazepines	Valium For Injection
Benzodiazepines	Benzodiazepine Derivatives
Non-Benzodiazepines Hypnotics And Anxiolytics	Buspirone
Non-Benzodiazepines Hypnotics And Anxiolytics	Buspirone Hydrochloride
Non-Benzodiazepines Hypnotics And Anxiolytics	Clonidine

Concomitant Medication Special Interest Category	**Standard Medication Name**
Non-Benzodiazepines Hypnotics And Anxiolytics	Diphenhydramine
Non-Benzodiazepines Hypnotics And Anxiolytics	Diphenhydramine Hydrochloride
Non-Benzodiazepines Hypnotics And Anxiolytics	Doxylamine Succinate
Non-Benzodiazepines Hypnotics And Anxiolytics	Eszopiclone
Non-Benzodiazepines Hypnotics And Anxiolytics	Etifoxine
Non-Benzodiazepines Hypnotics And Anxiolytics	Etifoxine Hydrochloride
Non-Benzodiazepines Hypnotics And Anxiolytics	Hydroxyzine
Non-Benzodiazepines Hypnotics And Anxiolytics	Hydroxyzine Embonate
Non-Benzodiazepines Hypnotics And Anxiolytics	Hydroxyzine Hydrochloride
Non-Benzodiazepines Hypnotics And Anxiolytics	Melatonin
Non-Benzodiazepines Hypnotics And Anxiolytics	Pregabalin
Non-Benzodiazepines Hypnotics And Anxiolytics	Ramelteon
Non-Benzodiazepines Hypnotics And Anxiolytics	Tasimelteon
Non-Benzodiazepines Hypnotics And Anxiolytics	Zolpidem
Non-Benzodiazepines Hypnotics And Anxiolytics	Zolpidem Tartrate
Non-Benzodiazepines Hypnotics And Anxiolytics	Zopiclone
Non-Benzodiazepines Hypnotics And Anxiolytics	Prothipendyl Hydrochloride
Non-Benzodiazepines Hypnotics And Anxiolytics	Dexmedetomidine

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