Janssen Research & Development *

Clinical Protocol

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
AMENDMENT 2

JNJ-54135419 (esketamine)

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United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).

Status: Approved
Date: 14 Jul 2020
Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-ERI-194910312, 3.0

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	14-Jul-2020
Amendment 1	13-Mar-2020
Original Protocol	26-Sep-2019

Amendment 2 (14 Jul 2020)

Overall Rationale for the Amendment: The amendment updates the protocol to remove post dose TSH testing, allow for video teleconferencing of MADRS assessments, and provide updates to the Schedule of Activities.

Section number and Name	Description of Change	Brief Rationale
Synopsis Efficacy Evaluations; Section 1.3. Schedule of Activities – Screening and Double-blind Phase; Schedule of Activities – For Participants Receiving Esketamine: Open-label Treatment/Observation Phase and Follow-up Phase; Section 8.1. Efficacy Assessments	Added that evaluation of Montgomery-Asberg Depression Rating Scale (MADRS) was via video teleconferencing.	In response to the ongoing pandemic and continued instability across the United States (US), this innovative approach aligns with recommendations to protect all parties involved in the study conduct, maintain consistency and protect study integrity, and reduce the potential of missing data due to this evolving public health emergency.
Section 1.3. Schedule of Activities – Screening and Double-blind Phase; Section 8. Study Assessments and Procedures	Removed thyroid-stimulating hormone (TSH) testing post dose and updated blood collection volume	Removed to reduce the burden of additional blood sampling since analyses of TSH data from the phase 3 treatment resistant depression (TRD) studies did not identify an increase in thyroid hormone levels with esketamine administration.
Section 1.3. Schedule of Activities – Screening and Double-blind Phase	Added footnotes g and i regarding increased window of assessment for MADRS on dosing visits to include 2 days before visit and visit window for MADRS at Day2 visit.	Increased visit window for MADRS assessment since this is now being assessed via video teleconferencing.
Section 1.3. Schedule of Activities – Screening and Double-blind Phase	Update to reflect all timepoints of menstrual cycle tracking (added Day 28 and screening week 1).	Added assessments to Schedule of Activities to align with collection times noted in text.
Section 5.1. Inclusion Criteria	Inclusion criterion #2 was modified to clarify that the duration of a single episode major depressive disorder (MDD) must be ≥2 years.	Modified to align with inclusion criteria in Phase 3 TRD studies.
Section 1.3. Schedule of Activities – Screening and Double-blind Phase	Footnotes re-ordered.	Minor errors were noted.

Section number and Name	Description of Change	Brief Rationale
Section 7.2. Participant Discontinuation/Withdrawal From the Study Withdrawal of Consent	Added that less frequent clinical visits were only allowed during the open label phase.	Clarified options for reduced follow-up.
Section 6.5 Dose Modification, Section 8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting, Section 8.6 Biomarkers, Section 9.3. Populations for Analysis Sets, 10.3. Appendix 3, 10.4. Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting; Section 10.5 Contraceptive and Barrier Guidance	Subsequent sections were renumbered accordingly, headings were updated, and subheadings were numbered.	To align with updated template.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

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1. PROTOCOL SUMMARY

1.1. Synopsis

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.

Esketamine nasal spray (SPRAVATO™) is a nonselective, noncompetitive N-methyl D-aspartate (NMDA) receptor antagonist approved in the United States for use in conjunction with an oral antidepressant (AD) for the treatment of treatment-resistant depression (TRD) in adults.

While several definitions of TRD are used in clinical practice, world health authorities, including the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), define patients with TRD as individuals with major depressive disorder (MDD) who have not responded to at least 2 different antidepressant treatments given at an adequate dose for an adequate duration in the current episode of depression. This definition was used in the Sponsor's clinical development program for esketamine nasal spray.

The TRD population suffers disproportionately from the morbidity and mortality associated with depression, and many patients do not experience relief from depressive symptoms after treatment with existing antidepressant medications. Esketamine has demonstrated efficacy in TRD when administered in combination with an oral AD. The current study will evaluate the efficacy of esketamine monotherapy in the TRD population.

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 TRD, 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).

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 from baseline in the MADRS total score from Day 1 (prerandomization) to Day 2.

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 from baseline 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 from baseline in MADRS total score from Day 1 (prerandomization) to Day 2.

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) 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) 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)

Hypothesis

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.

OVERALL 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.

The maximum duration of study participation is 24 weeks.

Screening Phase (up to 7 weeks)

Evaluations that will be performed at the screening visits are outlined in the Schedule of Activities (SoA).

The study population will include men and women, 18 years of age (or older if the minimum legal age of consent in the country in which the study is taking place is >18) or older, who meet the Diagnostic and Statistical Manual of Mental Disorders (5th Edition; DSM-5) diagnostic criteria for single episode MDD or recurrent MDD, without psychotic features, based upon clinical assessment, and confirmed by the Mini International Neuropsychiatric Interview (MINI). In addition, the participant must have an Inventory of Depressive Symptomatology-Clinician rated, 30-item (IDS-C_{30}) total score of ≥34, which corresponds to moderate to severe depression.

Participants can be screened for study participation whether or not they are currently taking an antidepressant medication.

At the start of screening, participants must have had nonresponse to ≥2 different oral AD treatments in the current episode of depression, as assessed by the Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire (MGH-ATRQ), and confirmed by documented records (eg, medical/pharmacy/prescription records or a letter from treating physician).

The participant's current major depressive episode, depression symptom severity, and AD treatment response in their current depressive episode must be deemed valid for participation in the clinical study based on the "State vs. Trait, Assessibility, Face Validity, Ecological Validity, Rule of Three P's" (SAFER) Interview, which is a site-independent qualification assessment.

If clinically indicated, a participant's current AD medication(s), including adjunctive treatment for MDD, should be tapered and discontinued during this phase per the local prescribing information, guidelines or clinical judgement. Tapering/discontinuation of any antidepressant medication(s) should not be started until the SAFER Interview is completed and the site has received confirmation that the participant has "passed" the SAFER Interview.

All participants will have a minimum of 2 weeks in the Screening Phase without any 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 taking benzodiazepines (at dosages equal to or less than the equivalent of 6 mg/day of lorazepam) and/or permitted non-benzodiazepine sleep medications (eg, zolpidem, zaleplon) during the screening phase can continue these medications. Temporary dose increases of benzodiazepines beyond the equivalent of 6 mg/day lorazepam or initiation of new benzodiazepines are permitted during the screening phase if needed to assist with AD taper/discontinuation and/or the antidepressant-free period. However, the dose of the current benzodiazepines is to be less than or equal to the equivalent of 6 mg/day of lorazepam before randomization in the double-blind treatment phase.

Potential participants will be excluded from participating in the study if they have used ketamine/esketamine (lifetime); previously demonstrated nonresponse of depressive symptoms to an adequate course of treatment with electroconvulsive therapy (ECT) in the current major depressive episode, defined as at least 7 treatments with unilateral/bilateral ECT; if they have received vagal nerve stimulation (VNS) or deep brain stimulation (DBS) in the current major depressive episode; if they have a current or prior DSM-5 diagnosis of a psychotic disorder or MDD with psychosis, bipolar or related disorders (confirmed by the MINI), obsessive compulsive disorder (current only), intellectual disability (DSM-5 diagnostic codes 317, 318.0, 318.1, 318.2, 315.8, and 319), autism spectrum disorder, borderline personality disorder, antisocial personality disorder, histrionic personality disorder, or narcissistic personality disorder; if they have homicidal ideation/intent or suicidal ideation with some intent to act within 6 months prior to the start of the screening phase per the investigator's clinical judgment and/or based on the Columbia Suicide Severity Rating Scale (C-SSRS) or suicidal behavior in the last year; or if they have a history of moderate or severe substance or alcohol use disorder according to DSM-5 criteria.

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. On all dosing days, all participants must remain at the clinical site for post-administration observation for at least 2 hours postdose, until the patient is safe to leave.

After receiving a treatment session, instruct participants not to engage in potentially hazardous activities, such as driving a motor vehicle or operating machinery, until the next day after a restful sleep.

Evaluations that will be performed during this phase are outlined in the Schedule of Activities.

Participants taking benzodiazepines and/or permitted non-benzodiazepine sleep medications (eg, zolpidem, zaleplon) during the screening phase can continue these medications during the double-blind treatment phase (at dosages equal to or less than the equivalent of 6 mg/day of lorazepam), however they may not be used within 12 hours prior to the start of each nasal spray treatment session. No dose increases beyond the equivalent of 6 mg/day of lorazepam, or new benzodiazepine medications, are permitted during the double-blind treatment phase, except for the use of permitted benzodiazepine rescue medication.

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/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. The Investigator needs to assess and confirm in source documentation that, based on clinical judgment, it is in the participant's best interest to participate in this 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. On all dosing days, all participants must remain at the clinical site for post-administration observation until at least 2 hours postdose until the patient is safe to leave.

After receiving a treatment session, instruct participants not to engage in potentially hazardous activities, such as driving a motor vehicle or operating machinery, until the next day after a restful sleep.

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.

Evaluations that will be performed during this phase are outlined in the Schedule of Activities.

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.

Further clinical/standard of care for the treatment of depression will be arranged by the study investigator and/or the participant's treating physician.

NUMBER OF PARTICIPANTS

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.

INTERVENTION GROUPS AND DURATION

This Phase 4 study will randomize approximately 446 participants into 1 of 3 treatment groups in the double-blind treatment phase:

Double-blind treatment phase:

- Placebo nasal spray, twice a week for 4 weeks
- Esketamine 56 mg nasal spray, twice a week for 4 weeks
- Esketamine 84 mg nasal spray, twice a week for 4 weeks

Participants who complete the double-blind treatment phase may be eligible to participate in an open-label treatment/observation phase.

Open-label treatment/observation phase:

- Esketamine nasal spray flexible dosing (56 and 84 mg). Recommended frequency of twice a week for 4 weeks (Weeks 5 to 8), once a week for the next 4 weeks (Weeks 9 to 12), and once a week or every other week for the last 4 weeks (Weeks 13 to 16), based on clinical judgment. Dosing frequency should be individualized to the least frequent dosing to maintain remission/response. Esketamine treatment can be used as monotherapy or with standard-of-care treatment for depression.
- Standard-of-care treatment for depression for 12 weeks. 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.

EFFICACY EVALUATIONS

The primary efficacy evaluation will be the MADRS total score.

The MADRS is a clinician-rated scale designed to measure depression severity and detects changes due to antidepressant treatment. It evaluates apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, inability to feel (interest level), pessimistic thoughts, and suicidal thoughts. The test exhibits high interrater reliability.

The MADRS assessment will be performed by site-based raters via video teleconferencing assessment during the study using the Structured Interview Guide for the MADRS. To minimize the risk of unblinding the treatment assignment, different site raters will perform efficacy and safety assessments; clinicians who perform the MADRS assessments will be different from those who evaluate safety assessments (eg, vital signs) and AEs. Raters for the MADRS will not be allowed to access or to review participant safety records or supervise/observe study drug administration; therefore, they will not provide clinical care for participants.

The Clinical Global Impression – Severity (CGI-S) scale will be used to assess severity of depressive illness.

The Patient Health Questionnaire 9-item (PHQ-9) is a participant-reported outcome measure that will be used to assess severity of depressive symptoms.

PHARMACOKINETIC EVALUATIONS

Plasma samples will be used to evaluate the PK of esketamine. The concentrations of esketamine and noresketamine or other metabolites (if warranted) will be measured in plasma.

PHARMACODYNAMIC AND BIOMARKER EVALUATIONS

Blood samples will be collected to explore biomarkers related to immune system activity, hypothalamic-pituitary-adrenal (HPA) axis activation, and neurotropic factors.

Biomarker samples will be collected to:

- evaluate the mechanism of action of esketamine or
- help explain inter-individual variability in clinical outcomes or
- help identify population subgroups that respond differently to a drug

At the conclusion of the biomarker analyses, these findings will be presented in a separate study report.

PHARMACOGENOMIC (DNA and RNA) EVALUATIONS

A pharmacogenomic blood sample will be collected from participants who consent separately to this component of the study to allow for pharmacogenomic research, as necessary. Whole blood samples for DNA and RNA analyses will be collected at the time points indicated in the Schedule of Activities. Participation in pharmacogenomic research is optional.

The goal of the pharmacogenomic component is to collect DNA and RNA to allow the identification of genetic, epigenetic, and transcription factors that may influence the pharmacokinetics (PK), pharmacodynamics (PD), efficacy, safety, or tolerability of esketamine and to identify factors associated with MDD.

SAFETY EVALUATIONS

Safety evaluations will include:

- Monitoring of TEAEs, including TEAEs of special interest, pregnancy testing (for women of childbearing potential), and vital signs.
- Columbia Suicide Severity Rating Scale (C-SSRS), to assess potential suicidal ideation and behavior.

STATISTICAL METHODS

Populations for Analyses

- Efficacy analyses for the double-blind treatment phase will be performed on the full efficacy analysis set, which is defined as all randomized participants who meet nonresponse criteria and have received at least one dose of double-blind study medication. Participants who do not meet nonresponse criteria will be summarized separately for efficacy.
- Safety analyses for the double-blind treatment phase will be performed on the safety analysis set, which is defined as all randomized participants (both participants who meet and do not meet nonresponse criteria) who receive at least one dose of double-blind study medication.
- The safety and efficacy analyses for the open-label treatment phase will be based on all participants who receive at least one dose of open-label esketamine study medication.
- The safety and efficacy analyses for the observational phase will be based on all participants who enter the observational phase but do not receive open-label esketamine study medication.

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.

Efficacy Analyses

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 after the null hypothesis for the primary endpoint is rejected for both doses.

Primary Endpoint

The primary efficacy variable, change from baseline in MADRS total score at Day 28, will be analyzed using a Mixed-Effect Model for Repeated Measures (MMRM) model based on observed case data. The model will include factors for treatment (esketamine 56 mg, esketamine 84 mg, placebo), center, antidepressant treatment status (on- or off-treatment) at screening entry, day, day-by-treatment interaction, and baseline MADRS total score as a covariate. The within-participant covariance between visits will be estimated via an unstructured variance-covariance matrix. Comparisons of the esketamine groups versus placebo will be performed using the appropriate contrast.

Key Secondary Endpoint

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.

Other Endpoints

Change from baseline in MADRS total score over time will be analyzed using the same MMRM model as described for the primary endpoint. Response and remission rates based on the MADRS total score will be summarized at each visit. Frequency distributions of the CGI-S scores at each scheduled timepoint will be provided. Change from baseline in PHQ-9 total score over time in the double-blind treatment phase will be analyzed using the same MMRM model as described for the primary endpoint. Response rates based on the PHQ-9 will be summarized at each visit. Descriptive summaries of efficacy data will be provided for the double-blind phase for participants who do not meet nonresponse criteria and for the open label/observational phase.

Safety Analyses

Adverse Events

Safety data will be analyzed separately for each phase. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported adverse events with onset during the treatment phase (ie, TEAEs and AEs that have worsened since baseline) will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by treatment group.

The TEAEs of special interest will be examined separately; AEs of special interest will be further listed in the statistical analysis plan (SAP). Participants who discontinue treatment due to an AE and serious AEs (SAEs) will be summarized separately. Narratives will be provided for deaths, SAEs, and participants who discontinue due to an AE.

Vital Signs

Descriptive statistics of temperature, pulse/heart rate, body weight measurements, and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time point. The percentage of participants with values beyond clinically important limits will be summarized.

C-SSRS

A frequency distribution of C-SSRS scores at each scheduled timepoint by treatment will be provided. Shifts from the baseline visit to the most severe/maximum score during each study phase will be summarized by treatment. The maximum score assigned for each participant will also be summarized into one of three categories: no suicidal ideation or behavior (0), suicidal ideation (1-5), suicidal behavior (6-10).

Other Analyses

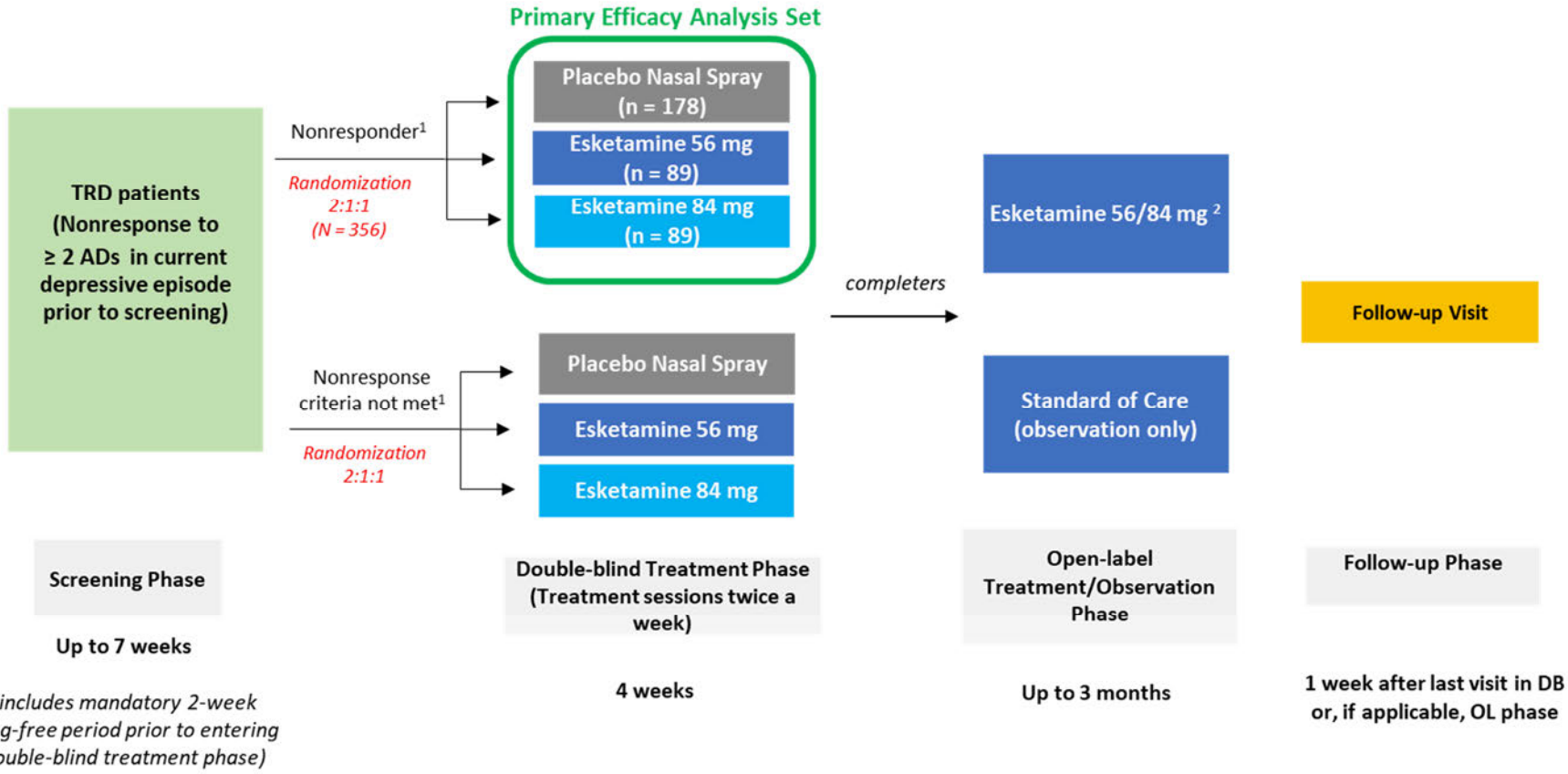
Pharmacokinetic Analyses

The plasma concentrations of esketamine and noresketamine or other metabolites (if warranted) will be listed for all participants and summarized descriptively.

Patient's Assessment of Treatment-arm Assignment

Descriptive statistics will be reported.

1.2. Schema



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*

1.3. Schedule of Activities (SoA)

Screening and Double-blind Phases

Phase	Screening							Double-blind									
Week	1	2	Optional weeks for tapering/DC[a]			2-week antidepressant-free period[b]		1			2		3		4		
Day						Day -14 to -8	Day -7 to -1	1	2	4	8	11	15	18	22	25	28/EW
Visit Window (days)		±2	±2			±2	±2		+2	±1	±1	±1	±1	±1	±1	±1	±1
Visit	1.1	1.2[c]	1.3	1.4	1.5	1.6[c]	1.7	2.1	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	2.10
Clinic visit (C) or Telephone contact (TC)	C	C	C/TC[a]	C/TC[a]	C/TC[a]	C	C	C	C	C	C	C	C	C	C	C	C
Study Procedure																	
Screening/Administrative																	
Informed consent (ICF)	X																
ICF for optional pharmacogenomic research samples	X																
Demographics	X																
Medical and psychiatric history	X																
Employment Status	X																
Inclusion/exclusion criteria[d]	X							X									
MINI	X																
IDS-C_{30}	X																
MGH-ATRQ	X																
SAFER Interview		X															
Prestudy therapy	X																
Preplanned surgery/procedure(s)	X																
Height	X																
Study Intervention Administration																	
Randomization								X[d]									
Practice session for use of nasal spray device								X[e]									
Dispense/administer study intervention								X		X	X	X	X	X	X	X	
Study intervention accountability								X		X	X	X	X	X	X	X	

Phase	Screening							Double-blind									
Week	1	2	Optional weeks for tapering/DC[a]			2-week antidepressant-free period[b]		1			2		3		4		
Day						Day -14 to -8	Day -7 to -1	1	2	4	8	11	15	18	22	25	28/EW
Visit Window (days)		±2	±2			±2	±2		+2	±1	±1	±1	±1	±1	±1	±1	±1
Visit	1.1	1.2[c]	1.3	1.4	1.5	1.6[c]	1.7	2.1	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	2.10
Clinic visit (C) or Telephone contact (TC)	C	C	C/TC[a]	C/TC[a]	C/TC[a]	C	C	C	C	C	C	C	C	C	C	C	C
Study Procedure																	
Efficacy Assessments																	
MADRS (7-day recall), video teleconferencing	X	X[f,g]				X[g]	X[g,h]	X[g,h]			X[g]		X[g]		X[g]		X[g]
MADRS (24-hour recall), video teleconferencing									X[i]								
CGI-S	X							X[e]	X		X[e]		X[e]		X[e]		X
PHQ-9 (patient-reported)						X		X[e]					X[e]				X
Safety Assessments																	
Physical examination	X							X[e]									X
Vital signs predose if applicable (blood pressure, heart rate, temperature)	X					X	X[h]	X	X	X	X	X	X	X	X	X	X
Vital signs postdose (blood pressure, heart rate)[j]								X		X	X	X	X	X	X	X	
Weight	X																X
12-lead ECG	X							X[e]									
C-SSRS: Baseline/Screening version	X																
C-SSRS: Since last visit version (predose on dosing days)		X	X	X	X	X	X[h]	X[e]	X	X	X	X	X	X	X	X	X
Patient's awareness of treatment arm assignment scale																	X
Clinical Laboratory Tests																	
TSH	X																
HbA1c	X																
Lipid panel (fasting)		X															
Hematology, chemistry	X							X[e]									
Urinalysis	X							X[e]									
Drug screen (urine)	X							X[e]									

Phase	Screening							Double-blind									
Week	1	2	Optional weeks for tapering/DC[a]			2-week antidepressant-free period[b]		1			2		3		4		
Day						Day -14 to -8	Day -7 to -1	1	2	4	8	11	15	18	22	25	28/EW
Visit Window (days)		±2	±2			±2	±2		+2	±1	±1	±1	±1	±1	±1	±1	±1
Visit	1.1	1.2[c]	1.3	1.4	1.5	1.6[c]	1.7	2.1	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	2.10
Clinic visit (C) or Telephone contact (TC)	C	C	C/TC[a]	C/TC[a]	C/TC[a]	C	C	C	C	C	C	C	C	C	C	C	C
Study Procedure																	
Serum pregnancy test (women of childbearing potential)	X																
Urine pregnancy test (women of childbearing potential)								X[e]					X				X
Pharmacokinetic Evaluations																	
Blood sample collection								X[k]									
Biomarker Evaluations																	
Blood sample collection								X[l]									X[l]
Pharmacogenomics (DNA and RNA)																	
Blood sample collection								X[l]									
Ongoing Participant Review																	
Concomitant therapy	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X
Other																	
Menstrual cycle tracking (start date of last menstrual period prior to study visit)	X							X									X
Patient's awareness of treatment arm assignment scale																	X

Footnotes:

Abbreviations: C: clinic visit; CGI-S: Clinical Global Impression – Severity; C-SSRS: Columbia Suicide Severity Rating Scale; DC: discontinue; DNA: deoxyribonucleic acid: ECG: electrocardiogram; EW: early withdrawal; HbA1c test: glycated hemoglobin test; IDS-C_{30}: Inventory of Depressive Symptomatology Clinician-rated, 30-item scale; MADRS: Montgomery-Asberg Depression Rating Scale; MGH-ATRQ: Massachusetts General Hospital - Antidepressant Treatment History Questionnaire; MINI: Mini-International Neuropsychiatric Interview; PHQ-9: Patient Health Questionnaire 9 item; RNA: ribonucleic acid; SAFER: State vs. Trait, Assessibility, Face Validity, Ecological Validity, Rule of Three P's; TC: Telephone contact; TSH: thyroid-stimulating hormone

a. After completion of the SAFER Interview and confirmation it was passed, participants who are continuing in the Screening Phase will discontinue all current medication(s) being used for depression treatment, including adjunctive/augmentation medications, prior to the start of the mandatory 2-week antidepressant-free period. If clinically indicated, a participant's current antidepressant treatment(s) may be tapered and discontinued per the local prescribing information or clinical judgment; additional, optional weeks are available in the Screening Phase to allow tapering/discontinuation prior to the start of the 2-week antidepressant-free

period. During tapering/discontinuation, a clinic visit or telephone contact for collection of C-SSRS, adverse events and concomitant therapies should be performed weekly. If the additional weeks are not required, the applicable visit (ie, Visit 1.3, 1.4, 1.5) should be omitted.

b. All participants must have a 2-week (±2 days) antidepressant free period in the Screening Phase just prior to randomization at Visit 2.1. For participants not taking any antidepressant medications at the start of screening, the mandatory 2-week antidepressant free period may start at entry. However, the screening phase will be at least 3 weeks in duration to ensure required procedures are completed.
c. For participants not taking any antidepressant medications at study entry (the start of screening), the mandatory antidepressant free period may start at entry (Visit 1.1). In this scenario only, the following visits would be required: Visits 1.1, 1.2, 1.6, and 2.1.
d. Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Source Documentation in Appendix 3, Regulatory, Ethical, and Study Oversight Considerations. Verify inclusion/exclusion criteria before randomization of each participant.
e. Predose (if applicable) and at the actual dosing day. On Day 1 performed pre-randomization.
f. Must be completed prior to start of tapering or discontinuation of current antidepressant treatment.
g. The MADRS should be administered no more than 2 days prior to the subject's targeted (not actual) clinic visit date (except Visit 2.1, which is within 1 day prior). If performed on the day of the scheduled clinic visit with an intranasal treatment session, the MADRS must be performed prior to the intranasal treatment session.
h. If Visit 1.7 and Visit 2.1 are performed on the same day, Visit 1.7 procedure can be omitted (ie, will be performed only as part of Visit 2.1).
i. The Day 2 MADRS assessment must be administered within the Day 2 to Day 4 window and prior to Day 4 intranasal treatment session.
j. Performed at t = 40 minutes and t =1.5 hours postdose, t = 0 is the time of the first spray of nasal spray study medication.
k. Collected at t = 40 minutes and t = 2 hours postdose, where t = 0 is the time of the first spray of nasal spray study medication.
l. The pharmacogenomic samples (DNA and RNA) should be collected at the specified time point predose under fasting condition, however, if necessary the sample may be collected at a later visit (predose, fasting) without constituting a protocol deviation.

For Participants Receiving Esketamine: Open-label Treatment/Observation Phase and Follow-up Phase

Phase	Open-label Treatment/Observation Phase																Follow-up
Week	5		6		7		8		9	10	11	12	13	14	15	16	~ 1 week after last visit
Day	28	31	35	38	42	45	49	52	56	63	70	77	84	91	98	105	-
Visit window		±2	±2	±2	±2	±2	±2	±2	±3	±3	±3	±3	±3	±3	±3	±3	
Visit	3.1	3.2	3.3	3.4	3.5	3.6	3.7	3.8	3.9	3.10	3.11	3.12	3.13	3.14	3.15	3.16	4.1
Clinic visit (C)	C	C	C	C	C	C	C	C	C	C	C	C	C[a]	C	C[a]	C	C
Study Intervention Administration																	
Recommended dosing frequency	*Twice weekly*[b]								*Weekly*[b]				*Weekly or every other week*[b]				
Dispense/administer study intervention	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Study intervention accountability	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Efficacy Assessments																	
MADRS (7-day recall): video teleconferencing, permitted window of -2 days			X		X		X		X	X	X	X	X	X	X	X	X
CGI-S		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Assessments																	
Physical examination																	X
Vital signs predose (blood pressure, heart rate, temperature)	X[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs postdose (blood pressure, heart rate)[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
C-SSRS: Since last visit version	X[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests																	
Drug screen (urine)	X							X				X				X	
Urine pregnancy test	X[c]							X				X				X	X
Ongoing Participant Review																	
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Footnotes: Abbreviations: C: clinic visit; CGI-S: Clinical Global Impression – Severity; C-SSRS: Columbia Suicide Severity Rating Scale; MADRS: Montgomery Asberg Depression Rating Scale

a. Only for participants receiving esketamine treatment session scheduled on that visit.
b. Dose frequency should not exceed what is recommended.
c. If assessment was performed as part of Visit 2.10 (on the same day), duplicate predose assessment is not required.
d. For participants receiving esketamine treatment session: Performed at t = 40 minutes and t =1.5 hours postdose, t = 0 is the time of the first spray of nasal spray study medication.

For Participants Receiving SOC only: Open-label Treatment/Observation Phase and Follow-up Phase

Phase	Open-label Treatment/Observation Phase																Follow-up
Week	5		6		7		8		9	10	11	12	13	14	15	16	~ 1 week after last visit
Day	28	31	35	38	42	45	49	52	56	63	70	77	84	91	98	105	-
Visit window		±2	±2	±2	±2	±2	±2	±2	±3	±3	±3	±3		±3		±3	
Visit	3.1	3.2	3.3	3.4	3.5	3.6	3.7	3.8	3.9	3.10	3.11	3.12	3.13	3.14	3.15	3.16	4.1
Clinic visit (C)	C	C	C	C	C	C	C	C	C	C	C	C		C		C	C
Study Procedure																	
Efficacy Assessments																	
MADRS (7-day recall): video teleconferencing, permitted window of -2 days			X		X		X		X	X	X	X		X		X	X
CGI-S	X[a]	X	X	X	X	X	X	X	X	X	X	X		X		X	X
Safety Assessments																	
Physical examination																	X
Vital signs (blood pressure, heart rate, temperature)	X[a]	X	X	X	X	X	X	X	X	X	X	X		X		X	X
C-SSRS: Since last visit version	X[a]	X	X	X	X	X	X	X	X	X	X	X		X		X	X
Clinical Laboratory Tests																	
Drug screen (urine)	X							X				X				X	
Urine pregnancy test	X[a]							X				X				X	X
Ongoing Participant Review																	
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X		X		X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X		X		X	X

Footnotes:

Abbreviations: C: clinic visit; CGI-S: Clinical Global Impression – Severity; C-SSRS: Columbia Suicide Severity Rating Scale; MADRS: Montgomery-Asberg Depression Rating Scale; SOC: standard of care

a. If assessment was performed as part of Visit 2.10 (on the same day), duplicate predose assessment is not required.

2. INTRODUCTION

Esketamine nasal spray (SPRAVATO™) is a nonselective, noncompetitive N-methyl D-aspartate (NMDA) receptor antagonist approved in the United States for use in conjunction with an oral antidepressant for the treatment of treatment-resistant depression (TRD) in adults.

While several definitions of TRD are used in clinical practice, world health authorities, including the Food and Drug Administration (FDA) and the European Medicines Agency, define patients with TRD as individuals with major depressive disorder (MDD) who have not responded to at least 2 different antidepressant treatments given at an adequate dose for an adequate duration in the current episode of depression. This definition is used in the Sponsor's clinical development program for esketamine nasal spray.

The TRD population suffers disproportionately from the morbidity and mortality associated with depression, and many patients do not experience relief from depressive symptoms after treatment with existing antidepressant medications. Esketamine provides clinically meaningful, rapid, and sustained improvement in depressive symptoms for this population. The efficacy results, combined with a well-characterized safety profile and comprehensive risk mitigation program, highlight the potential for esketamine to improve the treatment landscape for adult patients suffering from TRD.

For the most comprehensive nonclinical and clinical information regarding the study intervention esketamine, refer to the latest edition of the Investigator's Brochure[5] and SPRAVATO United States Prescribing Information (USPI)[11].

The term "study intervention" throughout the protocol, refers to esketamine/placebo nasal spray.

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

2.1. Study Rationale

The Phase 3 esketamine TRD studies all administered esketamine in conjunction with a newly-initiated, oral antidepressant (AD), or as adjunctive to prior oral antidepressants in the phase 2 studies. Accordingly, esketamine is indicated for use in patients with TRD along with a concomitant oral AD. As there is no conclusive data yet to support the efficacy of esketamine apart from the use of a concomitant AD, this study is being conducted to evaluate the efficacy of esketamine as monotherapy for TRD. In addition, two esketamine treatment groups will allow for assessment of the efficacy and safety of the 84 mg and the 56 mg doses.

2.2. Background

Nonclinical Studies

Nonclinical Pharmacology

Through N methyl D aspartate receptor (NMDAR) antagonism, esketamine produces a transient increase in glutamate release leading to increases in α-amino 3 hydroxy 5 methyl-4-isoxazole

propionic acid receptor (AMPAR) stimulation and subsequently increase neurotrophic signaling that restores synaptic function in the brain regions involved with the regulation of mood and emotional behavior. Unlike other AD therapies, esketamine's primary AD action does not directly involve monoamine, γ-amino butyric acid-ergic (GABA), or opioid receptors. Thus, as a noncompetitive, subtype nonselective, activity dependent glutamate receptor modulator, esketamine offers a novel mechanism of action that provides important advantages not previously available to patients with TRD.

Esketamine decreased IKr (human ether-à-go-go-related gene) with a 50% inhibition concentration (IC50) of 214 μM. Given that the maximum mean human plasma concentration of total esketamine produced by 84 mg esketamine nasal spray is 174 ng/mL (or 0.73 μM esketamine base, MW 237.7) (TRD1001), the IC50-based safety margin is approximately 400-fold based on free esketamine concentration assuming 40% protein binding. In dog, increases in heart rate and blood pressure were noted at clinically relevant exposures of esketamine.

Pharmacokinetics and Product Metabolism in Animals

Across species, fast absorption occurred following intranasal administration of esketamine, with peak plasma concentrations generally reached within 30 minutes for esketamine and shortly thereafter for its active metabolite noresketamine (M10). Following nasal dosing in mice and rats, C_{max} values of esketamine and noresketamine were comparable whereas the area under the concentration-time curve (AUC) values were higher for noresketamine than for the parent. In the dog, the AUC of noresketamine was lower than that of esketamine. Sublingual oral thin film (OTF) formulations resulted in fast systemic absorption in dogs, yielding high plasma exposure and almost complete bioavailability.

The tissue distribution of esketamine is characterized by a fast equilibrium between plasma and well perfused tissues leading to a rapid tissue uptake. Total brain concentrations of esketamine were 4- (rat) to 7-(human) fold higher compared to those in the systemic circulation. In general, the brain uptake of the more polar metabolites was less efficient than the parent drug.

The unbound fraction of esketamine in healthy participants was ~56%, and ~60% for noresketamine (M10).

Based on a human mass balance study, noresketamine (M10) is a major circulating metabolite, accounting for ~13% of the total drug-derived material. All other major phase-1 and all phase-2 metabolites individually represented <10% of the total-drug related material in plasma. N-Demethylation of esketamine to noresketamine (M10) is the initial metabolic pathway, followed by metabolization to numerous downstream metabolites via hydroxylation at the cyclohexanone ring, hydroxylamine formation, keto reduction, dehydrogenation or aromatic hydroxylation.

Most esketamine-derived metabolites were excreted in urine (rats, humans). Very low levels of unchanged drug were present in urine (<1% of the dose), indicating that esketamine is metabolically cleared.

Cytochrome P450 (CYP) 2B6 was the main enzyme involved in esketamine metabolism in human liver microsomes with a contribution close to 60%, while the contribution of CYP3A4 was estimated at 35 to 40%. CYP2A6 and CYP2B6 were the major enzymes involved in the downstream metabolism of noresketamine to hydroxy-noresketamine metabolites.

Esketamine and its major circulating metabolites had no clinically relevant inducing effect on CYP1A2, CYP3A4 or CYP2B6. In vitro, only a weak reversible inhibition of noresketamine on CYP3A4 was observed.

Esketamine and noresketamine were not substrates of transporters (P-glycoprotein [P-gp], breast cancer resistance protein [BCRP], organic anion-transporting polypeptide [OATP] OATP1B1, OATP1B3 for esketamine, and P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, organic cation transporter [OCT]1, OCT2 for noresketamine [M10]). Esketamine and its major circulating phase 1 metabolites were found not to be inhibitors of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, multidrug and toxin extrusion MATE1, or MATE2K transporters.

Toxicology

Following intranasal esketamine dosing of up to 6 months in rats and up to 9 months in dogs, clinical signs were noted reflecting the (exaggerated) pharmacological action of the test article. No notable lesions were noted in the nasal cavity or any peripheral organ. The No Observed Adverse Effect Levels (NOAELs) were 9 mg/day or ~27 mg/kg/day in rats, and 72 mg/day or ~10 mg/kg/day in dogs, respectively. Upon 3 months of daily dosing in rats and dogs, the AUC-based exposure ratios for esketamine compared to the 84 mg intranasal human dose were ~0.7- to 0.9-fold.

The maximum tolerated dose (MTD) for single oral administration of esketamine to rats was 160 mg/kg for male and 40 mg/kg for female rats. Repeated oral dosing with esketamine was tolerated for 14 days at these levels with clinical observations in line with those after intranasal dosing. Liver and kidney were identified as target organs.

In single dose tolerability studies in dogs, sublingual and buccal OTF formulations containing esketamine at ~24 mg and 28 mg, respectively, were well tolerated, with expected pharmacology-related signs, no oral cavity changes and no effects on electrocardiography.

Esketamine poses no genotoxic risk to humans. Esketamine was not carcinogenic in rat and mouse bioassays.

Intranasally administered ketamine or esketamine did not affect fertility, early embryonic development and pre- and postnatal development in rats. When pregnant rabbits were treated with ketamine at maternally toxic dose levels, skeletal malformations were noted in the offspring. There may be a relationship to ketamine treatment. Considering the published evidence on the developmental neurotoxicity potential of ketamine in animals during pregnancy and in early postnatal rodent pups, a similar risk with esketamine to humans cannot be excluded.

Esketamine is known for their abuse potential in animals and humans. In single dose and 14-day repeated-dose neurotoxicity studies with intranasally administered esketamine in adult rats, no histopathological brain lesions were noted. Furthermore, in the 6-month rat and 9-month dog repeat dose toxicology studies with intranasally administered esketamine, and in the pre- and postnatal developmental toxicity study in rats, no evidence of neurotoxicity was found. There were no histopathological brain lesions after single or 14-day repeated subcutaneous dosing of esketamine to juvenile rats. The risk of neurotoxicity associated with nasal administration of esketamine to adult and adolescent patients is considered to be low.

Clinical Studies

Human Pharmacokinetics

Healthy Participants

Esketamine is rapidly absorbed through the nasal mucosa following administration as a nasal spray and can be measured in plasma within 7 minutes following a 28-mg dose. The time to reach maximum concentrations (t_{max}) of esketamine is typically observed at approximately 20 to 40 minutes after the last nasal spray of a given dose. The maximum concentrations (C_{max}) and AUC from time 0 to the last measurable concentration (AUC_{last}) of esketamine increase with dose from 28 mg to 84 mg. The increases were less than dose proportional between 28 mg and 56 mg or 84 mg, but nearly dose proportional between 56 mg and 84 mg. The mean terminal half-life ($t_{1/2}$) ranged from approximately 7 to 12 hours. The pharmacokinetics (PK) of esketamine was similar after single and repeated (ie, twice a week) dose administration of nasal esketamine. No accumulation in plasma is observed when esketamine is administered twice a week (TRD1010).

The absolute bioavailability of esketamine nasal spray (84 mg) administered to healthy participants was approximately 48% (TRD1009).

In human mass balance Study TRD1016, esketamine was mainly excreted in urine as metabolites following oral and IV administration.

For the detailed PK results within subpopulations, see the latest edition of the Investigator's Brochure[5].

Participants with TRD

At corresponding esketamine nasal spray doses and timepoints, the mean plasma esketamine concentrations in samples collected in the Phase 2 and 3 studies were similar to the range of mean plasma esketamine concentrations in samples collected from healthy participants who enrolled in the Phase 1 studies.

Effects of Esketamine on Probes of Hepatic Cytochrome P450

Administration of 84 mg esketamine nasal spray twice a week for 2 weeks reduced the mean plasma AUC_{∞} produced by oral midazolam, a probe of hepatic CYP3A4 activity, by approximately

16% (TRD1010). The same regimen of esketamine nasal spray did not affect the mean plasma AUC_∞ produced by oral bupropion, a probe of hepatic CYP2B6 activity.

Effects of Potent Inducers of Hepatic Cytochrome P450

In Study TRD1008, mean esketamine C_{max} and AUC_∞ values were approximately 17% and 28% lower, respectively, when 56-mg esketamine nasal spray was administered by participants pretreated with rifampin, an inducer of CYP3A4 and CYP2B6 activity, compared to esketamine administration without rifampin pretreatment.

Effects of Potent Inhibitors of Hepatic Cytochrome P450

In Study TRD1009, pretreatment with oral clarithromycin, an inhibitor of CYP3A4 activity, produced small effects (ie, <11% increase) on the C_{max} and AUC_∞ of intranasal esketamine. Furthermore, the decline in plasma concentrations (ie, half-life) of esketamine was not affected by clarithromycin pretreatment.

In Study TRD1020, pretreatment with oral ticlopidine, an inhibitor of hepatic CYP2B6 activity, had no effect on the C_{max} of intranasally administered esketamine. The AUC_∞ of esketamine was increased by approximately 29%. The terminal half-life was not affected by ticlopidine pretreatment.

Effects of Nasal Mometasone and Nasal Oxymetazoline

The results of Study TRD1007 demonstrated that daily intranasal administration of mometasone furoate had no effects on the pharmacokinetics of intranasal esketamine (56 mg dose) in healthy participants. Furthermore, the pharmacokinetics of intranasal esketamine was similar with and without intranasal administration of oxymetazoline HCl in participants experiencing symptoms of nasal rhinitis.

Efficacy Studies in Participants with TRD

Phase 2 Studies (TRD2003)

The results of Phase 2 double-blind, placebo-controlled study in TRD population demonstrated a rapid onset and significant antidepressant effect for esketamine. In this adjunctive delayed start design Study TRD2003, consisting of a 2-week double-blind phase that included two 1-week treatment periods, twice weekly esketamine significantly improved depressive symptoms in adults with TRD, as measured by the change from baseline in MADRS total scores. Efficacy was dose-related, with doses of 56 mg and 84 mg demonstrating significantly greater efficacy than placebo. The 28 mg dose had a shorter duration of response, and the 14 mg dose was ineffective. The clinical effect was observed as early as 2 hours after the first dose. In the open-label phase (Days 15-74) following the double-blind period, in which the frequency of esketamine dosing was reduced to once weekly for 2 weeks and then to every 2 weeks, the antidepressant response appeared to persist for approximately 2 months after the last dose of esketamine.

Short-term Phase 3 Studies: TRD3001, TRD3002 and TRD3005

Phase 3 studies TRD3001, TRD3002, and TRD3005 were randomized, double-blind, multicenter, active controlled studies that evaluated the efficacy, safety, and tolerability of esketamine nasal spray plus an oral AD in participants with TRD. The efficacy of esketamine nasal spray was assessed at fixed dose (56 mg or 84 mg) in adult participants in Study TRD3001, at flexible-dose (56 mg or 84 mg) in adult participants in Study TRD3002 and at flexible-dose (28 mg, 56 mg or 84 mg) in elderly participants (65 years and older) in Study TRD3005.

Since the primary endpoints for these 3 short-term studies were the same, the results for the primary efficacy endpoint (mixed-effects model using repeated measures [MMRM] analyses) are presented together.

Change in MADRS Total Scores From Baseline to the End of the 4-Week Double-blind Induction Phases:

Across the 3 studies (TRD3001, TRD3002 and TRD3005), treatment group differences consistently showed larger improvements with esketamine + oral AD compared with oral AD + placebo. Moreover, results for each study were similar when analyzed using MMRM.

- For Study TRD3002, a statistical superiority of flexibly dosed esketamine 56 / 84 mg + oral AD vs oral AD + placebo nasal spray in improving symptoms of depression in a TRD population after 4 weeks of treatment was shown, with least-squares (LS) mean treatment differences (95% CI) of -4.0 (-7.31, -0.64) based on MMRM (2-sided p=0.020).
- For Study TRD3001, while treatment effects for esketamine + oral AD were not statistically significant relative to the oral AD + placebo nasal spray control, the median unbiased estimated treatment differences (based on MMRM analysis, 95% CI) of -4.1 (-7.53,-0.60) for the esketamine 56 mg dose group and -3.2 (-6.88,0.45) for the esketamine 84 mg dose group support a clinically meaningful benefit for both fixed-dose regimens in adults with TRD.
- For Study TRD3005, while the treatment effect for esketamine + oral AD was not statistically significant relative to the oral AD + placebo nasal spray control, the estimated treatment difference of -3.6 (-7.20,0.07) (MMRM, 95% CI) suggests a clinically meaningful benefit in the vulnerable and difficult to treat elderly population with TRD who were started at 28 mg and could be titrated to 56 or 84 mg as clinically appropriate.

The key secondary endpoints for studies TRD3002 and TRD3001 were the onset of clinical response by Day 2, and changes from baseline in Sheehan Disability Scale (SDS) and Patient Health Questionnaire 9 item (PHQ-9) total scores at Day 28. In Study TRD3005 with elderly participants, the onset of clinical response by Day 2 was not evaluated because all participants received a low-dose (28 mg) for tolerability as the initial dose.

For the key secondary endpoints analyses at the end of the Double-blind Induction Phase:

- Results for the rigorously-defined endpoint of onset of clinical response by Day 2 in studies TRD3002 and TRD3001 showed odds ratios numerically favoring the esketamine + oral AD groups compared to the oral AD + placebo nasal spray groups; however, the treatment group differences were not statistically significant for Study TRD3002 (2-sided p=0.321) and could not be tested statistically for Study TRD3001 due to the truncated fixed-sequence testing hierarchy.
- Treatment group differences in participant reported outcomes related to functional impairment and associated disability (SDS total score) and depressive symptoms (PHQ-9 total score) could not be tested statistically for TRD3002 and TRD3001 due to the fixed-sequence testing hierarchy and were not planned to be evaluated statistically for Study TRD3005. However, results in all 3 short-term studies numerically favored esketamine + oral AD treatment for both endpoints. The consistent advantages in these participant-reported outcomes supported the meaningfulness of the clinician-rated improvements in the primary endpoints.
- For the 3 short-term studies, remission rates at Day 28 (observed case) based on MADRS total score ≤12 in the esketamine + oral AD group among adult participants were 53% in Study TRD3002 and 36% to 39% in both dose groups in Study TRD3001 (vs 31% for oral AD + placebo nasal spray groups of both studies), and were 17.5% in the elderly population in Study TRD3005 (vs 7% in elderly oral AD + placebo nasal spray group). These remission rates indicate a treatment benefit in a treatment-resistant population, including the elderly population.
- For the 3 short-term studies, response rates (defined as ≥50% improvement from baseline in MADRS total score) in the adult studies after the first dose ranged from 16% to 19% in the esketamine + oral AD group compared with 8% to 11% for the oral AD + placebo nasal spray group. At Day 28, response rates in the esketamine + oral AD groups were 69% in Study TRD3002 (vs 52% for oral AD + placebo nasal spray) and 53% to 54% in both dose groups of Study TRD3001 (vs 39% for oral AD + placebo). In the elderly population in Study TRD3005, the response rate at the end of the induction phase was 27% in the esketamine + oral AD group (vs 13% for oral AD + placebo nasal spray). All these differences met the clinically meaningful threshold of 10 percentage points of difference between esketamine + oral AD and oral AD + placebo nasal spray. For elderly participants, these response rates indicate a treatment benefit.

Long-term Phase 3 Studies: TRD3003 and TRD3004

TRD3003

Study TRD3003 was a randomized, double-blind, multicenter, active-controlled efficacy study of esketamine nasal spray at flexible-dose (56 mg or 84 mg) plus an oral AD for relapse-prevention in adult participants with TRD.

Primary Efficacy Endpoint: Time to Relapse for Participants in Stable Remission After Treatment With Esketamine in Earlier Phases

Based on the weighted combination log-rank test, the difference between treatment groups for the time to relapse was statistically significant (2-sided p=0.003). Relapse events occurred in 26.7% of the esketamine group and 45.3% of the oral AD + placebo group.

Secondary Efficacy Endpoint: Time to Relapse for Participants With Stable Response (But Not Stable Remission) After Treatment With Esketamine in Earlier Phases

Relapse events occurred in 25.8% of the esketamine group and 57.6% of the oral AD + placebo nasal spray group. Participants randomized to continue esketamine showed a statistically significantly longer time to relapse compared to those randomized to discontinue esketamine (2-sided p<0.001).

TRD3004

Study TRD3004, was an open-label, long-term, safety and efficacy study of esketamine nasal spray at flexible-dose (28 mg, 56 mg or 84 mg) in adult participants with TRD.

Since this was an open-label study with no comparator group, efficacy was considered a secondary objective of this study. Only descriptive summaries of efficacy rating scales are presented.

Secondary Efficacy Endpoint:

MADRS total score

- The mean (SD) change from baseline in the MADRS total score at end point of the 4-week induction phase of -16.4 (8.76) remained largely unchanged throughout the 48-week optimization (OP)/maintenance (MA) phase for those participants who entered that phase, with the mean (SD) change from the baseline to end point of the OP/MA phase being 0.3 (8.12).

MADRS response and remission

- At the induction endpoint, the response rate (defined as ≥50% reduction in the MADRS total score from baseline) was 78.4% (593/756) and the remission rate (defined as a MADRS total score ≤12) was 47.2% (357/756). Of the participants proceeding to the OP/MA phase, 76.5% (461/603) had met the criteria for response and 58.2% (351/603) were in remission at end point (OP/MA).

Studies in Participants with MDSI

Esketamine was also studied in 3 completed Phase 2 and Phase 3 studies in participants with MDD who had active suicidal ideation with intent (assessed to be at imminent risk for suicide per the study protocols; referred to hereafter as MDSI). The Phase 3 studies (SUI3001 and SUI3002) and the Phase 2 study (SUI2001) were double-blind, randomized, placebo-controlled studies designed to evaluate the efficacy, safety, and tolerability of esketamine nasal spray 84 mg compared with placebo nasal spray in the treatment of participants with MDSI.

Safety findings from these studies are presented in the following sections.

Pharmacodynamic Studies

Evaluation of Effects on Cognitive Function

Phase 1 Studies

Study TRD1005 evaluated the effect of esketamine nasal spray (total dose of 84 mg) on cognitive functioning in healthy participants using the CogState computerized test battery. Esketamine was associated with an early, transient decline in cognitive function compared with placebo, which was restored to comparable levels in participants receiving esketamine or placebo by 2 hours postdose. The transient reductions in cognitive function in participants receiving esketamine were associated with early postdose sedation, as assessed by the Karolinska Sleepiness Scale (KSS), and the greater level of effort required to complete the CogState computerized test battery, as assessed using the Mental Effort Scale. The increases in sleepiness (at 40 minutes and 2 hours postdose) and the mental effort required (at 40 minutes postdose) returned to levels comparable to placebo by 4 and 2 hours postdose, respectively.

The on-road driving Study TRD1006 evaluated the effect of 84 mg esketamine nasal spray compared to placebo on sleepiness using KSS. Maximal increases in sleepiness were observed at 1- and 2-hour postdose while there was little change in the placebo group.

Phase 2 Studies

In Study TRD2003, cognitive data were collected in 9 participants in Panel A. Small changes in score on the Cogstate and Hopkins Verbal Learning Test-Revised (using a 12-item word list recall test) measures were observed throughout the study, consistent with typical, individual fluctuation over time and not suggestive of clinically meaningful change.

Phase 3 Studies

In the short-term Phase 3 studies (TRD3001, TRD3002, and TRD3005), treatment with esketamine + oral AD did not influence any aspect of cognition studied in adult participants with TRD and was not associated with any systematic changes in cognition in the elderly participants.

Similarly, in the long-term relapse-prevention Study TRD3003, comparison of the results for the double-blind MA phase suggested no evidence for deterioration of cognitive performance with repeated, longer-term intermittent esketamine dosing.

In the long-term open-label safety Study TRD3004, overall group mean performance on multiple cognitive domains including visual learning and memory, as well as spatial memory/executive function, either improved or remained stable postbaseline in adult participants. In the subset of elderly participants (≥65 years of age) from this study, a slowing of reaction time was observed starting at Week 20 and through the end of the study; however, this appeared to represent an isolated observation related to processing speed and not a broad attentional impairment. Performance on all other cognitive tests remained stable in elderly participants in this study.

On-the-road Driving Test

Two studies were conducted to assess the effects of esketamine on driving skills; one study in adult patients with major depressive disorder (TRD1019) and one study in healthy participants (TRD1006). On road driving performance was assessed by the mean standard deviation of the lateral position, a measure of driving impairment.

Results from these 2 studies guided recommendations in the esketamine product labeling that patients not engage in potentially hazardous activities such as driving and operating machinery after esketamine dosing until the next day following a restful sleep.

Abuse Potential

Study TRD1015 assessed the abuse potential of esketamine nasal spray in recreational users of perception altering drugs. The results were consistent with expected findings and showed that single doses of esketamine nasal spray (84 mg and 112 mg) and the positive control drug, IV ketamine (0.5 mg/kg infused over 40 minutes), produced significantly higher scores than placebo on subjective ratings of "drug liking" and on other measures of subjective drug effects in this population.

Cardiac Electrophysiology

A thorough corrected QT interval (QTc) study (TRD1013) was conducted in healthy participants. Participants were randomly assigned to receive placebo, oral moxifloxacin (positive control), or 84 mg esketamine nasal spray in the first 3 periods (ie, 1 treatment per period). They received 0.8 mg/kg esketamine as a 40-minute IV infusion in the fourth open-label period. No evidence of QT interval prolongation (based on a study-specific power model and Fridericia's correction methods) was found in participants treated with intranasal or intravenous esketamine. Moxifloxacin demonstrated QTc prolongation and established assay sensitivity.

Safety and Tolerability Findings Across Indications

Exposure to Esketamine Nasal Spray in Phase 2 and Phase 3 studies across indications

In 6 completed Phase 2 and 3 studies in TRD, 1,708 participants received esketamine [611 patient-years of exposure] and 486 participants received placebo [107 patient-years of exposure]). In the ongoing open-label extension safety study TRD3008, 1,140 adult and elderly participants who previously participated in the Phase 3 TRD studies received esketamine [1,198 patient-years of exposure]).

In 3 completed Phase 2 and Phase 3 studies in MDSI, 262 participants received at least 1 dose of esketamine (15.8 patient-years of exposure) and 256 received at least 1 dose of placebo (15.7 patient-years of exposure).

Analysis of Common Treatment-Emergent Adverse Events

Phase 1 Studies

In a pooled analysis (n=577) of 18 Phase 1 studies (TRD1001, TRD1002, TRD1003, TRD1004, TRD1005, TRD1006, TRD1007, TRD1008, TRD1009, TRD1010, TRD1011, TRD1012, TRD1013, TRD1014, TRD1015, TRD1016, TRD1018, and TRD1020), in the total esketamine group, TEAEs (at least 10% of the participants) were reported in 89.3% of participants. For the total esketamine group, frequently reported TEAEs (≥20%), were dizziness (38%), dysgeusia (30.4%), somnolence (26.4%), vertigo (21.5%), headache (21.3%), and feeling drunk (21%).

In the on-road driving Study TRD1019 in participants with MDD, all participants reported at least 1 or more TEAEs. The highest incidence of TEAEs during Part A of the study in the esketamine nasal spray 84 mg + oral placebo treatment group was dissociation (80.8%), in the placebo nasal spray + oral alcohol treatment group was headache (34.6%), and in the placebo nasal spray + oral placebo treatment group was fatigue (23.1%). The highest incidence of TEAEs during Part B of the study in the esketamine nasal spray treatment group was dissociation (96.0%), whereas in the placebo nasal spray treatment group, 3 participants (12.0%) each reported a TEAE of headache.

Studies in Participants with TRD

Phase 2 Study (TRD2003)

In Study TRD2003, for Panels A and B combined, 78.6% participants in the total esketamine nasal spray group and 61.1% participants in the placebo group experienced at least 1 TEAE during the double-blind phase. The most common TEAEs (in at least 10% of participants) were dizziness, headache, dysgeusia, dissociation, nausea, hypoesthesia, feeling abnormal, and somnolence. Common TEAEs that occurred more frequently in the placebo group than in the esketamine group were dysgeusia (20.4% vs 16.7%) and somnolence (13.0% vs 10.7%). During the open-label phase, 88.5% of participants experienced at least 1 TEAE. The most commonly reported TEAEs (≥10% of participants across panels) were generally similar to those reported by participants who received esketamine during the double-blind phase.

Phase 3 Short-term Studies (TRD3001, TRD3002, and TRD3005)

In studies TRD3001 and TRD3002, the most common TEAEs (reported by ≥10% of participants) in the total esketamine nasal spray + oral AD group were: nausea, dissociation, dizziness, vertigo, headache, dysgeusia, somnolence, paraesthesia, hypoaesthesia, hypoaesthesia oral; and in the oral AD + placebo nasal spray group: headache and dysgeusia. All of the most common TEAEs were observed more frequently (with a difference of at least 3%) in the total esketamine + oral AD group vs the oral AD + placebo nasal spray group: nausea (28.3% vs 8.6%), dissociation (26.6% vs 3.6%) dizziness (23.7% vs 6.8%), vertigo (22.5% vs 2.3%), headache (20.2% vs 17.1%), dysgeusia (18.8% vs 13.5%), somnolence (17.3% vs 9.0%), paraesthesia (12.4% vs 1.8%), hypoaesthesia (11.0% vs 1.4%), hypoaesthesia oral (10.7% vs 1.4%).

In Study TRD3005, most common TEAEs (reported by ≥10% participants) observed more frequently in the esketamine nasal spray + oral AD group vs the oral AD + placebo nasal spray group were: dizziness (20.8% vs 7.7%), nausea (18.1% vs 4.6%), headache (12.5% vs 3.1%), fatigue (12.5% vs 7.7%), BP increased (12.5% vs 4.6%), dissociation (12.5% vs 1.5%), and vertigo (11.1% vs 3.1%). The most common TEAE (reported by ≥5% participants) observed more frequently in the oral AD + placebo nasal spray group was anxiety (7.7% vs 2.8% in the esketamine nasal spray + oral AD group).

Phase 3 Long-term Studies (TRD3003 and TRD3004)

In Study TRD3003, in the double-blind MA phase, the most common TEAEs (≥10% participants) in the esketamine + oral AD group included dysgeusia, vertigo, dissociation, somnolence, dizziness, headache, nausea, vision blurred, and hypoaesthesia oral. No TEAEs were reported at this rate in the oral AD + placebo nasal spray group. Of the TEAEs reported in at least 5% of participants, all except viral upper respiratory tract infection were reported at higher rates in esketamine + oral AD group than in oral AD + placebo nasal spray group (with a difference of 3% or more).

Overall, of those participants treated in either of the treatment phases (induction and/or optimization/maintenance), most reported TEAEs (90.1%) and the most common TEAEs (≥10% of participants) were dizziness (32.9%), dissociation (27.6%), nausea (25.1%), headache (24.9%), somnolence (16.7%), dysgeusia (11.8%), hypoaesthesia (11.8%), vertigo (11.0%), vomiting (10.8%), and viral upper respiratory tract infection (10.2%).

Studies in Participants with MDSI

As observed in the TRD program, most TEAEs reported during esketamine treatment, including those that were most common, were mild or moderate in severity, were observed post dose on the day of dosing, and resolved the same day. In the pooled Phase 3 studies (SUI3001/3002), 89.9% of the participants in the esketamine + standard of care (SOC) group (n=227) and 75.6% in the placebo + SOC group (n=225) experienced at least 1 TEAE during the 4-week double-blind phase. The most common TEAEs (reported by ≥10% participants) observed more frequently in the esketamine + SOC group versus placebo + SOC group during the double-blind phase were: dizziness (38.3% versus 13.8%), dissociation (33.9% versus 5.8%), nausea (26.9% versus 13.8%), somnolence (20.7% versus 10.2%), dysgeusia (19.8% versus 12.9%), vision blurred (11.9% versus 4.9%), paresthesia (11.5% versus 3.1%), vomiting (11.5% versus 5.3%), blood pressure increased (11.5% versus 4.0%), sedation (10.1% versus 2.2%), and anxiety (10.1% versus 7.6%). Headache was observed in similar proportion of participants in both groups (20.3% vs. 20.4%). A similar pattern of results was observed in the Phase 2 study SUI2001.

Deaths, Serious Adverse Events and Other Significant Adverse Events

Deaths

Overall, across all completed and ongoing Phase 1, Phase 2, and Phase 3 studies with esketamine in the MDSI and TRD indications, 8 deaths have been reported up to 2 October 2019.

Participants with TRD:

- Completed Phase 2 and 3 TRD studies: There were 4 deaths reported among the 1,708 participants who had received treatment with esketamine + oral AD in the completed Phase 2 and 3 studies in TRD (611 patient-years exposure). The deaths included 2 completed suicides; 1 of which occurred during the follow-up phase of TRD2003 (20 days after last dose of esketamine) and the other occurred during the OP/MA phase of TRD3004 (last esketamine dose 12 days prior to death). Other causes of death in the completed TRD studies were multiple injuries sustained during a road traffic accident during the double-blind phase of TRD3002 and death as a result of acute cardiac and respiratory failure during the OP/MA phase of TRD3004.
- Ongoing Long-term open-label (OL) Extension Study TRD3008: 3 deaths were reported among the 1,140 participants treated with esketamine in the ongoing extension study TRD3008: 1 death due to PPD 1 death due to myocardial infarction, and 1 death due to multiple injuries (accidental polytrauma).

Participants with MDSI

In the completed Phase 2 and 3 MDSI studies, 1 death was reported in 262 participants who had been assigned to esketamine + SOC treatment in the double-blind treatment phase. This death (completed suicide) occurred during the follow-up phase of SUI3001

Serious Adverse Events

Participants with TRD

Three participants (<1% of those exposed to any formulation of esketamine) experienced serious adverse events (SAEs) in the 19 Phase 1 studies. One participant each reported an SAE of severe tooth abscess (TRD1004), an SAE of blighted ovum (TRD1013), and an SAE of substance induced psychotic disorder (TRD1015). All the events resolved after treatment, and only the SAE of blighted ovum was considered to be doubtfully related to esketamine nasal spray.

In the controlled Phase 3 TRD studies, SAEs were reported in participants receiving esketamine + oral AD at rates that were low and generally similar to those in participants receiving oral AD + placebo nasal spray (pooled TRD3001/3002: 0.9% [vs 0.5% for oral AD + placebo]; double-blind MA phase of Study TRD3003: 2.6% [vs 0.7% for oral AD + placebo nasal spray]; Study TRD3005: 4.2% [vs 3.1% for oral AD + placebo nasal spray]). Across both phases of the OL long-term safety study (TRD3004), 6.9% of participants experienced serious TEAEs. Across all studies, the most frequently reported SAEs were in the psychiatric disorders category and were associated with the underlying disease state.

SAEs in the esketamine + oral AD groups assessed by the investigator as related to study treatment included 1 participant each with depression, headache, blood pressure increased, and anxiety disorder across the Phase 3 short term studies; 1 participant each with disorientation, suicidal ideation, sedation, autonomic nervous system imbalance and simple partial seizures, lacunar stroke, and hypothermia in the relapse-prevention Study TRD3003 (all reported in induction phase); and 1 participant each with delirium, anxiety and delusion, suicidal ideation, and suicidal attempt in the long-term safety Study TRD3004.

Participants with MDSI

In the double-blind phase of the pooled Phase 3 studies SUI3001/3002, SAEs were reported for 4.0% participants in the esketamine + SOC group (suicide attempt, depression suicidal, depersonalization/derealization disorder, depression, suicidal ideation, and diabetic ketoacidosis) and 5.3% participants in the placebo + SOC group (suicide attempt, depression suicidal, depression, suicidal ideation, aggression, arrhythmia, pericardial effusion, hypertransaminasemia, and pneumothorax). After discontinuation from the double-blind phase, 1.3% participants in the esketamine + SOC group experienced SAEs (suicidal ideation and acute psychosis) versus 0.9% participants in the placebo + SOC group (depression suicidal, major depression, and suicide attempt). During the follow-up phase, SAEs were observed at similar rates in participants who were treated with esketamine + SOC during the double-blind phase and participants who were treated with placebo + SOC during the double-blind phase (11.6% and 11.9%, respectively). In the Phase 2 study SUI2001, SAEs were observed in 11.4% participants in the esketamine + SOC group and 0 participants in the placebo + SOC group during the double-blind phase, and in 3.7% participants and 22.7% participants, respectively, during the follow-up phase.

Adverse Events Leading to Discontinuation

Across the 19 Phase 1 studies, TEAEs led to withdrawal of 18 participants from study treatment in studies TRD1018 (6 participants); TRD1013 (4 participants); TRD1001 (2 participants); TRD1004, TRD1006, TRD1007, TRD1009, TRD1015 and TRD1020 (1 participant each).

Participants with TRD

In the Phase 2 Study TRD2003, 4 participants experienced TEAEs which led to withdrawal of study medication: 3 participants due to at least 1 TEAEs of syncope, headache or dissociative disorder in double-blind phase and 1 participant due to an SAE of ectopic pregnancy in the open-label phase. Except for ectopic pregnancy, all other events were considered as possibly or very likely related to the study drug.

TEAEs leading to discontinuation of esketamine were reported in approximately 5% to 6% of participants in the Phase 3 short-term studies in both adult and elderly participants, although rates were higher than for the oral AD + placebo groups (pooled TRD3001/TRD3002: 4.6% [vs 1.4% for oral AD + placebo]; Study TRD3005: 5.6% [vs 3.1% for oral AD + placebo]).

After longer-term exposure to esketamine in Study TRD3003, discontinuation rates for nasal study drug during the double-blind MA phase were similar for the esketamine + oral AD (2.6%) and oral

AD + placebo (2.1%) groups. The overall discontinuation rate due to TEAEs observed in the Phase 3 uncontrolled, open-label safety study (TRD3004) with long-term esketamine treatment (exposure of up to 1 year) was 9.5%.

Across the Phase 3 short term studies (TRD3001, TRD3002, and TRD3005), TEAEs leading to esketamine discontinuation in more than 2 participants (>0.1%) were: anxiety, depression, blood pressure increased, dizziness, suicidal ideation, dissociation, nausea, vomiting, headache, muscular weakness, vertigo, hypertension, panic attack, and sedation.

The rates of discontinuations of esketamine treatment due to TEAEs were generally highest immediately after treatment initiation. In the Phase 3 short-term studies in adults (TRD3001, TRD3002), nearly all discontinuations due to TEAEs in esketamine-treated participants occurred within the first 2 weeks of the double-blind phase. In the Phase 3 relapse-prevention (TRD3003) and open-label long term safety (TRD3004) studies, discontinuations due to TEAEs in esketamine-treated participants occurred in higher rates in the induction phase compared to the OP and/or MA phases (Study TRD3003: 5.0% vs 1.1% [OP] and 2.6% [MA]; Study TRD3004: 6.8% vs 3.8% [OP/MA combined]).

Participants with MDSI

In the pooled Phase 3 studies SUI3001/3002, 6.2% participants in the esketamine + SOC group and 3.6% participants in the placebo + SOC group experienced TEAEs leading to discontinuation of nasal spray study medication. TEAEs that led to discontinuation in >1 participant in the esketamine + SOC group were: dissociation (3 participants), depersonalization/derealization disorder, nausea, and blood pressure increased (2 participants each). In the Phase 2 study SUI2001, 14.3% participants in the esketamine + SOC group had a TEAE leading to discontinuation of study medication (dizziness, dysgeusia, aggression, agitation, ventricular extrasystoles, nausea, and dyspnea) versus 1 (3.2%) participant in the placebo + SOC group (dissociative disorder and panic attack).

Adverse Events of Clinical Interest/Special Safety Topics

Abuse Potential

Across all Phase 1, 2, and 3 studies of esketamine across indications, TEAEs suggestive of abuse potential, most commonly associated with esketamine were dizziness, somnolence, and dissociation. These symptoms were predominantly reported shortly after dosing on the day of esketamine administration, were transient and self-limiting, and mild or moderate in severity. Other events, such as euphoric mood, confusional state, feeling drunk or abnormal, and hallucinations, were also observed but occurred at lower rates. After up to 1 year of repeated intermittent dosing with esketamine in the open-label long-term safety study, the reporting frequencies of these other TEAEs were below 4%, while TEAEs of hallucinations were reported at rates not exceeding 1%.

Across Phase 3 TRD studies, the changes in withdrawal symptoms assessed by the 20-item Physician Withdrawal Checklist after cessation of treatment with esketamine + oral AD were

consistent with observed changes in symptoms of depression and anxiety. Based on these results, there was no evidence suggestive of a distinct withdrawal syndrome after cessation of treatment with esketamine + oral AD in Study TRD3003 or at 1, 2 or 4 weeks after cessation of treatment with esketamine + oral AD in Study TRD3004.

Suicidal Ideation and Behavior

In the Phase 1 studies, no postbaseline occurrences of suicidal ideation and/or suicidal behavior have been reported with the exception of 1 participant from Cohort 1 in Study TRD1012, which was conducted in healthy participants. This participant reported suicidal ideation throughout the study (ie, at screening, on Day 1, Day 2, and end-of-study) without any plan or intent to act, and without suicidal behavior. One other participant reported non-specific suicidal thoughts, which were not present at the end-of-study visit. No TEAEs related to suicidal ideation/behavior were observed in the Phase 1 studies.

Participants with TRD

Across all Phase 2 and 3 studies, suicidal ideation, assessed using the Columbia Suicide Severity Rating Scale (C-SSRS), showed a decrease from baseline to the endpoint in the esketamine treatment groups. Most participants reported no suicidal ideation or behavior during any of the completed TRD studies.

Most participants stayed within the same suicidality category throughout the duration of the Phase 3 studies. For participants with no suicidal ideation or behavior at baseline, the rates of reported suicidal ideation (based on C-SSRS) at least once during the treatment phase were similar for the esketamine + oral AD groups and the oral AD + placebo groups in the short term double-blind studies (TRD3001/3002: 10.2% vs 12.3%, respectively; TRD3005: 13.8% vs 16.7%) and in the double-blind MA phase of the relapse-prevention Study TRD3003 (2.4% vs 4.5%). Only a small number of participants with no suicidal ideation or behavior at baseline, all of whom had esketamine exposure, had suicidal behavior at any time postbaseline (1 [0.3%] participant in the induction phase of Study TRD3003; 2 [0.3%] participants in induction phase of Study TRD3004, and 2 [0.4%] in the OP/MA Phase of Study TRD3004).

Overall, across Phase 2 and 3 TRD studies, suicidality-related events were reported at a frequency of ~1% to 5%, and most of the reported cases were those of suicidal ideation. Severe suicidality-related TEAEs were reported at a low incidence (<1% for individual PTs) in each of the Phase 2 and 3 studies. Clinical review of suicidality-related TEAEs indicated that most of these events were likely associated with the underlying disease.

Participants with MDSI

The MDSI studies enrolled participants with MDD who had active suicidal ideation with intent (assessed to be at imminent risk for suicide per the study protocols). Study inclusion criteria corresponded with the level of severity of suicidal ideation considered to be predictive of suicidal behavior over the short term, and, in the physician's opinion, acute psychiatric hospitalization of the participant was to be clinically warranted due to imminent risk for suicide. In the pooled Phase 2 and 3 MDSI studies, the frequency of adverse events potentially related to suicidality occurring during the double-blind phase was similar in the 2 treatment groups (7.6% in the esketamine + SOC group and 6.6% in the placebo + SOC group). During the follow-up phase, the incidence of these events was similar in participants previously exposed to esketamine (10.6%) or placebo (11.6%). The reported frequencies of suicide attempts and completed suicides during the double-blind phase (1.5% in the esketamine + SOC group and 1.6% in the placebo + SOC group) and follow-up phase (3.7 in the esketamine + SOC group and 2.9% in the placebo + SOC group) for the pooled Phase 2 and 3 studies was similar in the 2 treatment groups. Across these studies, there were no completed suicides during the double-blind treatment phase, and 1 completed suicide during the follow-up phase.

Overall, the rate of suicide-related AEs observed in the ~3-month MDSI studies was not unexpected in light of reported findings in the literature in this high-risk population.

Clinician-Administered Dissociative States Scale (CADSS)

In all the reported studies, the majority of participants who were administered esketamine experienced dissociative symptoms as assessed by the CADSS. The symptoms peaked at around 40 minutes from the time of study drug administration and typically resolved by 2 to 4 hours after dosing.

Across completed Phase 2 and 3 studies across indications, consistent with the observations captured in the CADSS rating scale, median duration of the TEAEs of dissociation, feeling abnormal, and feeling drunk across dosing sessions did not exceed 2 hours. Dissociation was reported as severe in intensity at an incidence not exceeding 4% across studies, was not considered serious for any participants in completed Phase 2 and 3 studies, and rarely led to discontinuation of study drug.

Transient dissociative/perceptual changes (based on the CADSS scores, the overall TEAE incidence rates, and the severe TEAE incidence rates) were more pronounced in participants receiving higher doses of esketamine.

Brief Psychiatric Rating Scale – 4-Item Positive Symptom Subscale (BPRS+)

In the Phase 1 studies (TRD1001, TRD1002, TRD1003, TRD1004, TRD1005, TRD1006, TRD1007, TRD1009, TRD1010, and TRD1012), the majority of participants had total BPRS+ scores of 0.0, which remained unchanged during each study. When postdose increases in BPRS+ total scores were noted, they were generally seen at 40 minutes postdose and returned to baseline

levels by 2 hours postdose. Few participants experienced any increase in suspiciousness, hallucinatory behavior or unusual thought content. However, the Japanese participants showed higher mean BPRS+ total scores than the Caucasians. Results in elderly participants were similar to those in younger adults.

Across the Phase 2 and Phase 3 TRD studies, a small mean increase in BPRS+ total score from baseline was observed at 40-minute postdose assessment in esketamine + oral AD treatment groups (mean maximum values of <1, indicating symptoms were 'very mild'). After this transient, minimal worsening, mean scores generally returned to predose values at the 1.5-hour postdose assessment. Based upon review of TEAE data and BPRS+ data, treatment with esketamine nasal spray does not appear to be associated with development of potential psychotic-like symptoms. No TEAEs of psychosis were reported across the Phase 2 and 3 studies in TRD. In the MDSI studies, 1 participant in SUI3001 had a mild TEAE of psychotic symptom (mild severity) 2 days after his last esketamine dose, followed by an SAE of acute psychosis 2 days later; the investigator considered both events as not related to the study drug. Another participant in SUI2001 had a TEAE of psychotic disorder (moderate severity). As MDD (including TRD) with psychosis represents a more vulnerable population in whom esketamine may cause psychotomimetic symptoms, the product labeling for esketamine recommends that this drug product should be used with caution in patients with a presence or history of psychosis.

Anxiety

Across all Phase 2 and 3 studies across indications, TEAEs related to anxiety were primarily mild or moderate in severity, transient and self-limited. Most of these events occurred on the day of dosing and resolved spontaneously the same day. Anxiety was reported as severe in intensity in esketamine-treated participants at incidences below 2% across studies/study phases. Isolated cases of anxiety were reported as serious. Most of these events were considered by the investigator to be either not related to or doubtfully related to esketamine. Discontinuation of study drug due to anxiety was reported in under 2% of participants.

Transient Dizziness or Vertigo

Across all Phase 2 and 3 studies across indications, TEAEs related to dizziness or vertigo were primarily mild or moderate in severity, transient and self-limited. Most of these events occurred on the day of dosing and resolved spontaneously the same day, with the median duration not exceeding 2 hours across dosing sessions. Dizziness and vertigo were reported as severe in intensity at incidences under 3% across studies/study phases. No SAEs of dizziness or vertigo were reported in esketamine treated participants. Discontinuations of study drug due to dizziness or vertigo were reported at low rates (less than 1% of participants for each PT).

Sedation and Somnolence

Adverse effects of sedation were assessed using data based on the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) rating scale (measured each day of nasal spray dosing at 15-minute intervals from predose until 1.5 hours postdose or longer if necessary until the

participant had a score of 5 [awake]), as well as via review of the incidence, type, and severity of sedation related AEs. Across the Phase 1 studies, when sedation was reported it was limited in duration and generally returned to baseline levels within 1 to 2 hours after dosing. Results in elderly participants were similar to those in younger adults. The majority of the participants across all of the study cohorts experienced mild or no sedation (few participants had a MOAA/S score of less than 3, indicating at least moderate sedation) and remained alert after dosing with esketamine.

Based on the pattern of responses on the MOAA/S in the Phase 2 and 3 studies across indications, sedative effects of esketamine were generally mild, had an onset shortly after the nasal spray dosing peaking at 30 to 45 minutes postdose, and typically resolved by 1 to 1.5 hours postdose. Among esketamine treatment groups, 10% or fewer participants across the Phase 3 studies/study phases had a MOAA/S score of 3 or less (corresponding to moderate or greater sedation), although the occurrence of these scores was higher than that for the oral AD + placebo group. Across the Phase 3 studies in TRD, 10 of the 1,601 participants treated with esketamine + oral AD (and 1 of the 432 participants who received oral AD + placebo), had a MOAA/S score of 0 (no reaction to painful stimulus [trapezius squeeze]) and/or 1 (response to trapezius squeeze, including purposeful and reflexive withdrawal). Across the Phase 2 and 3 MDSI studies, 1 of 262 participants who received esketamine + SOC (and 0 of 256 participants who received placebo + SOC) had a MOAA/S score of 0. These isolated instances of severe sedation generally did not repeat with subsequent dosing. Among participants with a MOAA/S score of ≤3 (including those with a score of 0) across the Phase 3 studies, no symptoms of respiratory distress were observed, and hemodynamic parameters (including vital signs and oxygen saturation) remained within normal ranges.

The most commonly reported individual PTs (≥5%) related to sedation symptoms in the Phase 2 and 3 TRD studies were somnolence and sedation, and these events were reported at higher rates following treatment with esketamine + oral AD compared to oral AD + placebo in controlled Phase 3 studies/study phases (pooled TRD3001/TRD3002 studies: 17.3% vs 9.0%, respectively, for somnolence; 5.5% vs 0.9%, respectively, for sedation; Study TRD3003 double-blind MA phase: 21.1% vs 2.1% for somnolence; 6.6% vs 0.7% for sedation. However, in Study TRD3005, somnolence was reported at a higher rate in oral AD + placebo compared to esketamine + oral AD (4.6% vs 1.4%) [no TEAEs of sedation]). There were no TEAEs of respiratory depression among esketamine-treated participants across the Phase 1, 2, or 3 studies across indications.

Effects on Cognition

For the Phase 2 study (TRD2003), none of the participants experienced TEAE of impaired cognition. No TEAEs related to cognitive impairment (ie, preferred terms, cognitive disorder, minor cognitive motor disorder) were reported in the Phase 3 studies in TRD.

Based on the interim analysis of the ongoing long-term open-label extension study TRD3008 in 1,131 participants up to Week 76 an assessment of cognitive function based on a computerized cognitive test battery and the Hopkins Verbal Learning Test-Revised indicated that long-term treatment with esketamine was not associated with negative cognitive effects in the overall study population.

Nasal Tolerability and Nasal Examination

Across all Phase 1 studies, most participants did not report any nasal tolerability symptoms. Where nasal tolerability symptoms were reported, most were rated by the patient as mild. Abnormal findings during the nasal examination were generally mild. The results in Japanese participants were similar to those in Caucasian participants (TRD1002), and the results in elderly Japanese participants were similar to those in younger Japanese adults (TRD1018).

In the Phase 2 and 3 TRD studies nasal tolerability in participants self-administering esketamine nasal spray, including that following long term treatment, was good. There were no nasal examination findings or Nasal Symptom Questionnaire evidence to support an impact on nasal anatomy or function including the sense of smell.

Cardiovascular Effects

Blood Pressure Measurements

For many participants in the Phase 1 clinical studies (TRD1001, TRD1002, TRD1003, TRD1004, TRD1005, TRD1006, TRD1007, TRD1008, TRD1009, TRD1010, TRD1011, TRD1013, TRD1015, and TRD1020) there was a dose-dependent increase in systolic blood pressure (SBP) and diastolic blood pressure (DBP) which typically peaked at around 30 to 50 minutes and resolved at approximately 2 hours after esketamine administration. These changes generally returned to baseline within 2 to 4 hours postdose. Results in elderly participants ≥65 years of age were similar to those in younger adult participants, and results in Japanese participants were similar to those in Caucasian participants in these Phase 1 studies. For the majority of participants, no clinically relevant changes were observed in the mean blood pressure and HR.

Across all Phase 2 and 3 studies in participants with TRD transient, primarily asymptomatic, increases in systolic and diastolic BP were observed following esketamine administration, with maximum mean changes typically observed within 40 minutes of dosing and mean BP values subsequently returning to, or close to, predose values within the 1.5-hour postdose timepoint.

Pulse Rate Measurements

In Study TRD2003, abnormal increases in pulse rate were observed in no more than 2 participants in any treatment sequence and period. Across the Phase 3 studies/study phases, the rates of treatment-emergent abnormal decreases or increases in pulse rate relative to baseline at any time were less than 9%. Similar rates were reported for the esketamine + oral AD and oral AD + placebo groups in the controlled studies.

Cardiovascular TEAEs

In the QT Study TRD1013, 2 participants had an AE of palpitations (mild in intensity) that was considered very likely and possibly (1 participant each) related to the study treatment. No other TEAEs related to cardiac disorders were reported. No clinically meaningful effects in electrocardiogram (ECG) parameters (PR, RR, QRS, QT, QTcB, and QTcF intervals, heart rate [HR], and P-wave) were observed.

Across all Phase 2 and 3 TRD studies, TEAEs of increased BP in esketamine-treated participants were reported at the rates ranging from 6.6% to 13.9% across studies/study phases (based on the total esketamine + oral AD group in the pooled 3001/3002 studies), while TEAEs of increased HR occurred at lower incidences (all rates below 1.6%).

In the double-blind phases of Phase 2 Study TRD2003, the reporting rate for TEAEs related to increased blood pressure was 13.1% across all esketamine groups and 7.4% for the placebo group; no TEAEs related to increased heart rate were reported in the double-blind phases of this study. TEAEs related to increased heart rate occurred at low incidence rates (<2%) across the Phase 3 studies/study phases. By comparison, TEAEs related to increased blood pressure were reported at higher frequencies following treatment with esketamine + oral AD compared to oral AD + placebo in the controlled Phase 3 studies/study phases (pooled TRD3001/TRD3002 studies: 10.1% vs 2.7%, respectively; TRD3005: 13.9% vs 6.2%: double-blind MA phase of TRD3003: 8.6% vs 3.4%). Across the open-label long-term safety Study TRD3004, TEAEs related to increased blood pressure were reported for 12.8% of participants receiving esketamine + oral AD).

In the pooled Phase 3 MDSI studies (SUI3001/3002), TEAEs related to increased BP were reported at higher rates in the esketamine + SOC group than in the placebo + SOC group (15.0% vs. 6.2%). In the Phase 2 study SUI2001, TEAEs of increased BP were reported at low rates in both treatment arms (2 [5.7%] participants in the esketamine + SOC group and 1 [3.2%] participant in the placebo + SOC group).

Among esketamine-treated participants in the Phase 3 studies, very few of the TEAEs (individual preferred terms) of blood pressure increased or tachycardia were severe (≤0.2% in all study/study phases except Study TRD3005 where incidence of severe increased blood pressure TEAEs was 1.4% [representing 1 participant]). Further, TEAEs of increased blood pressure or tachycardia were reported as serious in only isolated cases, and discontinuation of esketamine treatment for these events occurred in <2% of participants across studies/study phases.

Between 90% and 100% of the reported TEAE preferred term of increased blood pressure occurred on the day of dosing in the Phase 3 studies/study phases and of these, >93% resolved spontaneously the same day.

Serious cerebrovascular TEAEs were reported in 2 of the 1,601 esketamine-treated participants across the Phase 3 studies (lacunar stroke after day of first esketamine dose with plausible mechanism of microatheroma; cerebrovascular accident occurring in follow-up phase 25 days after last esketamine dose in a participant with vasculitis).

Electrocardiogram

For most participants in the Phase 1 clinical studies (TRD1001, TRD1002, TRD1003, TRD1004, TRD1005, TRD1006, TRD1007, TRD1008, TRD1009, TRD1010, TRD1011, TRD1012, TRD1014, TRD1015, TRD1016, TRD1018, TRD1019, and TRD1020) no clinically relevant changes in ECG parameters or clinically meaningful treatment-related trends were observed.

Across Phase 1 studies, there were no cardiovascular SAEs reported. Two participants discontinued due to AEs from the Cardiac Disorders SOC (1 in Study TRD1006 for AE of atrial fibrillation and 1 in Study TRD1007 for AE of Wolff-Parkinson-White syndrome); the investigator did not consider these events to be related to the study agents.

In the thorough QT study (TRD1013), no clinically significant changes in ECG parameters were observed.

Across the completed Phase 2 and 3 studies across indications, there were no clinically relevant mean changes in ECG parameters (heart rate, PR duration, QRS duration, QTcB and QTcF intervals, QT duration, and RR duration) from average predose values over time in any group.

Bladder Pain/Interstitial Cystitis Symptom Score

The Phase 2 and 3 studies included monitoring for symptoms of cystitis or lower urinary tract symptoms using the BPIC-SS, a participant reported outcome measure developed to identify a bladder pain syndrome/interstitial cystitis population for clinical studies evaluating new treatments for bladder pain syndrome. Overall, there were no cases of interstitial cystitis or ulcerative cystitis in any of the esketamine studies across indications.

Other Safety Observations

Overall, no clinically relevant changes were observed in vital signs, clinical laboratory evaluations or clinically meaningful treatment related trends.

Safety in Participants with Hepatic Impairment (TRD1011)

Study TRD1011 evaluated the PK of esketamine nasal spray (28 mg) in participants with mild or moderate hepatic impairment in comparison to participants with normal hepatic function. Most of the observed TEAEs were mild and were reported to be resolved by the end of the study. There were no deaths, SAEs, persistent AEs, or discontinuations due to AEs. None of the laboratory abnormalities were considered clinically significant or reported as a TEAE. The safety profile in participants with hepatic impairment was similar to participants with normal hepatic function.

Phase 2 and 3 Findings

Elevations in ALT/AST >3xULN were reported at low rates across studies, were primarily asymptomatic, transient, and resolved spontaneously without worsening while treatment with esketamine and oral AD continued. No cases in any Phase 1, 2, or 3 esketamine studies across indications met the criteria for severe drug induced hepatocellular injury as defined by Hy's law.

2.2.1. Comparator Drug Combination Therapy

Not applicable.

2.3. Benefit-Risk Assessment

The totality of evidence supports a positive benefit-risk balance for esketamine nasal spray as a new treatment for adults with TRD. The extensive clinical study program for esketamine in TRD demonstrates the rapid, robust, and sustained efficacy for improving depression symptoms in this difficult-to-treat population. Benefit-risk assessments estimate that between 5 and 21 more patients per 100 treated achieve remission of depression symptoms after 4 weeks of treatment with esketamine + oral AD compared to initiating treatment with an oral AD alone. Further, once remission has been achieved on esketamine, continued maintenance treatment with esketamine + oral AD is estimated to result in 19 to 32 fewer relapses per 100 patients relative to those who discontinue esketamine. The safety experience with esketamine indicated that most of the adverse reactions seen with the drug, including those of common events such as dissociative symptoms, dizziness/vertigo, increased blood pressure, and sedation, occur shortly after dosing while the patient is under the supervision of a health care provider (HCP), and resolve the same day. In addition, certain adverse events such as dissociation, dizziness/vertigo, and nausea/vomiting tend to lessen in frequency with continued dosing. The benefits of esketamine are considered to outweigh the risks of the infrequent severe or treatment-limiting side effects in the TRD population. While the potential for abuse exists with esketamine, there were no TEAEs of drug abuse or overdose and no reports of confirmed diversion in clinical trials. Several risk mitigation initiatives are in place to lessen the potential for abuse and misuse. Patient preference study findings indicate that patients with TRD, both with and without esketamine treatment experience, place a higher value on improved depression symptoms over those of short-term unusual post dose sensations and drug administration logistics or hypothesized extreme safety risks associated with ketamine abuse.

More detailed information about the known and expected benefits and risks of esketamine may be found in the latest edition of the Investigator's Brochure[5] and USPI[11].

Taking into account the measures taken to minimize risk to participants of this study, the potential risks identified in association with esketamine are justified by the anticipated benefits that may be afforded to participants with TRD.

3. OBJECTIVES AND ENDPOINTS

Objectives

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 TRD, as assessed by the change from baseline in the MADRS total score from Day 1 (prerandomization) to the end of the 4-week double-blind treatment phase (Day 28).

Key Secondary Objective

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

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 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 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

Endpoints

Primary Endpoint

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

Key Secondary Endpoint

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

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) 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) 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)

HYPOTHESIS

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.

4. STUDY DESIGN

4.1. Overall 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.

The maximum duration of study participation is 24 weeks.

Screening Phase (up to 7 weeks)

This phase will assess the participant's eligibility for study participation.

Evaluations that will be performed at the screening visits are outlined in Section 1.3, Schedule of Activities (SoA).

The study population will include men and women, 18 years of age (or older if the minimum legal age of consent in the country in which the study is taking place is >18) or older, who meet the Diagnostic and Statistical Manual of Mental Disorders (5th Edition; DSM-5) diagnostic criteria for single episode MDD or recurrent MDD, without psychotic features, based upon clinical

assessment, and confirmed by the Mini International Neuropsychiatric Interview (MINI). In addition, the participant must have an Inventory of Depressive Symptomatology-Clinician rated, 30-item (IDS-C_{30}) total score of ≥34, which corresponds to moderate to severe depression.

Participants can be screened for study participation whether or not they are currently taking an antidepressant medication.

At the start of screening, participants must have had nonresponse to ≥2 different oral antidepressant treatments in the current episode of depression, as assessed by the Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire (MGH-ATRQ), and confirmed by documented records (eg, medical/pharmacy/prescription records or a letter from treating physician).

The participant's current major depressive episode, depression symptom severity, and AD treatment response in their current depressive episode must be deemed valid for participation in the clinical study based on the "State vs. Trait, Assessibility, Face Validity, Ecological Validity, Rule of Three P's" (SAFER) Interview, which is a site-independent qualification assessment.

If clinically indicated, a participant's current AD medication(s), including adjunctive treatment for MDD, should be tapered and discontinued during this phase per the local prescribing information, guidelines[6] or clinical judgement. Tapering/discontinuation of any antidepressant medication(s) should not be started until the SAFER Interview is completed and the site has received confirmation that the participant has "passed" the SAFER Interview.

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

For participants not taking any AD medications 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 taking benzodiazepines (at dosages equal to or less than the equivalent of 6 mg/day of lorazepam) and/or permitted non-benzodiazepine sleep medications (eg, zolpidem, zaleplon) during the screening phase can continue these medications. Temporary dose increases of benzodiazepines beyond the equivalent of 6 mg/day lorazepam or initiation of new benzodiazepines are permitted during the screening phase if needed to assist with AD taper/discontinuation and/or the antidepressant-free period. However, the dose of the current benzodiazepines is to be less than or equal to the equivalent of 6 mg/day of lorazepam before randomization in the double-blind treatment phase.

Potential participants will be excluded from participating in the study if they have used ketamine/esketamine (lifetime); previously demonstrated nonresponse of depressive symptoms to an adequate course of treatment with electroconvulsive therapy (ECT) in the current major depressive episode, defined as at least 7 treatments with unilateral/bilateral ECT; if they have received vagal nerve stimulation (VNS) or deep brain stimulation (DBS) in the current major depressive episode; if they have a current or prior DSM-5 diagnosis of a psychotic disorder or

MDD with psychosis, bipolar or related disorders (confirmed by the MINI), obsessive compulsive disorder (current only), intellectual disability (DSM-5 diagnostic codes 317, 318.0, 318.1, 318.2, 315.8, and 319), autism spectrum disorder, borderline personality disorder, antisocial personality disorder, histrionic personality disorder, or narcissistic personality disorder; if they have homicidal ideation/intent or suicidal ideation with some intent to act within 6 months prior to the start of the screening phase per the investigator's clinical judgment and/or based on the C-SSRS or suicidal behavior in the last year; or if they have a history of moderate or severe substance or alcohol use disorder according to DSM-5 criteria.

Participants meeting the inclusion/exclusion criteria (Section 5) 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 all treatment sessions. A treatment session consists of nasal administration of the study medication and post-administration observation. On all dosing days, all participants must remain at the clinical site for post-administration observation until at least 2 hours postdose until the patient is safe to leave. See Section 6, Study Intervention Administered, for blood pressure monitoring guidance on nasal spray treatment session days.

After receiving a treatment session, instruct participants not to engage in potentially hazardous activities, such as driving a motor vehicle or operating machinery, until the next day after a restful sleep.

Evaluations that will be performed during this phase are outlined in Section 1.3, Schedule of Activities.

Participants taking benzodiazepines and/or permitted non-benzodiazepine sleep medications (eg, zolpidem, zaleplon) during the screening phase can continue these medications during the double-blind treatment phase (at dosages equal to or less than the equivalent of 6 mg/day of lorazepam), however they may not be used within 12 hours prior to the start of each nasal spray treatment session. No dose increases beyond the equivalent of 6 mg/day of lorazepam, or new benzodiazepine medications are permitted during the double-blind treatment phase, except for the use of permitted benzodiazepine rescue medication.

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/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. The Investigator needs to assess and confirm in the source documentation that, based on clinical judgment, it is in the participant's best interest to participate in this 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 esketamine 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.

Evaluations that will be performed during this phase are outlined in the Schedule of Activities.

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. On all dosing days, all participants must remain at the clinical site for post-administration observation until at least 2 hours postdose. After receiving a treatment session, participants are not to engage in potentially hazardous activities, such as driving a motor vehicle or operating machinery, until the next day after a restful sleep. See Section 6, Study Intervention Administered, for blood pressure monitoring guidance on nasal spray treatment session days.

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.

Evaluations that will be performed during this phase are outlined in Section 1.3, Schedule of Activities.

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.

Further clinical/standard of care for the treatment of depression will be arranged by the study investigator and/or the participant's treating physician.

A diagram of the study design is provided in Section 1.2, Schema.

4.2. Scientific Rationale for Study Design

The sponsor has recently completed a phase 3 clinical program assessing the efficacy and safety of esketamine nasal spray used together with an oral antidepressant for the treatment of patients with TRD. Based on this program, esketamine nasal spray was registered by US FDA for this indication. However, there was insufficient information to confirm whether esketamine nasal spray is also effective in the treatment of participants with TRD when used as monotherapy. This protocol was designed in cooperation with FDA to provide the required data. In order to enable the comparison of results from this study with results from the phase 3 program, the study population, entry criteria, and study design were defined similarly to the phase 3 studies. This study will assess an onset of treatment effect on Day 2 and a durability of the treatment effect after 4 weeks of treatment with esketamine nasal spray used as monotherapy.

Study Phases

The screening phase (up to 7 weeks) will provide adequate time to assess participant eligibility according to the study entry criteria and to complete a mandatory 2-week antidepressant drug-free period prior to the start of a double-blind treatment phase. Participants taking antidepressant medications (for a complete list of antidepressant medications, please refer to Section 10.6, Appendix 6: Medications Used for the Treatment of Depression to be Discontinued During the Screening Phase) at entry will have these medications tapered (if applicable) and discontinued during this phase, per the local prescribing information or clinical judgment. This method of

recruitment allows for entry of participants being treated with various antidepressant medications or treatment regimens in the current depression episode. The mandatory 2-week antidepressant drug-free period will reduce any impact of the prior antidepressant medication(s) on the evaluation of the efficacy and safety of esketamine used as monotherapy in the double-blind treatment phase.

After the 2-week antidepressant drug-free period and assessment of nonresponse, there will be two groups of patients entering the double-blind treatment phase:

- Participants who meet the predefined nonresponse criteria: These participants will be randomized to receive nasal spray treatment with either placebo, esketamine 56 mg, or esketamine 84 mg.
- Participants who do not meet the predefined nonresponse criteria: For ethical reasons, these participants will also be randomized to receive nasal spray treatment with either placebo, esketamine 56 mg, or esketamine 84 mg, however they will not be included in the primary efficacy analysis set (ie, a separate randomization list will be used).

Previous studies have shown onset of efficacy with esketamine within a day, and durability of an antidepressant effect with repeated dosing. Based on the completed phase 2 and 3 studies, the treatment duration of 4 weeks was selected to demonstrate the treatment effect of esketamine (primary endpoint). To demonstrate an early onset of efficacy with esketamine treatment, Day 2 was selected as the key secondary endpoint.

The open label treatment/observation phase was designed to provide an opportunity for TRD patients completing the double-blind treatment phase to receive esketamine nasal spray, an effective treatment for TRD. This phase will have a recommended dosing frequency that allows for induction and stabilization of treatment with esketamine nasal spray. Participants not willing to receive esketamine can also enter this phase to be observed only, while receiving standard-of-care treatment for depression. A 3-month duration is provided to help participants receiving esketamine transition to available long-term care, if appropriate.

For participants entering the follow-up phase, the one-week duration following the last visit of the double-blind or open-label treatment phase will allow sufficient time to assess safety and tolerability after cessation of nasal spray study medication, including potential withdrawal symptoms.

Treatment Groups and Dose Selection

The 3 treatment groups in the double-blind treatment phase are:

- Esketamine nasal spray (56 mg)
- Esketamine nasal spray (84 mg)
- Placebo nasal spray

The treatment groups will allow for an evaluation of the efficacy, safety, and tolerability of 2 fixed doses of esketamine nasal spray as compared with placebo nasal spray in participants with TRD.

Study Drug

The data from Study ESKETINTRD2003 Panel A, phase 3 studies and MDSI studies support the hypotheses that both the 56-mg and 84-mg doses are effective as a treatment for depression in participants with TRD, that they have a rapid onset of effect, and that 2 treatment sessions per week can sustain the response throughout the 4 week duration of the double-blind treatment phase. In addition, the 56-mg and 84-mg dosages were generally well tolerated by participants.

The dosing frequencies selected for the open-label treatment/observation phase are based on the data from the completed phase 3 studies, ESKETINTRD3003 and ESKETINTRD3004. The dosing frequency reduced from twice a week to weekly for a duration of 4 weeks, and then individualized to either weekly or every other week based on clinical judgment, can stabilize and maintain the response throughout the long-term treatment.

Blinding, Control, Study Phase, Intervention Groups

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active intervention.

Randomization will be used to minimize bias in the assignment of participants to intervention groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across intervention groups, and to enhance the validity of statistical comparisons across intervention groups.

Blinded intervention will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

Blinded, site-based MADRS raters will be used to minimize the risk of unblinding the treatment assignment. Different site raters will perform efficacy and safety assessments; clinicians who perform the MADRS assessments will be different from those who evaluate safety assessments (eg, vital signs) and AEs. Raters for the MADRS will not be allowed to access or to review participant safety records, supervise administration of study medication nor observe patients in the 2-hour post dose observation period; therefore, they will not provide clinical care for participants.

Pharmacokinetic Assessments

PK samples will be obtained during the study for measurement of the plasma concentrations of esketamine, noresketamine, and/or additional metabolites, if warranted.

Pharmacogenomic (DNA & RNA) Evaluations

It is recognized that genetic variation and variations in transcription can be important contributory factors to inter-individual differences in drug distribution and response and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain inter-individual variability in clinical outcomes and may help to identify population subgroups that respond differently to a drug.

The goal of the pharmacogenomic component is to collect DNA and RNA to allow the identification of genetic, epigenetic, and transcription factors that may influence the PK, PD, efficacy, safety, or tolerability of esketamine and to identify factors associated with MDD.

4.2.1. Participant Input Into Design

Not applicable

4.2.2. Study-Specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled. Pharmacogenomic sample testing is optional and requires additional consent of the participant.

Clinical Study in Treatment-resistant Major Depression

Major depressive disorder is a common, severe, chronic, and often life-threatening illness. It is now the leading cause of disability worldwide. While there are a number of antidepressants approved for the treatment of depression, the response to them in patients who do not benefit after the first two antidepressants is much lower, which is often referred to as TRD. There is a clear need to develop novel and improved therapeutics for TRD.

Esketamine nasal spray was recently approved by the FDA for treatment of TRD in adults used in conjunction with an oral antidepressant. There is no systematic data available on use of esketamine as monotherapy. As patients may often not tolerate or discontinue the oral antidepressant for safety or tolerability, its necessary to know whether esketamine is efficacious when used as monotherapy.

Justification for Using Placebo

To assess the potential efficacy of a new compound for the treatment of major depression requires adequate and well-controlled clinical studies. For a new compound, this can be achieved either through a placebo-controlled study or through a study comparing it to an active comparator through a noninferiority design. For non-inferiority studies, previous placebo-controlled studies have to show consistently the superiority of the active standard drug to placebo. Nearly half of the studies with antidepressants fail even with previously proven antidepressants, making assay sensitivity difficult to establish and thus, a noninferiority design invalid.[8] Recent analyses have shown response to placebo varies considerably from 10% to 55%. Therefore, randomized, controlled studies that rely on comparison with standard antidepressants alone will generate unreliable results with limited assay sensitivity.

The completed phase 3 studies of esketamine in TRD all initiated esketamine with a newly initiated oral AD. This was done in part due to concerns about randomizing patients with a serious condition like TRD to placebo treatment. However, patients with TRD in the phase 3 studies showed an unexpectedly strong response to placebo nasal spray and oral AD, even at earlier timepoints where

oral AD was unlikely to have taken effect and appeared similar to that seen with other oral AD monotherapy studies.

Therefore, the use of a placebo-controlled study remains the gold standard for assessment of efficacy of new compound to allow for scientifically meaningful results. There is no known risk of irreversible harm in short term placebo-controlled studies. In a meta-analysis[7] of drug studies conducted in major depression, it was reported that participants did not have higher rates of suicide behaviors or attempts in the placebo group compared with those receiving an active AD. These studies show annual suicide rates of 0.8% on the investigational drug, 0.7% on the active comparator, and 0.4% on placebo. Placebo-controlled studies in major depression are ethically and scientifically justifiable.[1,8,13]

Precautions to Ensure Participant Safety in the Study

Participants may participate in the study only if they have adequate capacity to give consent and after fully understanding the potential risks and giving an informed consent. The probability of receiving placebo and the concept of random assignment will be explained to the participant. Only participants who have not adequately responded to their antidepressant medications and continue to have moderate to severe depression where a clinician would consider changing it for lack of response or poor tolerability, in addition to meeting the severity criteria for the study, will be enrolled. Current antidepressant medications will need to be tapered and discontinued prior to starting a mandatory 2-week antidepressant drug-free period prior to randomization. Withdrawal and/or discontinuation symptoms may be challenging for some patients. However, there are a number of strategies including use of rescue medications that may be used to minimize discomfort to participants.[6]

The duration of the study is short, minimizing the time on placebo. Participants in the study will be monitored very closely with in-person visits at least twice a week during the double-blind phase. Safety evaluations will include evaluation of suicidal ideation/behavior at each clinic visit. At any point in the study, the participant may withdraw consent, discontinue study intervention and receive standard-of-care therapy for depression, or be removed from the study by the investigator if there are any clinical concerns and provisions for appropriate and immediate clinical triage as necessary. A short-term placebo-controlled study may be conducted with reasonable expectation of patient safety.

Esketamine nasal spray is made available through an open label phase for all eligible participants who complete the 4-week double-blind treatment phase.

The total blood volume to be collected is considered to be within the normal range allowed for this participant population over this time frame. The approximate blood volume to be collected is 93.5 mL, which will be less than a Red Cross blood donation.

4.3. Justification for Dose

Doses selected (56 mg and 84 mg) are based on the United States Prescribing Information (FDA approved label)[11] for SPRAVATO™.

4.4. End of Study Definition

End of Study Definition

The end of study is considered as the last scheduled study assessment shown in the Schedule of Activities for the last participant in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

Phase and Study Completion Definitions

A participant will be considered to have completed the double-blind treatment phase of the study if the Day 28 study visit is completed. Note: If all scheduled study procedures for the Day 28 visit are not performed, at least the MADRS for this visit must be completed for the participant to be considered as having completed the double-blind treatment phase.

A participant will be considered to have completed the open-label treatment/observation phase of the study if the Week 16 study visit is completed.

A participant will be considered to have completed the study if he/she completed the double-blind treatment phase and the follow up visit (if the subject did not enroll in the open-label phase) or completed the double-blind, open-label phases and the follow-up visit.

5. STUDY POPULATION

Screening procedures for eligible participants will be performed per Section 1.3, Schedule of Activities. Refer to Section 5.3, Screen Failures, for conditions under which the repeat of any screening procedures are allowed.

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

For a discussion of the statistical considerations of participant selection, refer to Section 9.2, Sample Size Determination.

5.1. Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

1. At the time of signing the informed consent form (ICF), participant must be a man or woman 18 years of age (or older if the minimum legal age of consent in the country in which the study is taking place is >18) or older.

2. Criterion modified per Amendment 2

   2.1. Participant must meet the DSM-5 diagnostic criteria for single-episode MDD (if single episode MDD, the duration of the episode must be ≥2 years) or recurrent MDD, without psychotic features, based upon clinical assessment and confirmed by the MINI. Participants 65 years of age or older must have had the first onset of depression prior to 55 years of age.

3. Participant must have had nonresponse (≤25% improvement) to ≥2 oral antidepressant treatments in the current episode of depression, assessed using the MGH-ATRQ, and confirmed by documented records (eg, medical/pharmacy/prescription records or a letter from a treating physician).

4. Participant must have an IDS-C_{30} total score of ≥34.

5. The participant's current major depressive episode, depression symptom severity, and antidepressant treatment response in the current depressive episode, must be confirmed by the SAFER Interview.

6. Participant must be medically stable on the basis of physical examination, medical history, vital signs (including blood pressure), and 12-lead ECG performed in the screening phase. If there are any abnormalities that are not specified in the inclusion and exclusion criteria, the determination of their clinical significance must be determined by the investigator and recorded in the participant's source documents and initiated by the investigator.

7. Participant must be medically stable on the basis of clinical laboratory tests performed in the screening phase. If the results of the serum chemistry panel, hematology, or urinalysis are outside the normal reference ranges, the participant may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for the population under study. This determination must be recorded in the participant's source documents and initialed by the investigator.

   – Participants with a pre-existing history of thyroid disease/disorder who are treated with thyroid hormones must be on a stable dosage for 3 months prior to the start of the screening phase.

- For any participant (regardless of thyroid history), if the thyroid-stimulating hormone (TSH) value is out of range, a free thyroxine (FT4) will be conducted. If the FT4 value is abnormal and considered to be clinically significant (after discussion with the medical monitor), the participant is not eligible.

8. Participant must be comfortable with self-administration of nasal spray medication and be able to follow the nasal spray administration instructions provided.

9. Criterion modified per Amendment 1

   9.1. A woman of childbearing potential must have a negative highly sensitive serum (β-human chorionic gonadotropin [β-hCG]) at the start of screening and a negative urine pregnancy test must be obtained before the first dose of study drug on Day 1, prior to randomization.

10. Criterion deleted per Amendment 1

11. Criterion modified per Amendment 1

    11.1. A woman must be (as defined in Section 10.5, Appendix 5: Contraceptive and Barrier Guidance and Collection of Pregnancy Information)

    a. Not of childbearing potential
    b. Of childbearing potential and
       - Practicing a highly effective, user-independent (preferably) or user-dependent method of contraception (failure rate of <1% per year when used consistently and correctly) and agrees to remain on a highly effective method while receiving study intervention and until 6 weeks after last dose. Examples of highly effective methods of contraception are located in Section 10.5, Appendix 5 Contraceptive and Barrier Guidance and Collection of Pregnancy Information.

12. Criterion deleted per Amendment 1

13. Criterion modified per Amendment 1

    13.1. A male participant must agree not to donate sperm for the purpose of reproduction during the study and for a minimum of 90 days after receiving the last dose of study intervention.

    A male participant who is sexually active with a woman of childbearing potential must be practicing a highly effective method of contraception with his female partner (for examples of highly effective methods of contraception, please refer to Section 10.5, Appendix 5: Contraceptive and Barrier Guidance and Collection of Pregnancy Information) during the study (ie, from Day 1 of the double-blind treatment phase prior

to administration of the first dose of study intervention) and for a minimum of 90 days after receiving the last dose of the study intervention.

14. Criterion modified per Amendment 1

    14.1. Participant must be willing and able to adhere to the requirements and restrictions specified in this protocol.

15. Each participant must be able to read and write. The participant must sign an ICF indicating that he or she understands the purpose of and procedures required for the study and is willing to participate in the study.

16. Participant must sign a separate informed consent form if he or she agrees to provide optional samples for pharmacogenomic research. Refusal to give consent for the optional pharmacogenomic research samples does not exclude a participant from participation in the study.

5.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

1. The participant has used ketamine/esketamine (lifetime).

2. The participant's depressive symptoms have previously demonstrated nonresponse to an adequate course of treatment with ECT in the current major depressive episode, defined as at least 7 treatments with unilateral/bilateral ECT.

3. Participant has received vagal nerve stimulation (VNS) or has received deep brain stimulation (DBS) in the current episode of depression.

4. Participant has a current or prior DSM-5 diagnosis of a psychotic disorder or MDD with psychotic features, bipolar or related disorders (confirmed by the MINI), obsessive compulsive disorder (current only), intellectual disability (DSM-5 diagnostic codes 317, 318.0, 318.1, 318.2, 315.8, and 319), autism spectrum disorder, borderline personality disorder, antisocial personality disorder, histrionic personality disorder, or narcissistic personality disorder.

5. Participant has homicidal ideation/intent, per the investigator's clinical judgment, or has suicidal ideation with some intent to act within 6 months prior to the start of the screening phase, per the investigator's clinical judgment or based on the C-SSRS, corresponding to a response of "Yes" on Item 4 (active suicidal ideation with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent) for suicidal ideation on the C-SSRS, or a history of suicidal behavior within the past year prior to the start of the screening phase. Participants reporting suicidal ideation with intent to act or suicidal behavior prior to the start of the double-blind treatment phase should be excluded.

6. Participant has a history of moderate or severe substance or alcohol use disorder according to DSM-5 criteria, except nicotine or caffeine, within 6 months before the start of the screening phase.

    a. A history (lifetime) of ketamine, phencyclidine (PCP), lysergic acid diethylamide (LSD), or 3, 4-methylenedioxy-methamphetamine (MDMA) hallucinogen-related use disorder is exclusionary.

7. Participant has a current or history of seizures (uncomplicated childhood febrile seizures with no sequelae are not exclusionary).

8. Criterion modified per Amendment 1

    8.1. Participant has one of the following cardiovascular-related conditions:

    a. Cerebrovascular disease with a history of stroke, transient ischemic attack or history of intracerebral hemorrhage.

    b. Aneurysmal vascular disease (including intracranial, thoracic, or abdominal aorta, or peripheral arterial vessels) or arteriovenous malformation.

    c. Coronary artery disease with myocardial infarction, unstable angina, or revascularization procedure (eg, coronary angioplasty or bypass graft surgery) within 12 months before the start of the screening/prospective observational phase. Participants who have had a revascularization performed >12 months prior to screening and are clinically stable and symptom-free, per investigator's clinical judgment, can be included.

    d. Hemodynamically significant valvular heart disease such as mitral regurgitation, aortic stenosis, or aortic regurgitation.

    e. New York Heart Association (NYHA) Class III-IV heart failure of any etiology (details will be provided in an attachment to the full protocol).

9. Participant has a history of uncontrolled hypertension despite diet, exercise, or antihypertensive therapy at the start of the screening phase or any past history of hypertensive crisis or ongoing evidence of uncontrolled hypertension defined as a supine SBP >140 mmHg or DBP >90 mmHg during screening phase which continues to be above this range with repeated testing during this phase. Note: On Day 1 of the

double-blind treatment phase prior to randomization a supine SBP >140 mmHg or DBP >90 mmHg is exclusionary.

a. A potential participant may have his/her current antihypertensive medication(s) adjusted during the screening phase and be re-evaluated to assess their blood pressure control.

10. Criterion modified per Amendment 1

10.1. Participant has a history of, or symptoms and signs suggestive of, liver cirrhosis (eg, esophageal varices, ascites, and increased prothrombin time) OR alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values ≥3× the upper limit of normal (ULN) or total bilirubin >1.5× the ULN in the screening phase.

a. Repeat of screening test for abnormal ALT and AST is permitted during the screening period provided per investigator discretion and provided there is an alternative explanation for the out of range value.

b. For elevations in bilirubin if, in the opinion of the investigator and agreed upon by the sponsor's medical officer, the elevation in bilirubin is consistent with Gilbert's disease, the participant may participate in the study.

11. Criterion modified per Amendment 1

11.1. Participant has positive test result(s) for drugs of abuse (eg, barbiturates, methadone, opiates, cocaine, phencyclidine (PCP), MDMA, and amphetamine/methamphetamine) at the start of the screening phase or Day 1 of the double-blind treatment phase prior to randomization.

a. Participants who have a positive test result at screening due to prescribed psychostimulants (eg, amphetamine, methylphenidate) taken for any indication must discontinue the medication at least 2 weeks before Day 1 of the double-blind treatment phase (prior to randomization) in accordance with Section 6.5, Concomitant Therapy. The result of the Day 1 (prior to randomization) test for drugs of abuse must be negative for the participant to be randomized.

b. Otherwise, participants who have a positive test result at screening due to prescribed/over-the-counter opiates or barbiturates may be permitted to continue in the screening phase if the medication is discontinued at least 1 week or 5 half-lives, whichever is longer, before Day 1 of the double-blind treatment phase (prior to randomization) in accordance with Section 6.5, Concomitant Therapy. The result of the Day 1 (prior to randomization) test for drugs of abuse must be negative for the participant to be randomized.

- Retesting is not permitted for positive test result(s), except for reasons stated above.

c. Intermittent use of cannabinoids prior to the start of the screening phase is not exclusionary as long as the participant does not meet the criteria for substance-use disorder. A positive test for cannabinoids at the start of the screening phase

is not exclusionary; however, a positive test result for cannabinoids predose on Day 1 of the double-blind treatment phase is exclusionary.

12. Participant has uncontrolled diabetes mellitus, as evidenced by HbA1c >9% in the screening phase or history in the prior 3 months prior to the start of the screening phase of diabetic ketoacidosis, hyperglycemic coma, or severe hypoglycemia with loss of consciousness.

13. Participant has any anatomical or medical condition that, per the investigator's clinical judgment based on assessment, may impede delivery or absorption of nasal spray study drug.

14. Participant has a history of malignancy within 5 years before the start of the screening phase (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy that, in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence).

15. Participant has known allergies, hypersensitivity, intolerance, or contraindications to esketamine/ketamine and/or its excipients.

16. Participant has taken any prohibited therapies that would not permit dosing on Day 1, as noted in Section 6.5, Concomitant Therapy.

17. Participant is taking a total daily dose of benzodiazepines greater than the equivalent of 6 mg/day of lorazepam at the start of the screening phase.

    - Note: Temporary dose increases of benzodiazepines beyond the equivalent of 6 mg/day lorazepam, or initiation of new benzodiazepines, are permitted during the screening phase if needed to assist with antidepressant taper/discontinuation and/or the antidepressant-free period. However, the dose must be reduced to less than or equal to the equivalent of 6 mg/day of lorazepam before randomization in the double-blind treatment phase.

18. Participant has received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 60 days before the start of the screening phase, or has participated in 2 or more MDD or other psychiatric condition clinical interventional studies (with different investigational medication) in the previous 1 year before the start of the screening phase, or is currently enrolled in an investigational interventional study.

19. Participant is a woman who is pregnant, breastfeeding, or planning to become pregnant while enrolled in this study or within 6 weeks after the last dose of nasal spray study drug.

20. Participant plans to father a child while enrolled in this study or within 90 days after the last dose of study intervention.

21. Participant has a diagnosis of acquired immunodeficiency syndrome. Human immunodeficiency virus testing is not required for this study.

22. Participant has any condition or situation/circumstance for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

23. Participant is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.

24. Participant has severe renal impairment (creatinine clearance <30 mL/min).

25. Participant has not completed the mandatory 2-week antidepressant drug-free period prior to Day 1 of the double-blind treatment phase.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening and/or Day 1 prior to randomization (as applicable). If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that the participant no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. Section 5.3, Screen Failures, describes options for retesting. The required source documentation to support meeting the enrollment criteria are noted in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

5.3. Screen Failures

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened only after Sponsor's approval as assessed on a case by case basis.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

6.1. Study Interventions Administered

Esketamine will be supplied as a nasal spray device. Each device contains an aqueous solution of esketamine hydrochloride in water for injection, at a concentration of 161.4 mg/mL and an esketamine base equivalent concentration of 140 mg/mL, provided in a disposable single-use nasal spray device. The device dispenses two sprays (one to each nostril) delivering a total volume of 0.2 mL of drug product containing a total of 32.3 mg of esketamine hydrochloride (equivalent to 28 mg of esketamine).

Placebo will be supplied as in matching nasal spray devices. Each device contains a solution of water for injection with a bittering agent (0.001 mg/mL denatonium benzoate) added to simulate the taste of the nasal spray esketamine solution. Each nasal spray device contains 2 sprays of placebo solution.

Instructions for use documents (participant and healthcare provider versions) for nasal spray study drug administration will be provided as separate documents. Details regarding study drug administration will be recorded in the source documents and the eCRF.

If the participant has nasal congestion on the dosing day, an intranasal decongestant can be used to reduce congestion, or the dosing day can be delayed (per the permitted visit window; see the Schedule of Activities table). If an intranasal decongestant is used to reduce congestion, it cannot be used within 1 hour prior to nasal spray study drug dosing.

Food will be restricted for at least 2 hours before each administration of study drug. Drinking of any fluids will be restricted for at least 30 minutes before the first nasal spray. Participants must abstain from using alcohol within 24 hours before and after each nasal spray treatment session. If a participant appears intoxicated, dosing should not occur on that day.

Prior to the first nasal spray dose on Day 1, participants will practice spraying (into the air, not intranasally) a demonstration nasal spray device that is filled with a placebo solution.

Participants will be dosed as described in Section 4 under “Double-blind Treatment Phase (4 weeks)” and “Open-label Treatment/Observation Phase (up to 3 months)”**.**

Guidance for Blood Pressure Monitoring on Nasal Spray Treatment Session Days:

Given the potential for treatment-emergent transient elevation in systolic and diastolic blood pressure, the following guidance should be followed on dosing days:

- If subsequent to fulfilling the inclusion and exclusion criteria on Day 1 (ie, applicable for all other nasal spray treatment session days after Day 1), a participant’s predose SBP is >140 mmHg and/or DBP is >90 mmHg, it is recommended to repeat the blood pressure measurement after the participant rests in sitting or recumbent position. If after rest and repeated measurements, predose SBP is >140 mmHg and/or DBP is >90 mmHg, then dosing should be postponed, and the participant scheduled to return on the following day or within the given visit window. If the blood pressure elevation persists on the next visit, the participant

will be scheduled for a consultation by cardiologist, other specialist, or primary care physician, prior to further dosing.

- If at any postdose time point on the dosing day, the SBP is ≥180 mmHg but <200 mmHg and/or the DBP is ≥110 mmHg but <120 mmHg, further nasal spray dosing should be interrupted and the participant should be referred to a cardiologist, other specialist, or primary care physician for a follow-up assessment.
  - After the assessment by a cardiologist, other specialist, or primary care physician, if recommended by the referring doctor and considered appropriate according to the clinical judgment for the participant to continue in the study, then the participant may continue with nasal spray dosing if the predose blood pressure at the next scheduled visit is within the acceptable range (see bullet point above).
- If at any postdose time point on the dosing day the SBP is ≥200 mmHg and/or the DBP is ≥120 mmHg, the participant must discontinue from further dosing and the participant should be referred to a cardiologist, other specialist, or primary care physician for a follow-up assessment.
- At 1.5 hours postdose, if the SBP is ≥160 mmHg and/or the DBP ≥100 mmHg, assessments should continue every 30 minutes until:
  - the blood pressure is <160 mmHg SBP and <100 mmHg DBP, or
  - in the investigator's clinical judgment, the participant is clinically stable and can be discharged from the study site, or
  - the participant is referred for appropriate medical care, if clinically indicated.
- If the blood pressure remains ≥180 mmHg SBP and/or ≥110 mmHg DBP, 2 hours after dosing, the participant should be referred for immediate medical treatment.

Study intervention administration must be captured in the source documents and the CRF.

Esketamine nasal spray will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure[5] for a list of excipients.

For details on rescue medications, refer to Section 6.7.1, Rescue Medication. For a definition of study intervention overdose, refer to Section 8.4, Treatment of Overdose.

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

All study intervention must be stored at controlled room temperatures ranging from 59°F to 86°F (15°C to 30°C).

Refer to the study site investigational product and procedures manual (IP manual) for additional guidance on study intervention preparation, handling, and storage.

Accountability

The investigator is responsible for ensuring that all study intervention received at the site is inventoried and accounted for throughout the study. The dispensing of study intervention to the participant, and the return of study intervention from the participant must be documented on the intervention accountability form. Participants must be instructed to return all original containers, whether empty or containing study intervention. The study intervention administered to the participant must be documented on the intervention accountability form. All study intervention will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study intervention containers.

Study intervention must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet as per local requirements for Schedule III controlled substances, under appropriate environmental conditions. Unused study intervention, and study intervention returned by the participant, must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study intervention, or used returned study intervention for destruction, will be documented on the intervention return form. When the study site is an authorized destruction unit and study intervention supplies are destroyed on-site, this must also be documented on the intervention return form.

Study intervention should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel. Study intervention will be supplied only to participants participating in the study. Returned study intervention must not be dispensed again, even to the same participant. Study intervention may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study intervention from, nor store it at, any site other than the study sites agreed upon with the sponsor. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 3 intervention groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by study site and antidepressant treatment status (on- or off-treatment) at screening entry (refer to Section 10.6 for a list of applicable treatments). 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 interactive web response system (IWRS) will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the participant. The requestor must use his or her own user identification and personal

identification number when contacting the IWRS and will then give the relevant participant details to uniquely identify the participant.

Blinding

To maintain the study blind during the double-blind phase, the study intervention container will have a label containing the study name, study intervention number, and reference number. However, if it is necessary for a participant's safety, the study blind may be broken and the identity of the study intervention ascertained. The study intervention number will be entered in the CRF when the study intervention is dispensed. The study interventions will be identical in appearance and will be packaged in identical containers.

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual participant.

Conditions to maintain the blind of MADRS raters are specified in Section 8.1.

Data that may potentially unblind the intervention assignment (ie, study drug concentrations, study drug preparation/accountability data, treatment allocation, and biomarker or other specific laboratory data) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

Under normal circumstances, the blind should not be broken until all participants have completed the study and the database is finalized. The investigator may in an emergency determine the identity of the intervention by contacting the IWRS. While the responsibility to break the intervention code in emergency situations resides solely with the investigator, it is recommended that the investigator contact the sponsor or its designee if possible, to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented by the IWRS in the appropriate section of CRF, and in the source document. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

Participants who have had their intervention assignment unblinded should continue to return for scheduled evaluations, but the nasal spray treatment would be discontinued.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed.

6.4. Study Intervention Compliance

Participants will self-administer nasal spray treatment under the direct supervision of a healthcare provider to be compliant with study intervention administration. During the course of the study, the investigator or designated study-site personnel will be responsible for providing additional instruction to reeducate any participant who is not compliant with taking the study intervention.

6.5. Dose Modification

No dose modifications are allowed during the double-blind treatment phase.

Participants in the open-label treatment/observation 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. There will be a recommended dosing frequency of twice weekly (maximum) for Weeks 5 to 8, followed by once weekly dosing from Weeks 9 to 12. From Week 13 to Week 16, the dosing frequency (weekly or every other week) will be based on clinical judgment. Dosing frequency should be individualized to the least frequent dosing to maintain remission/response.

6.5.1. Retreatment Criteria

If applicable, a need for retreatment must be discussed with the sponsor medical monitor and a decision will be taken on a case by case basis.

6.6. Continued Access to Study Intervention After the End of the Study

There is no study intervention following the end of the study.

Participants will be instructed that study intervention will not be made available to them after they have completed/discontinued study intervention and that they should return to their primary physician to determine standard of care.

6.7. Concomitant Therapy

Prestudy therapies administered up to 30 days before entering screening phase must be recorded at the start of screening.

All antidepressant treatment(s) (pharmacological, including adjunctive treatments and/or non-pharmacological eg ECT, VNS, DBS, psychotherapy) taken during the current depressive episode (ie, including those taken more than 30 days prior to the start of the screening phase) will be recorded at the start of the screening phase. All antidepressant treatments listed on the MGH-ATRQ, as well as any not listed on the MGH-ATRQ, used as antidepressant treatment in the current depressive episode must be recorded in "Concomitant Therapy" eCRF.

Participants should continue to take their permitted concomitant medications (eg, antihypertensive medications) at their regular schedule; however, restrictions as outlined in this section under Prohibited Medications (table below) should be taken into account. Of note, if a participant has

routinely taken oral antihypertensive medications in the morning on dosing days, the morning dose should be taken prior to nasal spray dosing.

Concomitant therapies (including psychotherapy) must be recorded throughout the study beginning with signing of the informed consent and continuing up to the last visit.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens, or other specific categories of interest) different from the study intervention must be recorded in the CRF. Recorded information will include a description of the type of therapy, duration of use, dosing regimen, route of administration, and indication. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a participant into the study.

The following concomitant medications are allowed within the study.

- Participants who were taking benzodiazepines and/or permitted non-benzodiazepine sleep medications (eg, zolpidem, zaleplon) during the screening phase can continue these medications (at dosages equal to or less than the equivalent of 6 mg/day of lorazepam) during the double-blind treatment phase. No dose increases beyond the equivalent of 6 mg/day of lorazepam, or new benzodiazepine medications are permitted during the double-blind treatment phase, with the exception of the use of permitted benzodiazepine rescue medication. Benzodiazepines and non-benzodiazepine sleeping medication (eg, zolpidem, zaleplon, eszopiclone, and ramelteon) are prohibited within 12 hours prior to the start of each nasal spray treatment session. Close monitoring for sedation is necessary when used with esketamine.
- ECT, DBS, transcranial magnetic stimulation, and VNS are prohibited from study entry through the end of the double-blind treatment phase.
- Participants receiving psychotherapy (including cognitive behavioral therapy) can continue receiving psychotherapy; however, psychotherapy must have been ongoing for the last 3 months prior to the start of the screening phase. Any form of new psychotherapy is prohibited during the screening and double-blind phase of this study.

Prohibited Concomitant Medications With Nasal Spray Study Medication (esketamine or placebo)

This list of medications is **not all-inclusive**; if necessary, please contact the medical monitor for any questions regarding a medication(s).

Please refer to the local prescribing information of the participant's non-study medications for information regarding prohibited concomitant medications.

Except where specifically noted, the prohibited medications listed in the following table are prohibited from 1 week (or 5 half-lives, whichever is longer) prior to the first dose of nasal spray study medication until after the last dose of nasal spray study medication.

Note in the following table: N, Prohibited; Y, Permitted, with restrictions (please refer to the column labeled "Comments" for additional guidance).

Drug Class	Episodic Use (as needed)	Continuous Use	Comments	Reason for Prohibition
ADHD medications (eg, atomoxetine, guanfacine); psychostimulants (eg, amphetamines, methylphenidate)	N	N	Not allowed during the 2-week mandatory antidepressant-free period prior to randomization and during the double-blind phase. Allowed for patients switched to standard-of care treatment during the double-blind treatment phase and during the open-label treatment/observation phase, but must not be taken within 12 hours prior to the intranasal treatment session.	Safety Potential impact on efficacy
Anorexiants (eg, phentermine, phendimetrazine)	N	N		Safety
Anticholinesterase inhibitors	N	N		Participant population is excluded
Anticonvulsants	Y	Y	Participants with seizures are excluded. Note: Anticonvulsants used for indications other than seizures may be allowed (eg, valproate for migraine; pregabalin)	Safety and PD interaction
Antidepressants and medications used for treatment of depression	N	N	Not allowed within 2 weeks of mandatory antidepressant-free period prior to randomization and during the double-blind phase. Allowed for patients switched to standard-of care treatment during the double-blind treatment phase and during the open-label treatment/observation phase. Refer to Section 10.6 for a list of applicable medications.	Potential impact on efficacy
Antipsychotics	N	N	Not allowed within 2 weeks of mandatory antidepressant-free period prior to randomization and during the double-blind phase Allowed for patients switched to standard-of care treatment during the double-blind treatment phase and during the open-label treatment/observation phase.	Potential impact on efficacy
Benzodiazepines (at dosages equal to or less than the equivalent of 6 mg/day lorazepam except of temporary increases allowed during taper and antidepressant-free screening periods) and non-benzodiazepine sleeping medication (including: zolpidem, zaleplon, eszopiclone, and ramelteon)	Y	Y	Prohibited within 12 hours prior to the start of each nasal spray treatment session or cognition testing. Close monitoring for sedation is necessary when used as concomitant medication with esketamine.	Safety and PD interaction
Benztropine	Y	N	Prohibited if use is continuous and prohibited within 12 hours prior to the start of cognition testing	Safety and PD interaction

Drug Class	Episodic Use (as needed)	Continuous Use	Comments	Reason for Prohibition
Chloral hydrate, valerian	N	N		Safety and PD interaction
Clonidine	Y	Y	Use for blood pressure control is allowed.	
Corticosteroids (systemic)	Y	N	Inhaled, intranasal, topical, and ophthalmic steroids are not prohibited. Intermittent IM/IV/PO corticosteroids are permitted with sponsor approval (chronic use prohibited). Intranasally-administered corticosteroids should not be used from 1 hour prior to each nasal spray study medication administration.	PD interaction
Cough/cold preparations/nasal solutions containing vasoconstrictors, decongestants	Y	Y	Intranasally-administered decongestants (vasoconstrictors) should not be used from 1 hour prior to each nasal spray study medication administration. Pseudoephedrine- containing products should not be used within 12 hours prior to a nasal spray treatment session.	Safety and PD interaction
CYP3A4 inducers - Potent	N	N	Participants may not take a known potent inducer of hepatic CYP3A activity within 2 weeks of the first administration of nasal spray study medication until at least 24 hours after the last dose of nasal spray study medication. Examples (not all-inclusive): Efavirenz, nevirapine, barbiturates, carbamazepine, glucocorticoids, modafinil, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort	PK
Diphenhydramine	Y	N	Prohibited within 12 hours prior to the start of each nasal spray treatment session	Safety
Ketanserin	N	N		Safety
Memantine	N	N		PD interaction
Methyldopa	N	N		Safety and PD Interaction
Metyrosine	N	N		Safety and PD interaction
Non-vitamin K antagonist oral anticoagulation agents (eg, dabigatran, rivaroxaban, apixaban)	N	N		Safety
Opioids	N	N	With Sponsor approval, brief treatment with opiates may be allowed for treatment of acute injuries, etc.	Safety
Reserpine	N	N		PD interaction
Thyroid hormone supplement for treatment of thyroid condition only (not for depression)	N	Y		Safety

Drug Class	Episodic Use (as needed)	Continuous Use	Comments	Reason for Prohibition
Thyroxine/ triiodothyronine (T3), thyroid hormone prescribed for depression	N	N		Potential impact on efficacy

Abbreviations: ADHD: attention deficit hyperactivity disorder; IM: intramuscular; IV: intravenous; N: Prohibited; PD: pharmacodynamics; PK: pharmacokinetics; PO: oral; Y: Permitted, with restrictions (please refer to the column labeled "Comments" for additional guidance).

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

6.7.1. Rescue Medication

The study site will supply rescue medication that will be obtained locally. The following rescue medications may be used:

- For agitation or anxiety: As required, short-acting benzodiazepines, eg, lorazepam, alprazolam, midazolam.
- For nausea: As required, ondansetron 8 mg sublingually, metoclopramide (10 mg orally or IV or IM) or dimenhydrinate (25 to 50 mg, IV or IM)
- Transient increase in blood pressure should not be treated, as the blood pressure returns to predose values typically in 1.5-4 hours. The effect of any treatment may result in hypotension.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

A participant's study intervention must be discontinued if:

- The participant withdraws consent to receive study intervention
- The investigator believes that for safety reasons or tolerability reasons (eg, adverse event) it is in the best interest of the participant to discontinue study intervention
- The participant becomes pregnant Refer to Section 10.5, Appendix 5, Contraceptive Guidance and Collection of Pregnancy Information.
- Major protocol deviation (to be assessed on a case by case basis)
- Blind broken

If a participant discontinues study intervention for any reason (other than withdrawal of consent) before the end of the double-blind phase a participant should continue with the scheduled visits until end of the double-blind phase (Day 28). Completion of the double-blind treatment phase is required to enter the open-label treatment/observation phase of the study. For any participant who has not completed this phase (Day 28 visit or at least Day 28 MADRS assessment), an Early Withdrawal visit should be conducted within 1 week of the date of discontinuation.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent to participate in the study
- Death
- Major protocol deviation (to be assessed on a case by case basis)
- Positive Urine Drug Screen for PCP or cocaine at any time point during the study

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the CRF and in the source document. If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed.

Withdrawal of Consent

In the situation where a participant may be at risk for withdrawal of consent and is unable to return for scheduled visits at the protocol-defined frequency, the investigator may consider options for reduced follow-up. These may include (as local regulations permit):

- Less frequent clinical visits (OL phase only)
- Telephone, email, letter, social media, fax, or other contact with:
  - participant
  - relatives of the participant
  - participant's physicians (general or specialist)
- Review of any available medical records

Details regarding these contacts must be properly documented in source records including responses by participants.

7.2.1. Withdrawal From the Use of Research Samples

A participant who withdraws from the study will have the following options regarding the optional research samples:

- The collected samples will be retained and used in accordance with the participant's original informed consent for research samples.
- The participant may withdraw consent for research samples, in which case the samples will be destroyed, and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor study site contact of withdrawal of consent for the research samples and to request sample destruction. The sponsor study site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the samples have been destroyed.

Withdrawal From the Optional Research Samples While Remaining in the Main Study

The participant may withdraw consent for optional research samples while remaining in the study. In such a case, the optional research samples will be destroyed. The sample destruction process will proceed as described above.

Withdrawal From the Use of Samples in Future Research

The participant may withdraw consent for use of samples for research (refer to Long-term Retention of Samples for Additional Future Research in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

7.3. Lost to Follow-up

To reduce the chances of a participant being deemed lost to follow-up, prior to randomization attempts should be made to obtain contact information from each participant, eg, home, work, and mobile telephone numbers and email addresses for both the participant as well as appropriate family members.

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study-site personnel to contact the participant are deemed futile. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study-site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, to ascertain whether the participant wishes to or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls, e-mails, fax, and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods. Locator agencies may also be used as local regulations permit. These contact attempts should be documented in the participant's medical records.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

Should a study site close, eg, for operational, financial, or other reasons, and the investigator cannot reach the participant to inform them, their contact information will be transferred to another study site.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities summarizes the frequency and timing of efficacy, PK, PD, biomarker, pharmacogenomic, safety, and other measurements applicable to this study.

All participant-reported outcomes assessments should be conducted/completed before any tests, procedures, or other consultations to prevent influencing participant perceptions.

If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: MADRS, PHQ-9, CGI-S, C-SSRS, vital signs (predose), ECG, lab sampling, dosing of study medication, postdose vital signs and observation. Blood collections for PK and PD assessments should be kept as close to the specified time as possible. Actual dates and times of assessments will be recorded in the source documentation.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study.

The total blood volume to be collected from each participant will be approximately 93.5 mL (Table 1).

Table 1: Volume of Blood to be Collected From Each Participant

Type of Sample	Volume per Sample (mL)	No. of Samples per Participant	Total Volume of Blood (mL) [a]
Screening Phase			
TSH	2.5	1	2.5
Hematology, Chemistry [b, c]	3.5	1	3.5
Double-blind Treatment Phase			
Hematology, chemistry	2.5	2	5.0
Pharmacokinetics	2.0	2	4.0
Biomarker: Protein	30.0	2	60.0
Pharmacogenomics DNA [d]	6.0	1	6.0
Pharmacogenomics: RNA [d]	2.5	1	2.5
Open Label Treatment/Observational Phase			
Hematology, chemistry	2.5	3	7.5
Follow-up Phase			
Hematology, chemistry	2.5	1	2.5
Approximate volume of blood collected during the study			**93.5 mL**

Abbreviations: DNA, deoxyribonucleic acid; RNA, ribonucleic acid; TSH, thyroid-stimulating hormone

a) Calculated as number of samples multiplied by amount of blood per sample.
b) Hematology, chemistry includes serum β-hCG pregnancy tests (for women of childbearing potential), HbA1c, and lipid panel.
c) As needed, HbA1c will be measured from the sample collected for hematology.
d) Blood samples will be collected only from participants who have consented to provide optional samples for research.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the laboratory requisition form. If blood samples are collected via an indwelling cannula, an appropriate amount (1 mL) of serosanguineous fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken. After blood sample collection,

the cannula will be flushed with 0.9% sodium chloride, United States Pharmacopeia (or equivalent) and charged with a volume equal to the dead space volume of the lock. If a mandarin (obturator) is used, blood loss due to discard is not expected.

Refer to the Schedule of Activities for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

Study-Specific Materials

The investigator will be provided with the following supplies:

- Protocol
- Investigator's Brochure
- Pharmacy manual/study site investigational product and procedures manual
- Procedural documents for SAFER Interview
- Practice nasal spray devices
- Instructions for Use documents (participant and healthcare provider version) for nasal spray study medication
- Rater training procedural documents for select clinician administered assessments
- MGH-ATRQ guidance document
- Laboratory manual
- Clinician and patient reported outcome questionnaires
- Patient Reported Outcomes Completion Guidelines
- IWRS Manual
- ECG equipment and associated materials (eg, manual)
- Electronic data capture (eDC) Manual
- eSource Manual
- Device and instructions for conducting and recording of remote interviews
- Sample ICF

8.1. Efficacy Assessments

The primary efficacy evaluation will be the MADRS total score.

The MADRS is a clinician-rated scale designed to measure depression severity and detects changes due to antidepressant treatment. 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), for a total

possible score of 60. Higher scores represent a more severe condition. The MADRS evaluates apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, inability to feel (interest level), pessimistic thoughts, and suicidal thoughts. The test exhibits high interrater reliability.

The MADRS will be performed by site-based raters via video teleconferencing during the study using the Structured Interview Guide for the MADRS. To minimize the risk of unblinding the treatment assignment, different site raters will perform efficacy and safety assessments; clinicians who perform the MADRS assessments will be different from those who evaluate safety assessments (eg, vital signs) and adverse events. Raters for the MADRS will not be allowed to access or to review participant safety records or supervise/observe study drug administration; therefore, they will not provide clinical care for participants.

All MADRS assessments will be recorded for the purpose of quality monitoring.

The Clinical Global Impression – Severity (CGI-S) scale will be used to assess severity of depressive symptoms. 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.

The Patient Health Questionnaire 9-item (PHQ-9) is a participant-reported outcome measure that will be used to assess depressive symptoms. The 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 treatment 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.

8.2. Safety Assessments

Adverse events will be reported and followed by the investigator as specified in Section 8.3, Adverse Events and Serious Adverse Events and Section 10.4, Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the CRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in Section 1.3, Schedule of Activities:

- Monitoring of TEAEs, including TEAEs of special interest, pregnancy testing (for women of childbearing potential), and vital signs.

- C-SSRS, to assess potential suicidal ideation and behavior.

Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS will be used to assess potential suicidal ideation and behavior.

The C-SSRS is a low-burden measure of the spectrum of suicidal ideation and behavior that was developed in the National Institute of Mental Health Treatment of Adolescent Suicide Attempters Study to assess severity and track suicidal events through any treatment.[9] It is a clinical interview providing a summary of both 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 can also be used during treatment to monitor for clinical worsening.

Two versions of the C-SSRS will be used in this study, the Baseline/Screening version, and the Since Last Visit version. The Baseline/Screening version of the C-SSRS will be used in the screening/prospective observational phase. In this version, suicidal ideation will be assessed at 2 timepoints: "lifetime" and "in the past 6 months," and suicidal behavior will be assessed at 2 timepoints: "lifetime" and "in the past year." All subsequent C-SSRS assessments in this study will use the Since Last Visit version, which will assess suicidal ideation and behavior since the participant's last visit.

8.2.1. Physical Examinations

A full physical examination, including body weight will be carried out at screening, double-blind treatment phase, open-label treatment/observational phase and follow-up phase as specified in the Schedule of Activities. Height will be measured at screening as specified in the Schedule of Activities.

8.2.2. Vital Signs

Vital Signs (Temperature, Pulse/Heart Rate, Blood Pressure)

Blood pressure and pulse/heart rate measurements will be assessed supine with a completely automated device or using manual techniques.

Blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

For further details regarding blood pressure, see Section 6.1 under the subheading entitled "Guidance for Blood Pressure Monitoring on Nasal Spray Treatment Session Days."

Tympanic temperature is recommended.

8.2.3. Electrocardiograms

Single, 12-Lead ECGs

During the collection of ECGs, participants should be in a quiet setting without distractions (eg, television, cell phones). Participants should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs.

All ECG tracings will be sent to a central ECG laboratory. The ECGs will be read at the scheduled time points and summarized by a central ECG laboratory. The central ECG laboratory will send the sponsor an electronic copy of the data for inclusion in the clinical database. In addition, the investigator or subinvestigator is required to review all ECGs at the study visit to assess for any potential safety concerns or evidence of exclusionary conditions prior to dosing.

8.2.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology and a random urine sample for urinalysis will be collected as noted in Section 10.2, Appendix 2, Clinical Laboratory Tests. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the CRF. The laboratory reports must be filed with the source documents.

8.2.5. Suicidal Ideation and Behavior Risk Monitoring

Treatment resistant depression is associated with higher risk of suicide attempt than that with major depression. Esketamine is considered to be an antidepressant. There has been some concern that antidepressants may be associated with an increased risk of suicidal ideation or behavior when given to some participants with TRD. Although this study intervention or other similar treatments in this class have not been shown to be associated with an increased risk of suicidal thinking or behavior when given to this participant population, the sponsor considers it important to monitor for such events before or during this clinical study. In the completed esketamine programs there were 4 cases of completed suicide, but the overall trend was in reduction of suicidal ideation.

Participants being treated with esketamine should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior.

Baseline assessment of suicidal ideation and behavior and intervention-emergent suicidal ideation and behavior will be assessed during the study using C-SSRS and adverse event reporting.

8.2.6. Other Evaluations

Patient's Awareness of Treatment-Arm Assignment Scale

To assess participants assessment of blinding, they will be asked to respond to the question "Which medication did you receive?" Their responses will be captured and scored as indicated in Table 2 and used to determine whether the participants can differentiate between the 2 treatments they may receive (esketamine nasal spray or placebo nasal spray).

Table 2: Patient's Awareness of Treatment-Arm Assignment Scale

Question: Which medication did you receive?	
Response:	**Code as:**
Strongly believe the nasal spray treatment is **esketamine**	1
Somewhat believe the nasal spray treatment is **esketamine**	2
Don't know	3
Somewhat believe the nasal spray treatment is **placebo**	4
Strongly believe the nasal spray treatment is **placebo**	5

Menstrual Cycle Tracking

Menstrual cycle tracking (start date of last menstrual period) is captured only for women with a menstrual cycle at the study visits specified in the Schedule of Activities.

Massachusetts General Hospital - Antidepressant Treatment Response Questionnaire (MGH-ATRQ)

The MGH-ATRQ is used to determine treatment resistance in MDD.[3]

The MGH-ATRQ evaluates the adequacy of duration and dose of all antidepressant medications used for the current major depressive episode. In addition, the MGH-ATRQ assesses the degree of improvement on a scale from 0% (not improved at all) to 100% (completely improved). The MGH-ATRQ will be completed by the clinician in collaboration with the participant.

Inventory of Depressive Symptomatology - Clinician-rated, 30-item (IDS-C_{30})

The 30-item IDS-C_{30} was designed to assess all the criterion symptom domains designated by DSM, fourth edition to diagnose a major depressive episode[10]; these criteria have not changed in the DSM-5.[2] These assessments can be used to screen for depression, although they have been used predominantly as measures of symptom severity. The 7-day period prior to assessment is the usual time frame for assessing symptom severity. The psychometric properties of the IDS-C_{30} have been established in various study samples.[14]

This assessment will be audio-recorded for the purpose of quality monitoring.

SAFER Interview

Remote, independent psychiatrists/psychologists will perform the SAFER Interview[12] for all participants to assess the validity of a diagnosis of depression and eligibility for the study. SAFER refers to:

S = State versus trait: The identified symptoms must reflect the current state of illness and not longstanding traits. Traits do not generally change in 4–12 weeks.

A = Assessibility: The patient's symptoms are measurable with standard, reliable rating instruments. The symptoms of valid patients can be reliably assessed with standardized measurement tools

F = Face validity: The patient's presentation is consistent with our knowledge of the illness (symptoms map to the nosological entity; clear change from previous level of function; similar to previous episodes if recurrent)

E = Ecological validity: The patient's symptoms reflect the characteristics of the illness in a real-world setting (frequency, intensity, duration, course, impact over at least 4 weeks)

R = Rule of the Three P's Identified symptoms must be pervasive, persistent, and pathological and interfere with function and quality of life.

The interviewer will review participant screening information and conduct a live, remote interview with the participant. Depression severity, MGH-ATRQ, and SAFER Criteria Inventory will be evaluated during the interview. After the interview, the site will receive information regarding the SAFER Interview (ie, pass or fail) participant eligibility directly from the interviewer/designee.

This interview will be audio-recorded for the purpose of quality monitoring.

Further information regarding this assessment will be provided to sites in a separate document.

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's representative) for the duration of the study.

For further details on adverse events and serious adverse events (Definitions and Classifications; Attribution Definitions; Severity Criteria; Special Reporting Situations; Procedures) as well as product quality complaints, refer to Section 10.4, Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All adverse events and special reporting situations, whether serious or nonserious, will be reported from the time a signed and dated ICF is obtained until completion of the participant's last study-related procedure, which may include contact for follow-up of safety. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study intervention, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Serious Adverse Events

All serious adverse events occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the CRF, which must be completed and reviewed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and

follow-up reports of a serious adverse event should be transmitted electronically or by facsimile (fax).

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events or serious adverse events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about adverse event occurrence.

Solicited Adverse Events

Solicited adverse events are predefined local and systemic events for which the participant is specifically questioned.

Unsolicited Adverse Events

Unsolicited adverse events are all adverse events for which the participant is not specifically questioned.

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

Adverse events, including pregnancy, will be followed by the investigator as specified in Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

An anticipated event is an adverse event that commonly occurs in the study population independent of exposure to the drug under investigation. For the purposes of this study the following events will be considered anticipated events.[5]

For esketamine and major depressive disorder (MDD) (including TRD; based on DSM-5):

- Suicidal thinking, ideation, and behavior
- Sleep changes, difficulty sleeping, reduced sleep, abnormal sleep, tiredness, fatigue, and reduced energy
- Difficulty in sexual desire, performance or satisfaction
- Reduced appetite and weight changes (loss or increase)

- Activation or hypomania/ mania
- Irritability, anger, and impulsive behavior
- Agitation, tension, panic attacks, and phobia

These anticipated events will be periodically analyzed in aggregate by the sponsor during study conduct. The sponsor will prepare a safety report in narrative format if the aggregate analysis indicates that the anticipated event occurs more frequently in the treatment group than in the control group and the sponsor concludes there is a reasonable possibility that the drug under investigation caused the anticipated event.

The plan for monitoring and analyzing the anticipated events is specified in a separate Anticipated Events Safety Monitoring Plan. The assessment of causality will be made by the sponsor's unblinded safety assessment committee.

The sponsor assumes responsibility for appropriate reporting of the listed anticipated events according to the requirements of the countries in which the studies are conducted.

8.3.5. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any participant who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study intervention.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

8.3.6. Adverse Events of Special Interest

Clinically relevant TEAEs of special interest will be examined separately grouped in the following categories:

- Suggestive of abuse potential (Aggression, Confusional state, Decreased activity, Dependence, Disorientation, Dissociation, Dissociative disorder, Dizziness, Drug abuse, Drug abuser, Drug dependence, Drug use disorder, 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, synaesthetic, 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 (Agitation, Anticipatory anxiety, Anxiety, Anxiety disorder, 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);
- Suicidality (Completed suicide, Depression suicidal, Intentional overdose, Intentional self-injury, Multiple drug overdose intentional, Poisoning deliberate, Self-injurious behavior, Self-injurious ideation, Suicidal behavior, Suicidal ideation, Suicide attempt)

8.4. Treatment of Overdose

There is no specific antidote for esketamine overdose. In the case of overdose, the possibility of multiple drug involvement should be considered. Contact a Certified Poison Control Center for the most up to date information on the management of overdosage (1-800-222-1222 or www.poison.org).

8.5. Pharmacokinetics

Plasma samples will be used to evaluate the PK of esketamine. The concentrations of esketamine and noresketamine or other metabolites (if warranted) will be measured in plasma.

8.5.1. Evaluations

Venous blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of esketamine and noresketamine or other metabolites (if warranted) at the time points specified in the Schedule of Activities. Additional information about the collection, handling, and shipment of biological samples can be found in the Laboratory Manual.

8.5.2. Analytical Procedures

Pharmacokinetics

Plasma samples will be analyzed to determine concentrations of esketamine using a validated, specific, and sensitive achiral liquid chromatography/tandem mass spectrometry (LC MS/MS) method by or under the supervision of the sponsor.

If required, plasma samples may be analyzed to measure noresketamine using a validated assay or to document the presence of other circulating metabolites using a qualified research method. In addition, plasma PK samples may be stored for future analysis of the metabolite profile. The bioanalytical report, including a description of the assay and a summary of the assay performance data, will be included in the final study report as an addendum.

8.5.3. Pharmacokinetic Parameters and Evaluations

Parameters

The plasma concentration-time data of esketamine and noresketamine or other metabolites (if warranted) may be analyzed using population PK modeling. Data would be combined with those of other selected studies to support a relevant structural model. Typical population values of basic PK parameters would be estimated together with the inter individual variability. Effects of participant demographics, laboratory parameter values, and other covariates on the PK of esketamine would be explored. If performed, details will be provided in a population PK analysis plan and the results of the population PK analyses will be reported separately.

Pharmacokinetic/Pharmacodynamic Evaluations

The relationship between MADRS total score (and possibly selected adverse events as additional PD parameters), and PK metrics of esketamine may be evaluated. If there is any visual trend in graphical analysis, suitable models will be applied to describe the exposure-effect relationships. The results of the PK/PD analyses would be reported separately.

8.6. Biomarkers

Blood samples will be collected as indicated in Section 1.3, Schedule of Activities for exploratory analysis of biomarkers (protein and metabolites) related to immune system activity, hypothalamic-

pituitary-adrenal (HPA) axis activation, neurotrophic and metabolic factors. Exploratory analyses may be performed for additional biomarkers as well. Biomarker samples will be collected to:

- evaluate the mechanism of action of esketamine or
- help explain inter-individual variability in clinical outcomes or
- help identify population subgroups that respond differently to a drug

At the conclusion of the biomarker analyses, these findings will be presented in a separate study report.

If possible, blood samples should be collected under fasting conditions (minimum 8 hours prior to biomarker sample collection, water is permitted). When fasting is not feasible, participants should follow a low-fat diet for at least 8 hours prior to sample collection. Participants should refrain from exercise/strenuous physical activity and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) for 24 hours prior to blood collection. Not following these recommendations will not constitute a protocol violation. Biomarkers may be added or deleted based on scientific information or technical innovations under the condition that the total volume of blood collected will not be increased. All biomarker data obtained during this study may be included in ongoing cross-study analyses to investigate the relationship between depression severity and phenotypes and biomarkers.

Information on menstrual cycle (date of first day of last period, average length of cycle) will be recorded at each visit when blood samples for biomarker analysis are collected.

8.6.1. Pharmacodynamics

The mechanism of action and inter-individual variability in clinical outcomes of esketamine is evaluated in this study through biomarker and pharmacogenomic evaluations (see Section 8.6.2 and 8.7 for more details).

8.6.2. Pharmacogenomic (DNA and RNA) Evaluations

A pharmacogenomic blood sample will be collected from participants who consent separately to this component of the study to allow for pharmacogenomic research, as necessary. Whole blood samples for DNA and RNA analyses will be collected at the time points indicated in Section 1.3, Schedule of Activities. Participation in pharmacogenomic research is optional.

DNA and RNA samples will be analyzed for the assessment of genetic variation and transcription of genes in pathways relevant to MDD. Additional analyses may be conducted if it is hypothesized that this may help resolve issues with the clinical data.

DNA and RNA samples will be used for research related to esketamine or MDD. They may also be used to develop tests/assays related to esketamine and MDD. Pharmacogenomic research may consist of the analysis of one or more candidate genes or of the analysis of genetic markers throughout the genome (as appropriate) in relation to esketamine or MDD clinical endpoints.

All genetic data obtained during this study may be included in ongoing cross-study analyses to investigate the relationship between depression severity and phenotypes and biomarkers.

8.7. Immunogenicity Assessments

Not applicable

8.8. Health Economics/Medical Resource Utilization and Health Economics

Not applicable.

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

9.1. Statistical Hypotheses

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.

9.2. 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,[4] 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.

9.3. Populations for Analysis Sets

For purposes of analysis, the following populations are defined:

- Efficacy analyses for the double-blind phase will be performed on the full efficacy analysis set, which is defined as all randomized participants who meet nonresponse criteria and have received at least one dose of double-blind study medication. Participants who do not meet nonresponse criteria will be summarized separately for efficacy.

- Safety analyses for the double-blind phase will be performed on the safety analysis set, which is defined as all randomized participants (both participants who meet and do not meet nonresponse criteria) who receive at least one dose of double-blind study medication.
- The safety and efficacy analyses for the open-label phase will be based on all participants who receive at least one dose of open-label esketamine study medication.
- The safety and efficacy analyses for the observational phase will be based on all participants who enter the observational phase but do not receive open-label esketamine study medication.

9.4. Statistical Analyses

The statistical analysis plan (SAP) will be finalized prior to database lock (DBL) and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

Analyses of primary, key secondary, and other endpoints, and the safety parameters are described below.

Efficacy Analyses

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 after the null hypothesis for the primary endpoint is rejected for both doses.

9.4.2. Primary Endpoint

Primary Estimand

The primary estimand, the main clinical quantity of interest to be estimated in this study, is defined by the following 5 components:

- **Population**: participants with TRD who have met the inclusion/exclusion criteria and the nonresponse criteria
- **Endpoint**: change from baseline to Day 28 in the MADRS total score
- **Treatment**: placebo, esketamine 56 mg, esketamine 84 mg
- **Intercurrent Events**: All intercurrent events leading to changes in randomized treatment, such as premature discontinuation of the randomized treatment with or without a switch to

alternative antidepressant therapies, will be handled by a hypothetical strategy to estimate what the outcome would have been if all participants adhered to their randomized treatment. That is, post-treatment observations will not be included in the primary analysis.

- **Population Level Summary:** the difference in means between each dose and placebo for the change from baseline in MADRS total score at Day 28.

Missing data will be closely monitored and if necessary, to assess the robustness of conclusions from the primary analysis to missing data assumptions, additional sensitivity analyses and/or estimands will be specified in the SAP. The key assumption in the primary analysis is that missing data arise from a Missing at Random (MAR) mechanism. This assumption is aligned with the estimand and the hypothetical strategy.

The primary efficacy variable, change from baseline in MADRS total score at Day 28, will be analyzed using a Mixed-Effect Model for Repeated Measures (MMRM) model based on observed case data. The model will include factors for treatment (esketamine 56 mg, esketamine 84 mg, placebo), center, antidepressant treatment status (on- or off-treatment) at screening entry, day, day-by-treatment interaction, and baseline MADRS total score as a covariate. The within-participant covariance between visits will be estimated via an unstructured variance-covariance matrix. Comparisons of the esketamine groups versus placebo will be performed using the appropriate contrast.

9.4.3. Key Secondary Endpoint

Key Secondary Estimand

The key secondary estimand, the secondary clinical quantity of interest to be estimated in this study, is defined by the following 5 components:

- **Population**: participants with treatment-resistant depression who have met the inclusion/exclusion criteria and the nonresponse criteria
- **Endpoint**: change from baseline to Day 2 in the MADRS total score
- **Treatment**: placebo, esketamine 56 mg, esketamine 84 mg
- **Intercurrent Events**: All intercurrent events leading to changes in randomized treatment, such as premature discontinuation of the randomized treatment with or without a switch to alternative antidepressant therapies, will be handled by a hypothetical strategy to estimate what the outcome would have been if all participants adhered to their randomized treatment. That is, post-treatment observations will not be included in the key secondary analysis.
- **Population Level Summary**: the difference in means between each dose and placebo for the change from baseline in MADRS total score at Day 2

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.

9.4.4. Other Endpoints

Change from baseline in MADRS total score over time will be analyzed using the same MMRM model as described for the primary endpoint. Response and remission rates based on the MADRS total score will be summarized at each visit. Frequency distributions of the CGI-S scores at each scheduled timepoint will be provided and change from baseline over time will be summarized. Change from baseline in PHQ-9 total score over time in the double-blind treatment phase will be analyzed using the same MMRM model as described for the primary endpoint. Response rates based on the PHQ-9 will be summarized at each visit. Descriptive summaries of efficacy data will be provided for the double-blind phase for participants who do not meet nonresponse criteria and for the open label/observational phase.

9.4.5. Safety Analyses

Adverse Events

Safety data will be analyzed separately for each phase. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported adverse events with onset during the treatment phase (ie, treatment-emergent adverse events, and adverse events that have worsened since baseline) will be included in the analysis. For each adverse event, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by treatment group.

Treatment emergent AEs of special interest will be examined separately grouped in the following categories: suggestive of abuse potential, increased blood pressure, increased heart rate, transient dizziness/vertigo, impaired cognition, cystitis, anxiety, and anticipated dosing-related AEs (See Section 8.3.6 for details).

Adverse events of special interest will be further listed in the SAP. Participants who discontinue treatment due to an adverse event and serious adverse events (SAEs) will be summarized separately. Narratives will be provided for deaths, SAEs, and participants who discontinue due to an AE.

Vital Signs

Descriptive statistics of temperature, pulse/heart rate, body weight measurements, and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time point. The percentage of participants with values beyond clinically important limits will be summarized.

C-SSRS

A frequency distribution of C-SSRS scores at each scheduled timepoint by treatment will be provided. Shifts from the baseline visit to the most severe/maximum score during each study phase will be summarized by treatment. The maximum score assigned for each participant will also be summarized into one of three categories: no suicidal ideation or behavior (0), suicidal ideation (1-5), suicidal behavior (6-10).

9.4.6. Other Analyses

Pharmacokinetic Analyses

The plasma concentrations of esketamine and noresketamine or other metabolites (if warranted) will be listed for all participants and summarized descriptively.

Patient's Assessment of Treatment-arm Assignment

Descriptive statistics will be reported.

9.5. Interim Analysis

Not applicable.

9.6. Data Monitoring Committee or Other Review Board

Not applicable.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

AD	antidepressant
ADHD	attention deficit hyperactivity disorder
ALT	alanine amino transferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{∞}	area under the concentration-time curve at infinity
AUC_{last}	area under the concentration-time curve at last measurable concentration
β-hCG	β human chorionic gonadotropin
BCRP	breast cancer resistance protein
BP	blood pressure
BPRS+	Brief Psychiatric Rating Scale-4-Item Positive Symptom Subscale
CADSS	Clinician-Administered Dissociative States Scale
CGI-S	Clinical Global Impression – Severity
CI	confidence interval
C_{max}	maximum concentrations
CNS	central nervous system
eCRF	electronic case report form(s)
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	Cytochrome P450
DBP	diastolic blood pressure
DBS	deep brain stimulation
DNA	deoxy ribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders (5th edition)
ECG	electrocardiogram
ECT	electroconvulsive therapy
eDC	electronic data capture
FDA	Food and Drug Administration
FT4	free thyroxine
KSS	Karolinska Sleepiness Scale
GABA	γ-amino butyric acid-ergic
GCP	Good Clinical Practice
HbA1c	Haemoglobin A1c
IC50	50% inhibition concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IDS-C_{30}	Inventory of Depressive Symptomatology-Clinician rated, 30-item
IEC	Independent Ethics Committee
IM	intramuscular
IRB	Institutional Review Board
IV	intravenous
IWRS	interactive web response system
MADRS	Montgomery-Asberg Depression Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MDD	major depressive disorder
MDSI	Major depressive disorder with suicidal ideation
MGH-ATRQ	Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire
MINI	Mini International Neuropsychiatric Interview
MMRM	mixed-effects model using repeated measures
MOAA/S	Modified Observer's Assessment of Alertness/Sedation
MTD	maximum tolerated dose
NYHA	New York Heart Association
NMDA	N-methyl D-aspartate
NMDAR	N-methyl D-aspartate receptor
NOAELs	No Observed Adverse Effect Levels

OATP	organic anion-transporting polypeptide
OCT	organic cation transporter
OP	optimization
OTF	oral thin film
PCP	phencyclidine
PD	pharmacodynamic(s)
PHQ-9	Patient Health Questionnaire 9 item
PK	pharmacokinetic(s)
P-gp	P-glycoprotein
PQC	Product Quality Complaint
PT	preferred term
QTc	corrected QT
QTcB	QT corrected according to Bazett's formula
QTcF	QT corrected according to Fridericia's formula
RNA	ribonucleic acid
SAE	Serious adverse event
SAFER	State vs. Trait, Assessibility, Face Validity, Ecological Validity, Rule of Three P's
SBP	Systolic blood pressure
SD	Standard deviation
SDS	Sheehan Disability Scale
SOC	Standard of care
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal half-life
t_{max}	Time to reach maximum concentrations
TEAE	Treatment-emergent adverse events
TRD	Treatment resistant depression
TSH	thyroid-stimulating hormone
ULN	Upper limit of normal
VNS	vagal nerve stimulation

10.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed according to the Schedule of Activities by the central laboratory:

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Platelet count Red blood cell count Hemoglobin Hematocrit	<u>RBC Indices:</u> MCV MCH % Reticulocytes	<u>White Blood Cell (WBC) count with Differential:</u> Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. A RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.		
Clinical Chemistry	Sodium Potassium Chloride Bicarbonate Blood urea nitrogen (BUN) Creatinine Glucose [fasting] Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic Alanine aminotransferase (ALT)/Serum glutamic-oxaloacetic Gamma-glutamyltransferase (GGT)	Total and Direct bilirubin Alkaline phosphatase Creatine phosphokinase (CPK) Lactic acid dehydrogenase (LDH) Uric acid Calcium Phosphate Albumin Total protein Magnesium	
	Note: All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured which may indicate severe liver injury (possible Hy's Law), must be reported as a serious adverse event (excluding studies of hepatic impairment or cirrhosis).		
Routine Urinalysis	<u>Dipstick</u> Specific gravity pH Glucose Protein Blood Ketones Bilirubin Urobilinogen Nitrite Leukocyte esterase	<u>Sediment (if dipstick result is abnormal)</u> Red blood cells White blood cells Epithelial cells Crystals Casts Bacteria	
	If dipstick result is abnormal, flow cytometry will be used to measure sediment. In case of discordance between the dipstick results and the flow cytometric results, the sediment will be examined microscopically.		

Laboratory Assessments	Parameters
Other Screening Tests	• Serum and Urine Pregnancy Testing for women of childbearing potential only • Urine Drug Screen opiates (including methadone), cocaine, MDMA amphetamines, methamphetamines, cannabinoids and barbiturates. • TSH • HbA1c

10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

10.3.1. Regulatory and Ethical Considerations

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study intervention to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)

- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.2, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.2.

10.3.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) for details on financial disclosure.

10.3.3. Informed Consent Process

Each participant must give written consent according to local requirements after the nature of the study has been fully explained. Pharmacogenomic testing is optional, each participant must provide additional consent to pharmacogenomic testing.

The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent should be in accordance with

principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive for the treatment of his or her disease. Participants will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The participant will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the participant's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

10.3.4. Data Protection

Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps

will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory DNA/RNA, PD, biomarker and PK research is not conducted under standards appropriate for the return of data to participants. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

10.3.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand esketamine, to understand TRD, to understand differential intervention responders, and to develop tests/assays related to esketamine and TRD. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section 7.2.1, Withdrawal From the Use of Research Samples).

10.3.6. Committees Structure

A Data Monitoring Committee is not needed for this study because this is a post marketing commitment for an approved drug.

10.3.7. Publication Policy/Dissemination of Clinical Study Data

All information, including but not limited to information regarding esketamine or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic or exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of esketamine, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the

study will be used to determine a coordinating investigator for the study. Results of pharmacogenomic or exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and sub-study approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law. The disclosure of the final study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

10.3.8. Data Quality Assurance

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, and periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study-site personnel before the start of the study.

The sponsor will review CRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

10.3.9. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each participant in electronic format. Data relating to the study must be recorded in CRF where applicable. All CRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the participant's source documents. Data must be entered into CRF in English. The CRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

All participative measurements (eg, MADRS and CGI-S) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

10.3.10. Source Documents

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; intervention receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following data will be recorded directly into the CRF and will be considered source data:

- Race
- History of smoking, all nicotine use, eg, cigarettes (including e-cigarettes or the equivalent of e-cigarettes), cigars, chewing tobacco, patch, gum

The minimum source documentation requirements for Section 0, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An eSource system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If eSource is utilized, references made to the CRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the CRF.

10.3.11. Monitoring

The sponsor will use a combination of monitoring techniques central, remote and on-site monitoring to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

10.3.12. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

10.3.13. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The

investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

10.3.14. Study and Site Start and Closure

First Act of Recruitment

The first site open is considered the first act of recruitment and it becomes the study start date.

Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.4. Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.4.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the intervention. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to All Adverse Events under Section 8.3.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study intervention and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For esketamine, the expectedness of an adverse event will be determined by whether or not it is listed in the IB.

10.4.2. Attribution Definitions

Assessment of Causality

The causal relationship to study treatment is determined by the Investigator. The following selection should be used to assess all adverse events (AE).

Related

There is a reasonable causal relationship between study treatment administration and the AE.

Not Related

There is not a reasonable causal relationship between study treatment administration and the AE.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

10.4.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

10.4.4. Special Reporting Situations

Safety events of interest on a sponsor study intervention in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study intervention
- Suspected abuse/misuse of a sponsor study intervention

- Accidental or occupational exposure to a sponsor study intervention
- Any failure of expected pharmacologic action (ie, lack of effect) of a sponsor study intervention
- Unexpected therapeutic or clinical benefit from use of a sponsor study intervention
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without patient exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Exposure to a sponsor study intervention from breastfeeding

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the CRF.

10.4.5. Procedures

All Adverse Events

All adverse events, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study intervention or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a participant's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

The cause of death of a participant in a study within 30 days of the last dose of study intervention, whether or not the event is expected or associated with the study intervention, is considered a serious adverse event.

10.4.6. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

10.4.7. Product Quality Complaint Handling

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure

appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

10.5. Appendix 5: Contraceptive and Barrier Guidance

Participants must follow contraceptive measures as outlined in Section 0, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.5, Pregnancy and Section 10.4, Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Woman Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
  If there is a question about menopausal status in women on HRT, the woman will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
- **permanently sterile**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered.

Contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] – oral – injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of ≥1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Male or female condom with or without spermicide[c]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method (LAM)

a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.
b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention.
c) Male condom and female condom should not be used together (due to risk of failure with friction).

10.6. Appendix 6: List of Pharmacological Treatments Commonly Used for Treatment of Depression (not all-inclusive)

Class	Medications
Anticonvulsants	Carbamazepine
	Gabapentin
	Lamotrigine
	Phenytoin
	Tiagabine
	Topiramate
	Valproate
Anxiolytics	Buspirone
Atypical Antipsychotics	Aripiprazole
	Brexpiprazole
	Olanzapine
	Paliperidone
	Quetiapine
	Risperidone
Monoamine Oxidase Inhibitors (MAOIs)	Isocarboxazid
	Moclobemide
	Phenelzine
	Pirlindole
	Selegiline
	Tranylcypromine
Mood-stabilizing Agents	Lithium
Norepinephrine–dopamine reuptake inhibitor (NDRI)	Bupropion
Other	Mianserin
	Mirtazapine
	Olanzapine/fluoxetine
Psychostimulants	Amphetamine
	Atomoxetine
	Dextroamphetamine
	Lisdexamphetamine
	Methamphetamine
	Methylphenidate
	Mixed amphetamine salts
	Modafinil
	Pemoline
Serotonin Modulators	Nefazodone
	Trazodone
	Vilazodone
	Vortioxetine
Selective Serotonin Reuptake Inhibitors (SSRIs)	Citalopram
	Escitalopram
	Fluoxetine
	Fluvoxamine
	Paroxetine
	Sertraline
Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)	Desvenlafaxine
	Duloxetine
	Levomilnacipran
	Milnacipran
	Venlafaxine

Class	Medications
Thyroid hormones	Liothyronine
Tricyclic Agents (TCAs)	Amitriptyline
	Amoxapine
	Clomipramine
	Desipramine
	Doxepin
	Imipramine
	Nortriptyline
	Maprotiline
	Protriptyline
	Noxiptiline
	Pipofezine
	Trimipramine

1. Herbal agents or supplements used for the treatment of depression should be discontinued as well unless agreed for continuation by Medical Monitor.
2. Any other treatments currently taken by the participant for the treatment of depression and not listed here should be reported in eCRF and if needed discussed with sponsor Medical Monitor.

10.7. Appendix 7: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 1 (13 March 2020)

Overall Rationale for the Amendment: The amendment updates the protocol design to align with comments received from a regulatory agency on the original protocol.

Section number and Name	Description of Change	Brief Rationale
Synopsis Objectives and Endpoints; 3. Objectives and Endpoints	Specified the primary objective is to evaluate the efficacy of esketamine assessed by the change from baseline in MADRS total score from Day 1 to Day 28 and the key secondary objective is to evaluate efficacy of esketamine as the change from baseline in MADRS total score from Day 1 to Day 2.	The primary and key secondary objectives were revised as requested by a regulatory agency.
Synopsis Objectives and Endpoints, Statistical Methods; 3. Objectives and Endpoints; 4.2. Scientific Rationale for Study Design; 9.4.1. General Considerations; 9.4.2. Primary Endpoint; 9.4.3. Key Secondary Endpoint	Specified the primary endpoint as the change from baseline in MADRS total score from Day 1 to Day 28 and the key secondary endpoint as the change from baseline in MADRS total score from Day 1 to Day 2. Description of the efficacy analyses was revised to align with the change to the primary and key secondary endpoints. Updated text in Section 4.2. Scientific Rationale for Study Design for selection of primary and secondary endpoints.	The primary and key secondary endpoints were revised as requested by a regulatory agency.
Synopsis Overall Design, Number of Participants, Intervention Groups and Duration, Statistical Methods;	The sample size determination was revised based on a standardized treatment effect for the primary endpoint at Day 28 compared to the placebo arm of 0.45. The	The sample size was revised to ensure that the study is adequately powered for the Day 28 endpoint.

Section number and Name	Description of Change	Brief Rationale
1.2. Schema; 4.1. Overall Design; 9.2. Sample Size Determination	minimum number of patients meeting the predefined nonresponse criteria who need to be randomized was increased to 356.	
Synopsis Statistical Methods; 9.4.6. Other Analyses, 1.3. Schedule of Activities (SoA)	Patient's Assessment of Treatment-arm Assignment scale was categorized under "Other Analyses/Assessments".	The assessment was previously incorrectly categorized under Safety Analyses/Assessments.
Synopsis Pharmacogenomic (DNA and RNA) Evaluations; 1.3. Schedule of Activities (SoA); 4.2.2. Study-Specific Ethical Design Considerations; 5.1. Inclusion Criteria; 8. Study Assessments and Procedures; 8.7. Pharmacogenomic (DNA and RNA) Evaluations; 10.3. Appendix 3	Specified that participation in pharmacogenomic research is optional and that participants must sign a separate informed consent form to participate in the pharmacogenomic research component.	The requirement of mandatory participation in pharmacogenomic research for all study participants was changed to optional participation with a separate informed consent form to align with regulatory guidelines on clinical pharmacogenomic testing.
Synopsis Overall Design; 4.1. Overall Design; 7.1. Discontinuation of Study Intervention	The text was updated to clearly state that participants who discontinue study medication but continue in the study until Day 28 may be eligible to participate in the open-label treatment/observation phase. Participants who discontinue completely from double-blind treatment phase (and do not complete the Day 28 visit) are not allowed to participate in the open-label phase.	The wording was updated to clarify that participants who discontinue study medication during the double-blind treatment phase (for a reason other than withdrawal of consent) but continue attending scheduled visits (through Day 28) will be allowed to participate in the open-label treatment/observation phase.
Synopsis, Overall Design, Intervention Groups and Duration; 4.1. Overall Design	Redundant text was deleted, and text was added to state that: 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. 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. 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.	Statements were added to specify which treatments are allowed during the study.
1.2. Schema	Added randomization ratio to nonresponder group.	Update to clarify that the same randomization ratio is applicable

Section number and Name	Description of Change	Brief Rationale
		to the nonresponder and responder groups.
1.3. Schedule of Activities (SoA)	Modified visit windows for Visits 2.3 – 2.10 in the double-blind phase.	Updated for consistency with the study design of the Phase 3 trials.
	Added visit windows for Visits 1.2 – 1.7 in the Screening period.	Visit windows added to allow for more flexibility.
	Option of clinic visit added during taper of antidepressant medication(s).	Option of clinic visit was added to allow for more flexibility during taper of antidepressant medication(s) and better control of patient safety when considered necessary by the investigator.
	Height measurement, temperature measurement, and menstrual cycle tracking were added to the Schedule of Activities.	These measurements were not specifically listed in the Schedule of Activities in original protocol.
	SAFER Interview can be scheduled and completed anytime within Week 1 and 2 and as soon as the site collects and enters all required information into EDC.	Change in timing window of the procedure to establish subject eligibility for inclusion into the study as soon as possible, to limit the duration of time until the study treatment is implemented.
	Added MADRS assessment at Screening Week 2 visit.	MADRS assessment was added due to change in the scope of the SAFER interview, which now includes IDS-C_{30} scale instead of previously planned MADRS assessment. In order to have this important measure at the 2-week time point, it will be completed by the site-based rater.
	Modified footnote “c” to clarify that selected procedures at Day 1 must be completed prior to randomization and not only prior to dosing. Also, predose vital signs must be measured on the actual dosing day.	Footnote was modified to clarify that certain procedures must be completed prior to randomization on Day 1 to confirm participant eligibility. Clarify that the predose vital signs must be measured on the actual dosing day. When the dosing is postponed to another day, the predose vital signs must be repeated on the new dosing day.
	Updated footnote “h” to clarify visit schedule for participants not taking any AD medication at study entry. Added “h” for Visits 1.2 and 1.6 in the screening phase.	Footnote was updated to specify mandatory visits for participants not taking any AD medication at study entry.
	Revised the Schedule of Activities For Participants Receiving Standard of Care (SOC) only to indicate that the MADRS, CGI-S and C-SSRS will be administered to participants in the Standard of Care group on the same schedule as those in the esketamine group during the open-label treatment/observation and follow-up	The schedule of visits and MADRS, CGI-S, C-SSRS and other applicable assessments during the open-label phase for participants in the Standard of Care arm was updated to match the schedule of these assessments in the esketamine arm to

Section number and Name	Description of Change	Brief Rationale
	phases. The applicable clinic visits (with visit windows) including vital signs measurements and collection of concomitant medications and AEs were added to match the updated schedule of assessments. Updated time-points for drug screen (urine) and urine pregnancy test in the SOC group.	minimize differences in participant experience and to allow for greater attribution of any differences between groups to drug rather than procedural effects such as closer follow-up in the esketamine arm. Updated time-points for drug screen (urine) and urine pregnancy test to match time-points in the esketamine arm.
2.2. Background	Updated the cutoff date for reporting of deaths across all completed and ongoing esketamine studies.	The date was revised to reflect the cutoff date of the most recent safety update.
4.2.2. Study-Specific Ethical Design Considerations	Text revised to add that at any point in the study the participant may discontinue study intervention and receive standard-of-care therapy for depression.	Text revised to clarify that participants may discontinue study intervention at any time.
4.4. End of Study Definition	Text revised to state that a participant will be considered to have completed the study if he/she completed the double-blind treatment phase and the follow up visit (if the subject did not enroll in the open-label phase) or completed the double-blind, open-label phases and the follow-up visit.	Text revised to clarify the definition of completing the study.
5.1. Inclusion Criteria	Inclusion criterion #9 was modified to add that a negative urine pregnancy test must be obtained before the first dose of study drug on Day 1, prior to randomization.	Inclusion criterion #9 was modified to confirm that a female participant is not pregnant before receiving the first dose of study drug.
	Inclusion criterion #10 was removed.	Inclusion criterion #10 was removed because it was not consistent with Appendix 5.
	Inclusion criterion #11 was modified to provide clarification of the acceptable methods of contraception.	Inclusion criterion #11 was modified to be consistent with Appendix 5.
	Inclusion criteria #12 was deleted and inclusion criterion #13 was modified to convey that a male participant who is sexually active with a woman of childbearing potential must be practicing a highly effective method of contraception with his female partner during the study and for at least 90 days after receiving the last dose of study drug.	Inclusion criteria #12 and #13 modified to provide further clarification regarding the contraceptive requirements for male participants who are sexually active with a woman of childbearing potential.
	Inclusion criterion #14 was modified to replace “prohibitions” with “requirements”.	Inclusion criterion #14 was modified for clarity.
5.2. Exclusion Criteria	Exclusion criterion #8 was modified to add to cardiovascular-related conditions.	Exclusion criterion #8 was modified for consistency with the approved US label.
	Exclusion criterion #10 was modified to remove “once” for repeat testing of abnormal ALT and AST.	Exclusion criterion #10 was modified to allow for multiple testing if applicable during the screening period. Since the

Section number and Name	Description of Change	Brief Rationale
		screening period can last up to 7 weeks, a change in the abnormal liver test enzyme levels is possible.
	Exclusion criterion #11 was modified to add MDMA to the examples of drugs of abuse. Text was modified to specify that any treatments with psychostimulants must be discontinued at least 2 weeks prior to randomization and the result of the Day 1 test for drugs of abuse must be negative for the participant to be randomized.	Exclusion criterion #11 was modified to clarify that participants who have positive test results for MDMA at screening or Day 1 will be excluded from the study. Pyschostimulant medication treatments are considered to have antidepressant effect and the study is designed to assess the efficacy of esketamine nasal spray in monotherapy.
	Exclusion criterion #25 added to specify that a participant who has not completed the mandatory 2-week antidepressant drug-free period prior to Day 1 will be excluded.	Exclusion criterion #25 added because the 2-week antidepressant drug-free period is mandatory, and participants who do not complete this period during screening will be excluded from the study.
	Note to investigators was updated as follows: Investigators should ensure that all study enrollment criteria have been met at screening and/or Day 1 prior to randomization (as applicable).	Added text for clarification since some criteria can be assessed only at Day 1, eg completion of 2-week antidepressant drug-free period.
	Updated text for antidepressant treatments: All antidepressant treatment(s) (pharmacological, including adjunctive treatments and/or non-pharmacological eg ECT, VNS, DBS, psychotherapy) taken during the current depressive episode (ie, including those taken more than 30 days prior to the start of the screening phase) will be recorded at the start of the screening phase.	Clarified applicable antidepressant treatments.
6.5. Concomitant Therapy	Added text in Section 6.5. and in list of prohibited concomitant medications "Close monitoring for sedation is necessary when used with esketamine."	Text was added to be consistent with information included in the approved US label that concomitant use of benzodiazepines with esketamine requires monitoring for symptoms of sedation.
	Modified the conditions of use for ADHD medications in the list of prohibited concomitant medications with the comment that these medications are allowed for patients who discontinued the double-blind treatment and switched to the standard-of-care treatment in the open label phase.	ADHD medications are not allowed as concomitant therapies because they are considered to have antidepressant effect and the study is designed to assess efficacy of esketamine in monotherapy. Clarification was added that these medications are

Section number and Name	Description of Change	Brief Rationale
		prohibited during the 2-week antidepressant-free period.
	Antidepressants and medications used for treatment of depression were added to the list of prohibited concomitant medications with the comment that these medications are allowed for patients who are switched to standard-of care treatment during the double-blind or open-label phases.	Antidepressants and medications used for treatment of depression are not allowed as concomitant therapies because the study is designed to assess efficacy in monotherapy. Clarification was added that these medications are also prohibited during the 2-week antidepressant-free period.
	A comment was added to the list of prohibited concomitant medications to note that antipsychotics are allowed for patients who switched to standard-of care treatment during the double-blind or open-label phases.	Text was added to specify when use of antipsychotics are allowed during the study. Clarification was added that these medications are prohibited during the 2-week antidepressant-free period.
	Melatonin was removed from the list of prohibited concomitant medications.	Melatonin was removed from the list of prohibited medications based on updated safety information for esketamine.
	A comment was added for use of intranasal corticosteroids that they should not be used from 1 hour prior to each nasal spray study medication administration.	Text was added to be consistent with information included in the approved US label for concomitant use of nasal corticosteroid with esketamine.
6.6. Dose Modification	Text revised to indicate that no dose modifications are allowed during the double-blind treatment phase.	Text was modified to clarify that dose modifications during the double-blind treatment phase are not allowed due to the double-blind nature of the phase and potential issues with interpretation of the study data.
7.2. Participant Discontinuation/Withdrawal From the Study	Text added to specify that a participant will be withdrawn from the study if the participant has a positive urine drug screen for phencyclidine (PCP) or cocaine at any time point during the study	Text added to clarify that participants are not permitted to continue in the study if they test positive for phencyclidine or cocaine.
8. Study Assessments and Procedures	Text was modified to recommend that the MADRS is performed first when multiple assessments are performed.	The MADRS assessment should be performed as the first assessment during a visit to limit the influence of other assessments on participant responses to the primary assessment tool.
	Added information that necessary equipment and manuals for audio recording will be provided to the site.	Equipment and manuals will be provided to ensure consistent quality of audio recordings across all sites.
8.1. Efficacy Assessments; 8.2.6. Other Evaluations	Added information that specified assessments (MADRS, IDS-C_{30} and SAFER Interview) will be audio recorded for the purpose of quality monitoring and necessary	Audio recording was implemented to ensure high quality of key assessments performed in the study.

Section number and Name	Description of Change	Brief Rationale
	equipment and manuals will be provided to the site.	
8.2.6. Other Evaluations	Revised the Patient's Awareness of Treatment-Arm Assignment Scale (Table 2) to code the response "Don't know" as 3 and the response "Strongly believe the nasal spray treatment is placebo" as 5.	This scale was revised to be coded on an ordinal bipolar scale to facilitate exploratory regression analyses involving belief in treatment assignment.
8.3. Adverse Events and Serious Adverse Events	Revised text for participant's representative and removed "legally acceptable".	Updates made to text since participants who require legally acceptable representatives cannot participate in the study.
8.3.6. Adverse Events of Special Interest	Added adverse events related to suicidality as a category of clinically relevant TEAEs of special interest that will be examined.	Added for consistency with the esketamine clinical program.
9.4.2. Primary Endpoint; 9.4.3. Key Secondary Endpoint	Statements regarding missing data were added to the description of the primary analysis and deleted from description of the key secondary analysis. For the primary and key secondary estimands, text describing the intercurrent events component was revised.	Statements revised to align with changes to the primary and key secondary endpoints.
	Text describing the primary and key secondary endpoints was rearranged.	Text rearranged for clarity.
	For the primary and key secondary estimands, a treatment component was added.	Treatment component was omitted in the original protocol.
10.2. Appendix 2	Benzodiazepines were removed from the list of drugs included in the urine drug screen.	Benzodiazepines are allowed medications during all phases of the study and positive results in the urine drug screen could confound proper assessment of participant eligibility.
	XTC was removed and MDMA was added to the list of drugs included in the urine drug screen.	This list was modified to align terminology between protocol and other study documents (eg, laboratory manual).
10.4. Appendix 4	The following text was removed from the list of exceptions to the requirement to report hospitalizations as SAEs: For convenience the investigator may choose to hospitalize the participant for the duration of the intervention period.	This text was removed to avoid misinterpretation that such hospitalizations are permitted per protocol and the cost reimbursed by the sponsor.
10.6. Appendix 6	A list of medications used for the treatment of depression that will be tapered (if applicable) and discontinued during the screening phase was added as Section 10.6. Appendix 6. Added cross references to Section 10.6. Appendix 6 in Section 4.2. Scientific Rationale for Study Design, Section 6.3. Measure to Minimize Bias: Randomization and Section 6.5. Concomitant Therapy	The list of medications used for the treatment of depression was added to provide guidance to sites about which medications must be discontinued in the screening period.

Section number and Name	Description of Change	Brief Rationale
10.7. Appendix 7	The appendix showing the Protocol Amendment History was renumbered to Appendix 7, and the text was updated to note that the Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).	The text in the appendices was revised to note where the summary of changes table for the current amendment is located in the document.
11. References	Updated citations for references 12, 13 and 14.	Citations were corrected from original protocol.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted

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INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD _____

Institution: PPD _____

Signature: _____ Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Janssen Research & Development *

Clinical Protocol

COVID-19 Appendix

Protocol Title

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

JNJ-54135419 (esketamine)

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; Janssen Sciences Ireland UC; Janssen Biopharma Inc.; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).

Status: Approved
Date: 14 Jul 2020
Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-RIM-77286

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

COVID-19 APPENDIX

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with health authority guidance, the sponsor is providing options for study related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's safety is considered to be at risk, study intervention will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow-up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation with the participant, investigator, and with agreement of the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations.

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a participant has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

GUIDANCE SPECIFIC TO THIS PROTOCOL

These provisions are meant to minimize the risk of exposure to COVID-19 and to safely maintain participants on study intervention while site capabilities are compromised by COVID-19-related restrictions. As restrictions are lifted and the acute phase of the COVID-19 pandemic resolves, sites should revert to original protocol conduct as soon as feasible.

At each contact, participants will be interviewed to collect safety data. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Evaluate the participant's situation on a case by case basis and contact the study responsible physician for discussion and decision if necessary. Certain measures, such as those listed below, may be necessary and should be instituted in accordance with applicable (including local) laws, regulations, guidelines, and procedures.

- The safety of study participants is priority; investigators may make the decision to provide other available therapy to participants in the study. Please discuss any decision to provide other therapy outside of the protocol with the study responsible physician and ensure that this is recorded in the source document and the CRF along with the reason for administration.

Reminder: missed esketamine dosing of itself does not result in withdrawal from the study, and treatment can resume if considered beneficial per clinical judgement.

Discontinuations of study intervention and withdrawal from the study due to COVID-19 adverse events (AEs)/ serious adverse events (SAEs) should be documented as discontinuation due to AE. If a participant dies due to COVID-19, "death" should be selected as the reason for treatment discontinuation. Discontinuations for other COVID-19 reasons should be documented with the prefix "COVID-19-related" in the CRF.

Screening / Prospective Observational Phase

The following recommendations apply to those sites within regions where there is a high localized rate of COVID-19 infection:

Screening of new subjects should be postponed until the rate of COVID-19 infection is reduced and under control.

Due to uncertainty around the ability to conduct on-site clinical visits, subjects that are currently in screening should be screen failed and clinical standard of care for the treatment of depression should be arranged by the study investigator and/or the subject's treating physician. The decision to continue with the subject's current oral antidepressant treatment regimen should be at the discretion of the investigator.

The sponsor will evaluate and approve / reject requests to rescreen an individual subject on a case by case basis after the COVID-19 infection is under control.

Dosing/Administration

In the event that it is not feasible for the participant to be assessed and dosed at the study site (eg, due to temporary site closure), the following options may be used on a temporary basis after consultation with the sponsor and with the agreement of the participant and investigator:

Double-blind phase

- Continue administering study intervention within the study site, with adjustments for temporary changes in dates/hours site is open for study participants;
- Administer at an alternative location (to include the equipment/supplies needed for the care/treatment of a participant post dose) in the vicinity of the site, with the participant remaining there during the post dose observation period, under the supervision of site staff. This condition will be evaluated on a case by case basis with the study responsible physician or delegate.

Open Label phase

- Administer at an alternative 54135419TRD4005 study site (data to stay with primary study site) after consultation with the sponsor (at which time specific guidance on the process will be provided) and if permitted by local regulations.
- The post dose observation period can be reduced (minimum 1 hour of monitoring) per investigator discretion on a case by case basis; this condition is valid only under public health emergency declaration by the US Department of Health and Human Services and following consultation with the study responsible physician (only allowed after at least 8 administrations of esketamine in the open label phase).
- Administer the study intervention at the patient's home in the presence of a designated site staff member during dosing and post dose observation period (home visit); this condition is valid only under public health emergency declaration by the US Department of Health and Human Services and following consultation with the study responsible physician (only allowed after at least 8 administrations of esketamine in the open label phase).
- If neither proposed dosing option is feasible, the sponsor medical monitor or delegate should be contacted for directions.

Other Study-related procedures

- Rating scales/ safety assessments can continue to be administered via video teleconferencing (MADRS) or phone (other assessments). Every effort should be made to complete the MADRS assessment via video teleconferencing and within the scheduled timeframe; if this cannot occur, the sponsor medical monitor or delegate should be contacted for direction.
- Missed/ out of window visits or individual assessments should be documented with “COVID-19-related” in the comment section of the CRF.
- It is recommended that close contact be maintained with study participants and remote contact arranged consistent with the participant’s regularly scheduled visit interval.
  - If the participant is on a biweekly schedule, attempt to contact the participant biweekly. If the participant is on weekly schedule, attempt to contact the participant weekly.

- If the participant is on every other week schedule, attempt to contact the participant every other week.

Study participants who show worsening or who are at high risk for relapse may require more frequent monitoring as per investigator discretion.

Laboratory Assessments

If laboratory samples cannot be collected by Covance, sample collection and analysis can be performed using the site's local laboratory at the discretion of the investigator.

- If the investigator does not feel laboratory assessments are required at this time, and participant(s) want to avoid any risk to COVID-19 exposure, this rationale should be documented in the source documents.

Exposure to COVID-19

- If a participant develops COVID-19 infection (or suspected) during the screening, double-blind, or open label phases, the investigator should contact the sponsor's medical monitor to discuss the best course of action based on individual symptoms/ participant setting and risk benefit relationship.
- If a participant develops COVID-19 infection (or suspected) during the follow-up period, the investigator should contact the sponsor's medical monitor and assessments should be completed remotely.
- Resumption of treatment: When a participant recovers from suspected or confirmed COVID-19 infection, study intervention may be resumed when safe to do so as determined by the treating study physician in consultation with the sponsor.

Data Collection

- For clinician-completed (C-SSRS, CGI-S) and participant-completed (PHQ-9)[a] scale assessments conducted by a telephone or video contact, the data should be entered directly onto the paper assessment. Ensure that the correct date is present on the assessment form in the CRF.
- Missed doses should be documented in the CRF in accordance with the CRF completion guidelines.
- For missed doses, the dosing form should be inactivated and a "COVID-19 related" comment entered on the Comments form.
- All COVID-19-related deviations from the main study protocol will be documented according to the CRF completion guidelines.
- A mitigation plan has been created to address the impact of the COVID-19 global pandemic on the completion of in-person COA assessments.

[a] C-SSRS=Columbia Suicide Severity Rating Scale; CGI-S=Clinical Global Impression – Severity; PHQ-9=Patient Health Questionnaire, 9-Item; SDS=Sheehan Disability Scale.

Statistical Analysis

The sponsor will evaluate the totality of the impact of COVID-19 on collection of key study data, and additional data analyses will be outlined in the statistical analysis plan.

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

Signature: _____ Date: _____
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature

User	Date	Reason
PPD	15-Jul-2020 11:47:14 (GMT)	Document Approval