Janssen Research & Development *

Clinical Protocol

A Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy and Safety of Intranasal Esketamine in Addition to Comprehensive Standard of Care for the Rapid Reduction of the Symptoms of Major Depressive Disorder, Including Suicidal Ideation, in Adult Subjects Assessed to be at Imminent Risk for Suicide

Protocol 54135419SUI3002; Phase 3
AMENDMENT 2

JNJ54135419 (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 Sciences Ireland UC; 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.

This compound is being investigated in Phase 3 clinical studies.

This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

EudraCT NUMBER: 2016-003992-23

Status: Approved
Date: 31 January 2018
Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-ERI-132549001, 3.0

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

Confidentiality Statement

The information in this document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by applicable law or regulations. In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. These restrictions on disclosure will apply equally to all future information supplied to you that is indicated as privileged or confidential.

TABLE OF CONTENTS

LIST OF ATTACHMENTS

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

FIGURES

PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	8 December 2016
Amendment 1	20 April 2017
Amendment 2	31 January 2018

Amendments below are listed beginning with the most recent amendment.

Amendment 2 (31 January 2018)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reason for the amendment is to remove the interim analysis from the 54135419SUI3002 protocol; to clarify that Module 3 Suicide Ideation and Behavior Assessment Tool (SIBAT) is an exploratory objective; to modify the timing of screening procedures in Figure 1 to be consistent with the Time and Events Schedule; to clarify which potential subjects are not excluded from participation in the 54135419SUI3002 study due to having a positive screening test for prescribed psychostimulants that are permitted during the study; and updated text regarding the presentation of nasal examination data.

Applicable Section(s)	Description of Change(s)
Rationale: The interim analysis was removed from the 54135419SUI3002 protocol to ensure that the study has sufficient numbers of subjects from key global regions/countries needed to support global health authority registration.	
Synopsis Overview of Study Design; 3.1. Overview of Study Design; 11.2. Sample Size Determination; 11.3. Efficacy Analyses	Deleted text stating that an interim analysis will be conducted when 60% of randomized subjects have completed Day 2 of the double-blind phase.
Synopsis Statistical Methods; 11.9. Independent Data Monitoring Committee	The following text was deleted from the Synopsis Statistical Analysis section (Interim Analysis subsection): A 2-stage group-sequential design with 1 interim analysis will be implemented to allow for early stopping if there is significant evidence of efficacy or futility based on the interim analysis after 60% of the subjects have been randomized and have completed Day 2 of the double-blind phase. If the study is not stopped based upon the interim analysis, it will be continued until the maximum sample size (224 subjects) has been reached. An external independent Data Monitoring Committee (IDMC) will provide recommendations about stopping or continuing the study based on the results of an interim efficacy and safety analysis. Section 11.3, Interim Analysis was removed. As a result, the numbered headings following Section 11.3 were updated. Cross-references to Section 11.3 Interim Analysis (in Sections 3.1 [Overview of Study Design], 11.2 [Sample Size Determination], 11.3 [Efficacy Analyses]) were also deleted. The following text was modified in Section 11.9 Independent Data Monitoring Committee (strikeout text deleted): An external Independent Data Monitoring Committee will be established to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study.

Applicable Section(s)	Description of Change(s)
	~~In addition, the committee will review 1 interim analysis for efficacy.~~ The committee will meet every 6 months to review safety data ~~and will meet once to review efficacy data after the interim analysis has been completed~~. After the reviews, the IDMC will make recommendations regarding the continuation of the study ~~or, in the case of the interim analysis for efficacy, to either stop the study due to efficacy or futility~~. The details will be provided in a separate IDMC charter.
Synopsis Secondary Efficacy Endpoints; 10.2 Discontinuation of Study Treatment/Withdrawal From the Study; 11.3. Efficacy Analysis	In the Synopsis (Secondary Efficacy Endpoints), deleted text stating that 1 interim analysis for efficacy and futility will be performed. The following bullet point text was removed from Section 10.2 Discontinuation of Study Treatment/Withdrawal From the Study: • Study is terminated by the sponsor for futility Section 11.4, Efficacy Analysis became Section 11.3 since the Interim Analysis section was deleted.
5. Treatment Allocation and Blinding	The following text was deleted in the Blinding subsection: However, if an interim analysis is specified, the randomization codes and, if required, the translation of randomization codes into treatment and control groups will be disclosed to those authorized and only for those subjects included in the interim analysis.
Rationale: Module 3 SIBAT My Current Thinking assessment was changed from a secondary to an exploratory objective as Module 3 My Current Thinking was not designed as a stand-alone endpoint.	
Synopsis, Objectives, Endpoints, Hypothesis, Exploratory Objectives, Endpoints; 2.1.1. Objectives; 2.1.2. Endpoints; 3.2.5.2. Suicidal Ideation and Behavior Assessment Tool (SIBAT)	Text regarding Module 3 SIBAT Assessment was removed from the secondary objective and endpoint subsections and moved to the exploratory objective subsections of the 54135419SUI3002 protocol.
Rationale: Modified Figure 1 to be consistent with the Time and Events Schedule timing of screening procedures prior to the first dose.	
3.1. Overview of Study Design (Figure 1)	"24 hours" was replaced with "48 hours" in the Screening text box of Figure 1. Footnote c text was modified as follows (bold text added; strikethrough text deleted): ~~Screening phase may be extended to up to 48 hours prior to Day 1 intranasal dose.~~ **If possible, screening should be performed within 24 hours prior the Day 1 intranasal dose.**

Applicable Section(s)	Description of Change(s)
Rationale: Exclusion criterion #8 was modified to clarify which potential subjects are not excluded from participation in the study due to having a positive screening test for prescribed psychostimulants that are permitted during the study.	
4.2. Exclusion Criteria	The following text was added to exclusion criterion #8: 8.2 Criterion modified per Amendment 2 - Subjects, who have a positive test result at screening due to prescribed psychostimulants (eg. amphetamine, methylphenidate, etc) that are permitted during the study in accordance with Attachment 1, are eligible for study participation.
Rationale: Updated text regarding presentation of nasal examination data.	
Synopsis, Safety Analyses; 11.8. Safety Analyses	The following text was modified (bold text added; strikethrough text deleted): **Abnormalities observed during the targeted nasal examinations at screening and post-baseline will be summarized and listed by treatment group.**~~Changes in findings from the baseline nasal examination (including the upper respiratory tract/throat) will be listed by treatment group. Examinations will provide ratings (absent, mild, moderate, or severe) that are based on a visual inspection of the nostrils, nasal mucosa, and throat for nasal erythema, rhinorrhea, rhinitis, capillary/blood vessel disruption and epistaxis. A shift table for changes from baseline in ratings for each examination will be presented by treatment group at each scheduled visit.~~
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 1 (20 April 2017)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reason for the amendment is to update and/or clarify protocol content based on feedback received during study initiation activities.

Applicable Section(s)	Description of Change(s)
Rationale: Exclusion criterion #5 was revised to clarify which potential subjects are excluded from participation in the study due to substance or alcohol use disorder.	
Synopsis, Subject Population; 4.2. Exclusion Criteria	Exclusion criterion #5 was revised as follows (bold text added; strikeout text deleted): Subject ~~has a history of~~ **meets the DSM-5 severity criteria for** moderate or severe substance or alcohol use disorder~~, as defined by DSM-5 criteria,~~ **(**except **for** nicotine or caffeine**)**~~,~~ within **the** 6 months before screening. • **A history (lifetime) of ketamine, phencyclidine (PCP), lysergic acid diethylamide (LSD), or 3, 4-methylenedioxy-methamphetamine (MDMA) hallucinogen-related use disorder is exclusionary.**

Applicable Section(s)	Description of Change(s)
3.2.1. Study Population	Text in this section modified as follows (bold text added) for consistency with exclusion criterion #5: Subjects with a **recent** history **(< 6 months)** of moderate or severe substance or alcohol use disorders will be excluded to ensure the subject's depression is not attributed to substance or alcohol use (ie, substance-induced depressive disorder).
Rationale: The text was updated to amend the duration of hospitalization without the need for discussion with the Sponsor and to clarify that shorter or longer hospitalizations should follow local practice.	
9.1.3. Double-blind Treatment Phase	Text was revised as follows (bold text added; strikeout text deleted): Subjects will remain in the inpatient psychiatry unit for a recommended duration of 5 days, with shorter or longer hospitalizations permitted if clinically warranted **per local standard of care**. The discharge decision will be made based upon the investigator's judgment that the subject is no longer imminently suicidal and meets standard discharge criteria **per local practice**. Discharge **before**~~after less than~~ 5 days must be discussed and approved by the sponsor's medical monitor. The investigator must discuss ~~in advance~~ the need for continued hospitalization beyond **10**~~7~~ days and thereafter on a weekly basis with the sponsor's medical monitor.
Synopsis, Overview of Study Design and Dosage and Administration; Time and Events Schedule; 3.1. Overview of Study Design; 6.1. Intranasal Study Drug;	The text in these sections and Figure 1 (Schematic Overview of the Study) were revised for consistency with the changes described above in Section 9.1.3.
12.3.2. Serious Adverse Events	The following text was corrected for clarity and consistency with the above text in Section 9.1.3 (strikeout text deleted): • Inpatient hospitalizations that extend beyond the protocol-~~required~~ recommended 5 days (not due to adverse event, ie, clinical worsening)
Rationale: A remote contact was added at Day 35 with evaluations to be performed according to the revised Time and Events Schedule to ensure twice weekly monitoring for the first two weeks (Days 28, 32, 35, and 39) after study drug treatment.	
Time and Events Schedule	– A remote contact has been added at Day 35 (35 RC) for MADRS assessment (recall since last assessment) and adverse event collection. – MADRS assessments at Days 32 and 39 were changed to recall since last assessment from 7-day recall. – Visit numbers for Days 39, 46, 53, 67, and 90 were changed to Visits 14, 15, 16, 17, and 18, respectively. – The window for the Day 32 visit has been changed to ±1 day from ±3 days (ie, footnote for Visit 12 was changed to "b" from "a"). – Rows for "Prior and concomitant therapy" and "Adverse events" were modified to indicate when these data are reviewed during the follow-up phase.
SIBAT Time and Events Schedule	An additional column was added for the Day 35 remote contact and the visit numbers were revised for consistency with the main Time and Events Schedule.

Applicable Section(s)	Description of Change(s)
Synopsis, Overview of Study Design; 3.1. Overview of Study Design; 3.2.2. Treatment and Study Duration; 9.1.4. Posttreatment Phase (Follow-up)	Text has been revised to include the Day 35 remote contact and mention the frequency of monitoring during the follow-up phase, ie, to mention that during the follow-up phase, subjects will be monitored twice weekly for the first two weeks (Days 28, 32, 35, and 39) after study drug treatment. Subjects will then be followed up weekly for the next two weeks (Days 46 and 53) and every two weeks for the rest of the follow-up period (Days 67 and 90).
3.1. Overview of Study Design, Figure 1	Figure 1 has been revised to include remote contacts at Days 28 and 35 during the follow-up phase.
Rationale: The text regarding discontinuation of study treatment was modified to add that if the legal status of a subject changes during the study and the subject's participation can no longer be considered voluntary, then he/she will be discontinued from study treatment.	
10.2. Discontinuation of Study Treatment/Withdrawal From the Study	The following bullet point was added to the list of reasons for which a subject's study treatment will be discontinued: • Change in the in-patient hospitalization status from voluntary to involuntary as a result of a judicial or other legal administrative order
Rationale: The text regarding discontinuation of study treatment was modified to include worsening of underlying condition as an example of a safety or tolerability reason which would result in discontinuation of study treatment.	
10.2. Discontinuation of Study Treatment/Withdrawal From the Study	Worsening of underlying condition was added as an example of a safety or tolerability reason which would result in discontinuation of study treatment. Bold text added as shown below: • The investigator believes that for safety reasons or tolerability reasons (eg, adverse event **or worsening of underlying condition**) it is in the best interest of the subject to discontinue study treatment
Rationale: Exclusion criteria were revised to explicitly specify a detailed list of important medical conditions which are exclusionary.	
Synopsis, Subject Population; 4.2. Exclusion Criteria	Exclusion criterion #6 was revised as follows (strikeout text deleted; bold text added): Subject has **any of the following conditions:** – a history or current signs and symptoms of liver or renal insufficiency ~~or of~~ – clinically significant cardiac **(including unstable coronary artery disease and congestive heart failure, tachyarrhythmias and recent myocardial infarction)**~~,~~ **or** vascular, pulmonary, gastrointestinal, endocrine **(including uncontrolled hyperthyroidism)**, neurologic (including current or past history of seizures except uncomplicated childhood febrile seizures with no sequelae), hematologic, rheumatologic, or metabolic **(including severe dehydration/hypovolemia)** disease.

Applicable Section(s)	Description of Change(s)
Synopsis, Subject Population; 4.2. Exclusion Criteria	Exclusion criterion #7 was revised as follows (bold text added): Subject has uncontrolled hypertension (systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg) despite diet, exercise or a stable dose of anti-hypertensive treatment for at least 2 weeks at screening; or any past history of hypertensive crisis. – **Subjects with conditions in which the elevation of blood pressure could be a serious risk (including unstable heart failure, severe cardiovascular disease, recent cerebral injury, increased intracranial pressure / intracranial mass lesion, intracranial bleeding or acute stroke, untreated glaucoma or perforating eye injury) are excluded.** – An abnormal blood pressure value at screening can be repeated once after 5 minutes of relaxation for subject eligibility. On Day 1 of the double-blind phase prior to randomization, a supine or semi-supine systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg is exclusionary.
Synopsis, Subject Population	Corrections were made to the text of exclusion criterion #7 shown in the synopsis to maintain consistency with the text of exclusion criterion #7 shown in Section 4.2.
Rationale: Exclusion criteria were revised to clarify which subjects are excluded due to a positive urine test result.	
4.2. Exclusion Criteria	Exclusion criterion #8 was revised as follows (bold text added): Subject has a positive urine test result(s) for phencyclidine (PCP), cocaine, or amphetamines **(inclusive of amphetamine, methamphetamine [mAMP], and 3, 4-methylenedioxy-methamphetamine [MDMA])** at screening. – Subjects who have a positive test due to the appropriate use of prescribed opiates, benzodiazepines, or barbiturates may be eligible for study participation per clinician judgment. In addition, subjects who have a positive test for opiates, benzodiazepines, or barbiturates used without a prescription, may be considered eligible per clinician judgment and in consultation with the sponsor's medical monitor. **Subjects known to be using heroin should be excluded from the study.** – Subjects who have a positive test due to opiates, benzodiazepines, or barbiturates taken in a suicide attempt (eg, overdose) may be eligible for study participation per clinician judgment and in consultation with the sponsor's medical monitor.
Rationale: Exclusion criterion #13 was revised to clarify that subjects who were previously enrolled in this study or the Sponsor's other studies in this population (54135419SUI3001 and ESKETINSUI2001) are excluded from participation in this study.	
4.2. Exclusion Criteria	Exclusion criterion #13 was revised as follows (bold text added): Subject has received an investigational drug (including esketamine, ketamine, or investigational vaccines) or used an invasive investigational medical device within 60 days before the planned first dose of study drug or is currently enrolled in an investigational study **or was previously enrolled in this study or the Sponsor's other studies in this population, 54135419SUI3001 and ESKETINSUI2001**.

Applicable Section(s)	Description of Change(s)
Rationale: Text was added to further describe how the effect size of 0.45 for MADRS total score (at 24 hours post first dose) was computed in the sample size determination.	
Synopsis, Sample Size Determination; 11.2. Sample Size Determination	The following bold text was added: The effect size used in this calculation was based on results of the ESKETINSUI2001 study **where the effect size for the change from baseline to Day 2 was 0.65 (mean difference between treatment groups of -7.2 and a pooled SD of 11.02) for MADRS total score. Given that the ESKETINSUI2001 study was a Phase 2 study carried out in only one country, the maximum sample size for this Phase 3 study was determined using a smaller effect size of 0.45 to allow for greater variability that can be expected for a study conducted globally.**
Rationale: The statistical methods were revised to add that summary statistics by study center for the primary efficacy endpoint will be provided.	
Synopsis, Primary Efficacy Endpoint; 11.4. Efficacy Analyses, Primary Efficacy Endpoint	The following statement has been added: In addition, descriptive statistics (N, mean, standard deviation, median, minimum and maximum) of the primary efficacy variable will be provided by study center.
Rationale: The statistical methods were revised to confirm that treatment differences will be estimated using the Hodges-Lehman estimate for the key secondary variable.	
Synopsis, Secondary Efficacy Endpoints; 11.4. Efficacy Analyses, Secondary Efficacy Endpoints	The following statement has been added: The treatment difference will be estimated using the Hodges-Lehmann estimate, which is the median of all possible paired differences for the change from baseline for CGI-SS-R at 24 hours.
Rationale: Text was added to state which summary (descriptive) statistics will be used for continuous variables and categorical variables.	
Synopsis, Secondary Efficacy Endpoints; 11.4. Efficacy Analyses, Secondary Efficacy Endpoints	The following statement has been added: Descriptive statistics (N, mean, standard deviation, median, minimum and maximum) will be provided for continuous variables and frequency distributions will be provided for categorical variables.
Rationale: The statistical methods have been revised to add descriptions of confidence intervals for treatment differences based on analysis of covariance (ANCOVA) model, mixed model with repeated measures (MMRM), and nonlinear mixed-effects model analyses.	
Synopsis, Primary Efficacy Endpoint; 11.4. Efficacy Analyses, Primary Efficacy Endpoint	The following statement has been added: A point estimate and 95% confidence interval for the treatment difference will be provided.
Synopsis, Secondary Efficacy Endpoints; 11.4. Efficacy Analyses, Secondary Efficacy Endpoints	The following statement has been added: Point estimates and 95% confidence intervals for the treatment differences will be provided.

Applicable Section(s)	Description of Change(s)
Synopsis, Pharmacokinetic Analyses; 11.5 Pharmacokinetic Analyses	The following statement has been added: For the parameter estimates, the standard error and 95% confidence interval will be provided. This will be determined after the population pharmacokinetic modeling of the data is completed.
Rationale: Text was added to emphasize that subjects may participate in the study only if they have adequate capacity to give consent and after fully understanding the potential risks, benefits, and potential adverse events of the study.	
16.1 Study-Specific Design Considerations	The following text has been added in the subsection "Selection of Subjects": Subjects may participate in the study only if they have adequate capacity to give consent and after fully understanding the potential risks, benefits, and potential adverse events of the study. Determination of a subject's decisional capacity will be made by the study investigator.
Rationale: Time and Events Schedule was clarified to note that the Remote Contact on Day 90 is the same for subjects who discontinue during double-blind phase and those who discontinue during the follow-up phase.	
Time and Events Schedule; SIBAT Time and Events Schedule	– Footnote "d" in the Time and Events Schedule and footnote "f" in the SIBAT Time and Events Schedule were revised as follows (bold text added; strikeout text deleted): For subjects who discontinue from double-blind treatment with reasons other than lost to follow up, death, or withdrawal of consent, Remote Contact (RC) will be implemented 3 days after the last dose of intranasal study medication (if the date of the DB ET visit is less than 3 days after the last dose of intranasal study medication)~~,~~ **and** on Day 25 ~~and on Day 90~~ for MADRS assessment and adverse event collection. – The following statement was added to footnote "dd" in the Time and Events Schedule and footnote "h" in the SIBAT Time and Events Schedule: Subjects who discontinue during the double-blind treatment phase prior to Day 25 will also have a Remote Contact on Day 90 for MADRS assessment and adverse event collection.
Rationale: Text added to state that subjects should refrain from using alcohol within 24 hours before and after each intranasal treatment session.	
4.3. Restrictions and Prohibitions; 6.1. Intranasal Study Drug	The following text was added: Subjects should refrain from using alcohol within 24 hours before and after each intranasal treatment session. If a subject appears intoxicated, dosing should not occur (delayed per the permitted visit window; see the Time and Events Schedule).
Rationale: Text revised to clarify procedures regarding collection of the Healthcare Resource Use Questionnaire.	
9.6. Medical Resource Utilization	Text was revised as follows (bold text added; strikeout text deleted): Medical resource utilization data, associated with medical encounters, will be collected using the Healthcare Resource Use Questionnaire (HRUQ) **on an ongoing basis whenever an encounter occurs,** and will be reviewed as indicated in the Time and Events Schedule.
Time and Events Schedule	Text revised to indicate that medical resource utilization data is collected using the Healthcare Resource Use Questionnaire.

Applicable Section(s)	Description of Change(s)
Rationale: The text describing evaluation of pulse oximetry and Modified Observer's Assessment of Alertness/Sedation (MOAA/S) was corrected to accurately describe when these data are collected.	
9.7. Safety Evaluations, Pulse Oximetry	The following text was revised (bold text added; strikeout text deleted): Pulse oximetry will be used to measure arterial oxygen saturation (SpO_2). On each dosing day, the device will be attached to the finger, toe, or ear ~~at approximately 15 minutes before the first nasal spray~~, and SpO_2 will be monitored and documented every 15 minutes **from predose to** ~~for approximately~~ 1.5 hours **postdose**~~after the first nasal spray is administered (ie, SpO2 will be measured at t = -15 minutes, 0 [after administration of the first intranasal device], 15 minutes, 30 minutes, etc.)~~.
9.7. Safety Evaluations, Modified Observer's Assessment of Alertness and Sedation (MOAA/S)	The following text was revised (strikeout text deleted): On each intranasal dosing day, the MOAA/S will be performed every 15 minutes from ~~t = 15 minutes (~~predose~~)~~ to 1.5 hours postdose ~~(ie, at t= -15 minutes, 0 [after administration of the first intranasal device], 15 minutes, 30 minutes, etc.)~~.
Time and Events Schedule	– Collection of pulse oximetry and MOAA/S data on Day 1 revised to state "every 15 min" instead of "-15 min to 1.5 hr" – Footnotes "r" and "t" revised for consistency with the revisions in Section 9.7 (described above) regarding evaluation of pulse oximetry and MOAA/S.
Rationale: The restriction on drinking before administration of intranasal study medication was revised to clarify.	
Synopsis, Dosage and Administration; 4.3. Prohibitions and Restrictions; 6.1. Intranasal Study Drug	Text has been revised as follows (bold text added; strikeout text deleted): Drinking of ~~water or~~ any ~~other permitted beverage~~**fluids** will be restricted at least 30 minutes before the first nasal spray on each dosing day.
Rationale: Text was revised to indicate that biomarker evaluations are not considered optional in this study.	
Synopsis, Biomarker and Pharmacogenomic (DNA) Evaluations, and Overview of Study Design; 3.1. Overview of Study Design; 9.1.1. Overview, Table 4; 9.5. Biomarker and Pharmacogenomic (DNA) Evaluations	Statements which indicated that site participation in biomarker evaluations is optional based on operational capabilities have been deleted.
Time and Events Schedule	– The following text was deleted from footnote "y": Optional site participation based on operational capabilities; required for subjects at participating sites. – The following text was deleted from the subheading "Biomarkers" as indicated below (strikeout text deleted): Biomarkers ~~(optional site participation)~~ ~~y~~

Applicable Section(s)	Description of Change(s)
9.1.1. Overview, Table 4	– Deleted row showing approximate total blood volume for double-blind treatment phase without biomarker and pharmacogenomic/epigenetic samples. – Text in footnote "c" was deleted and replaced with text in footnote "e". Footnote "e" deleted.
Rationale: Procedure for collection of menstrual cycle information was revised to clarify.	
Time and Events Schedule	– The following text was added to footnote "y" (replacing deleted text described above): Menstrual cycle information will be collected on these visits. – Footnote "y" was added at Day 1, Predose and Day 25 in the row for "Blood sample collection (serum and plasma biomarkers)".
9.5. Biomarker and Pharmacogenomic (DNA) Evaluations	Text was modified as follows for consistency with revisions to the Time and Events Schedule (bold text added; strikeout text deleted): Information on menstrual cycle (date of first day of last period, average length of cycle) will be recorded ~~at each visit~~ **on Day 1 (predose) and Day 25** when blood samples for biomarker analysis are collected.
Rationale: Text was revised to clarify procedures for clinical laboratory assessments and electrocardiogram recording.	
9.7. Safety Evaluations, Clinical Laboratory Tests	Text revised to indicate that the urine pregnancy test and urine drug screen will be performed on-site.
9.7. Safety Evaluations, Electrocardiogram (ECG)	The following statement was deleted: If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.
Rationale: Minor errors were noted	
Synopsis, Study Population	Lists of key inclusion and exclusion criteria revised to use bullets instead of numbers.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

A Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy and Safety of Intranasal Esketamine in Addition to Comprehensive Standard of Care for the Rapid Reduction of the Symptoms of Major Depressive Disorder, Including Suicidal Ideation, in Adult Subjects Assessed to be at Imminent Risk for Suicide

Major depressive disorder (MDD) is the most prevalent mental health condition and the psychiatric diagnosis most commonly associated with suicide. Epidemiology studies suggest that nearly 60% of those who die by suicide suffer from affective disorders, and at least one-half of people who complete suicide are depressed at the time of their deaths. Although MDD with imminent risk for suicide is a potentially lethal condition that requires immediate intervention, there is no approved treatment. The current standard of care is hospitalization and treatment with antidepressant medication. However, hospitalization is temporary and not completely effective, and the risk for suicide remains high in the weeks after discharge. As standard antidepressants may take up to 4-6 weeks to exert their full effect, there is a significant unmet therapeutic need for effective drugs with rapid onset of effect.

Ketamine and esketamine (the *S*-enantiomer of ketamine) are approved and widely used for the induction and maintenance of anesthesia via intramuscular (IM) or intravenous (IV) administration. The anesthetic effects of esketamine are attributed to the blockade of ionotropic *N*-methyl-D-aspartate (NMDA) glutamate receptors. Janssen Research & Development (JRD) is developing intranasal esketamine as an antidepressant therapy. The mechanism of action of esketamine is distinct from conventional monoaminergic antidepressant treatments, and esketamine profoundly affects fast excitatory glutamate transmission, increases brain-derived neurotrophic factor (BDNF) release, and stimulates synaptogenesis. In addition, a higher NMDA receptor binding affinity of esketamine compared to ketamine allows a lower volume of medication to be administered via the non-invasive and rapidly-absorbed intranasal route.

The current study is being conducted to evaluate the efficacy and safety of intranasal esketamine in addition to comprehensive standard of care in subjects with MDD who are at imminent risk for suicide as a pivotal Phase 3 study in support of regulatory agency requirements for registration of intranasal esketamine.

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

Primary Objective

The primary objective is to evaluate the efficacy of intranasal esketamine 84 mg compared with intranasal placebo in addition to comprehensive standard of care in reducing the symptoms of MDD, including suicidal ideation, in subjects who are assessed to be at imminent risk for suicide, as measured by the change from baseline on the Montgomery-Asberg Depression Rating Scale (MADRS) total score at 24 hours post first dose.

Key Secondary Objective

The key secondary objective is to assess the efficacy of intranasal esketamine compared with intranasal placebo in reducing severity of suicidality as measured by the clinical global impression of severity of suicidality revised version (CGI-SS-R) at 24 hours post first dose.

Other Secondary Objectives

The other secondary objectives are:

- To evaluate the efficacy of intranasal esketamine compared with intranasal placebo in remission of MDD (defined as MADRS total score ≤12) at 4 hours and 24 hours post first dose, and through the end of the double-blind treatment phase (Day 25).

- To evaluate the efficacy of intranasal esketamine compared with intranasal placebo in reducing symptoms of MDD as assessed by the MADRS total score at 4 hours post first dose on Day 1, and through the end of the double-blind treatment phase (Day 25).
- To assess the efficacy of intranasal esketamine compared with intranasal placebo in reducing severity of suicidality as measured by the CGI-SS-R at 4 hours post first dose on Day 1, and through the end of the double-blind treatment phase (Day 25).
- To assess the efficacy of intranasal esketamine compared with intranasal placebo in achieving resolution of suicidality as measured by the score of 0 (normal, not at all suicidal) or 1 (questionably suicidal) of the CGI-SS-R at 4 hours and 24 hours post first dose, and through the end of the double-blind treatment phase (Day 25).
- To assess the efficacy of intranasal esketamine compared with intranasal placebo in reducing imminent suicide risk as measured by the clinical global impression of imminent suicide risk (CGI-SR-I) at 4 hours and 24 hours post first dose, and through the end of the double-blind treatment phase (Day 25).
- To assess the impact of intranasal esketamine compared with intranasal placebo on the following patient-relevant concepts through the end of the double-blind treatment phase (Day 25)
  - Hopelessness as measured by Beck Hopelessness Scale (BHS)
  - Health related quality of life and health status, using the European Quality of Life (EuroQol) Group, 5-Dimension, 5-Level (EQ-5D-5L)
  - Health related quality of life using the Quality of Life in Depression Scale (QLDS)
  - Treatment satisfaction using the Treatment Satisfaction Questionnaire for Medication (TSQM-9)
  - Patient-reported suicidality using the Suicidal Ideation and Behaviors Assessment Tool (SIBAT), including Module 5 My Risk, Question 3 (patient-reported frequency of suicidal thinking)
- To assess the safety and tolerability of intranasal esketamine during the double-blind treatment phase and the follow-up phase, with special attention given to the following assessments:
  - Potential effects on suicidal ideation and behavior using the SIBAT
  - On dosing days:
    - Effect on heart rate, blood pressure, respiratory rate, and blood oxygen saturation
    - Effect on alertness and sedation using the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale
    - Treatment-emergent dissociative symptoms using the Clinician Administered Dissociative States Scale (CADSS)
- To assess the pharmacokinetics of intranasal esketamine.

Exploratory Objectives

The exploratory objectives are:

- To evaluate the efficacy of intranasal esketamine compared with intranasal placebo in reducing symptoms of MDD as assessed by the MADRS total score and remission rate through the end of the follow-up phase (Day 90).

- To assess the efficacy of intranasal esketamine compared with intranasal placebo in reducing severity of suicidality as measured by the CGI-SS-R through the end of the follow-up phase (Day 90).
- To assess the efficacy of intranasal esketamine compared with intranasal placebo in reducing imminent suicide risk as measured by the CGI-SR-I through the end of the follow-up phase (Day 90).
- To assess the impact of intranasal esketamine compared with intranasal placebo through the end of the follow-up phase (Day 90) on the following patient-relevant concepts:
  - Hopelessness (BHS)
  - Health related quality of life and health status (EQ-5D-5L)
  - Health related quality of life (QLDS)
  - Subject treatment satisfaction (TSQM-9)
- To assess the effect of intranasal esketamine compared with intranasal placebo on the SIBAT Module 3 My Current Thinking through the double-blind treatment (Day 25) and follow-up (Day 90) phases.
- To assess medical resource utilization as measured by the Healthcare Resource Use Questionnaire (HRUQ) of intranasal esketamine compared with intranasal placebo through the end of the follow-up phase (Day 90), including 30-day and 60-day readmission, and emergency room visits related to MDD and suicidality.
- To evaluate whether pretreatment concentrations or post-treatment change in MDD-related biomarkers (eg, hypothalamic-pituitary-adrenal [HPA] axis function, immune system activation, growth factors, metabolic markers) correlate with clinical response or non-response as measured by the MADRS, following intranasal administration of esketamine.

Endpoints

The primary efficacy endpoint will be the change from baseline (Day 1, predose) to 24 hours post first dose in depressive symptoms, as measured by the MADRS total score.

The key secondary efficacy endpoint will be the change from baseline (Day 1, predose) at 24 hours post first dose in severity of suicidality, as measured by the CGI-SS-R.

The other secondary endpoints are:

- MADRS
  - Remission rate (MADRS ≤12) at 4 hours and 24 hours post first dose, and through the end of the double-blind treatment phase (Day 25)
  - Change from baseline of MADRS total score at 4 hours post first dose and through the end of the double-blind treatment phase (Day 25)
- CGI-SS-R
  - Change from baseline at 4 hours post first dose and through the end of the double-blind treatment phase (Day 25).
  - Proportion of subjects achieving resolution of suicidality (CGI-SS-R score of 0 or 1) at 4 hours and 24 hours post first dose, and through the end of the double-blind treatment phase (Day 25)
- CGI-SR-I: Change from baseline at 4 hours and 24 hours post first dose, and through the end of the double-blind treatment phase (Day 25)

- BHS: Change from baseline through the end of the double-blind treatment phase (Day 25)
- EQ-5D-5L: Change from baseline through the end of the double-blind treatment phase (Day 25)
- QLDS: Change from baseline through the end of the double-blind treatment phase (Day 25)
- TSQM-9: Scores through the end of the double-blind treatment phase (Day 25)
- SIBAT: Change from baseline in Module 5 My Risk, Question 3 (patient-reported frequency of suicidal thinking), through the end of the double-blind treatment phase (Day 25)
- Pharmacokinetics: Plasma esketamine and noresketamine concentrations will be summarized; plasma concentrations of esketamine (and noresketamine concentrations, if warranted) will be included in a population analysis
- Safety endpoints will be evaluated throughout the study:
  - Monitoring of treatment emergent adverse events (TEAEs)
  - Clinical laboratory tests, physical examination, nasal examination, 12-lead electrocardiogram (ECG), and vital signs
  - SIBAT
  - On dosing days: MOAA/S, CADSS, and pulse oximetry

The exploratory endpoints include:

- Change from baseline in MADRS, CGI-SS-R, CGI-SR-I, BHS, QLDS, and EQ-5D-5L through the end of the follow-up phase (Day 90)
- TSQM-9 scores, medical resource utilization, and biomarkers through the end of the follow-up phase (Day 90)
- SIBAT: Change from baseline in Module 3 My Current Thinking through the end of the double-blind (Day 25) and follow-up (Day 90) phases

Hypothesis

The primary hypothesis is that, in addition to comprehensive standard of care, intranasal esketamine 84 mg is superior to intranasal placebo in rapidly reducing the symptoms of MDD, including suicidal ideation, as assessed by the change from baseline in the MADRS total score at 24 hours post first dose in subjects who are assessed to be at imminent risk for suicide.

OVERVIEW OF STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, multicenter study. A target of 224 male and female subjects, 18 to 64 years of age, with MDD presenting to an emergency room (ER) or other permitted setting and assessed to be at imminent risk for suicide will be enrolled in this study.

The study will consist of a screening evaluation performed within 48 hours prior to the Day 1 intranasal dose (if possible, screening should occur within 24 hours prior to the Day 1 intranasal dose), immediately followed by a 25-day double-blind treatment phase (Day 1 to 25), and a 65-day follow-up phase (Day 26 to Day 90). The total study duration for each subject will be approximately 13 weeks.

On Day 1 of the double-blind treatment phase, approximately 224 subjects will be randomized in a 1:1 ratio to 1 of 2 treatments: intranasal esketamine 84 mg (n = 112) or intranasal placebo (n = 112), administered two times per week for 4 weeks (Days 1, 4, 8, 11, 15, 18, 22, and 25). Randomization will be stratified by study center and by the physician's assessment of the subject's need of standard of care

antidepressant treatment (ie, antidepressant monotherapy or an antidepressant plus augmentation therapy); the standard of care will be determined prior to randomization on Day 1.

The first dose of study medication will be administered in the ER or other permitted setting, including the inpatient psychiatric unit. All subjects will be treated in the context of comprehensive standard clinical care, including hospitalization and the initiation or optimization of antidepressant treatment, which will be determined by the treating physician(s). The standard of care antidepressant treatment will be initiated or optimized for all subjects on Day 1.

After the first dose (ie, starting with the Day 4 dose or later), a one-time dose reduction to intranasal esketamine 56 mg or intranasal placebo is allowed if a subject is unable to tolerate the intranasal esketamine 84 mg or placebo dose assigned at randomization. No further dose adjustment is allowed during the double-blind treatment phase.

Dose titration/adjustments of newly initiated or optimized standard of care antidepressant treatment should occur during the first 2 weeks of double-blind treatment (ie, by Day 15), with doses remaining stable thereafter through the end of the double-blind phase (Day 25). During the follow-up phase, the antidepressant treatment will be managed based on clinician's judgment.

Subjects will remain in the inpatient psychiatry unit for a recommended duration of 5 days, with shorter or longer hospitalizations permitted if clinically warranted per local standard of care. Discharge before 5 days must be discussed and approved by the sponsor's medical monitor. Following discharge from the inpatient psychiatric unit, subsequent visits for the double-blind treatment phase will be conducted twice-weekly at an outpatient psychiatric facility through Day 25. During the follow-up phase, subjects will be monitored twice weekly for the first two weeks (Days 28, 32, 35, and 39) after study drug treatment. Subjects will then be followed up weekly for the next two weeks (Days 46 and 53) and every two weeks for the rest of the follow-up period (Days 67 and 90).

Efficacy, safety, pharmacokinetic, biomarker, and pharmacogenomic evaluations will be performed as described in the Time and Events Schedule.

The primary efficacy evaluation is the MADRS, the key secondary evaluation is CGI-SS-R, and other efficacy evaluations include the SIBAT, BHS, EQ-5D-5L, QLDS, and TSQM-9.

Safety evaluations include monitoring and collection of adverse events and concomitant therapies, physical examination, nasal examination, body weight, height, vital signs, 12-lead ECG, pulse oximetry, respiratory rate, clinical laboratory tests, SIBAT, MOAA/S, and CADSS.

Blood samples will be collected for measurement of plasma concentrations of esketamine, noresketamine, and other metabolites if warranted.

Blood samples will be collected for biomarker evaluations.

Pharmacogenomic blood samples will be collected from subjects who consent separately to this component of the study (where local regulations permit). Subject participation in pharmacogenomic research is optional.

An Independent Data Monitoring Committee will be commissioned for this study.

SUBJECT POPULATION

The key inclusion and exclusion criteria for enrolling subjects in this study are described below.

Key Inclusion Criteria

- Subject must be a man or woman, 18 to 64 years of age, inclusive.
- Subject must meet Diagnostic and Statistical Manual of Mental Disorders (5th edition) (DSM-5) diagnostic criteria for MDD, without psychotic features, based upon clinical assessment and confirmed by the Mini International Psychiatric Interview (MINI).
- Subjects must have current suicidal ideation with intent, confirmed by a "Yes" response to Question B3 [Think (even momentarily) about harming or of hurting or of injuring yourself: with at least some intent or awareness that you might die as a result; or think about suicide (ie, about killing yourself)?] AND Question B10 [Intend to act on thoughts of killing yourself?] obtained from the MINI. Note: the response to B3 must refer to the present, whereas the response to B10 may reflect the past 24 hours. If the screening period is longer than 24 hours, assessment of B3 and B10 of MINI must be repeated prior to randomization to confirm eligibility.
- In the physician's opinion, acute psychiatric hospitalization is clinically warranted due to subject's imminent risk of suicide.
- Subject has a MADRS total score of >28 predose on Day 1.
- As part of standard of care treatment, subject agrees to be hospitalized voluntarily for a recommended period of 5 days after randomization (may be shorter or longer if clinically warranted in the investigator's opinion) and take prescribed non-investigational antidepressant therapy(ies) for at least the duration of the double-blind treatment phase (Day 25).

Key Exclusion Criteria

- Subject has a current DSM-5 diagnosis of bipolar (or related disorders), antisocial personality disorder, or obsessive compulsive disorder.
- Subject currently meets DSM-5 criteria for borderline personality disorder.
  - Subjects not meeting full DSM-5 criteria for borderline personality disorder but exhibiting recurrent suicidal gestures, threats, or self-mutilating behaviors should also be excluded.
- Subject has a current clinical diagnosis of autism, dementia, or intellectual disability
- Subject has a current or prior DSM-5 diagnosis of a psychotic disorder, or MDD with psychotic features.
- Subject meets the DSM-5 severity criteria for moderate or severe substance or alcohol use disorder (except for nicotine or caffeine) within the 6 months before screening.
  - A history (lifetime) of ketamine, phencyclidine (PCP), lysergic acid diethylamide (LSD), or 3, 4-methylenedioxy-methamphetamine (MDMA) hallucinogen-related use disorder is exclusionary.
- Subject has any of the following conditions:
  - a history or current signs and symptoms of liver or renal insufficiency
  - clinically significant cardiac (including unstable coronary artery disease and congestive heart failure, tachyarrhythmias and recent myocardial infarction) or vascular, pulmonary, gastrointestinal, endocrine (including uncontrolled hyperthyroidism), neurologic (including current or past history of seizures except uncomplicated childhood febrile seizures with no sequelae), hematologic, rheumatologic, or metabolic (including severe dehydration/hypovolemia) disease.

- Subject has uncontrolled hypertension (systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg) despite diet, exercise or a stable dose of anti-hypertensive treatment for at least 2 weeks at screening; or any past history of hypertensive crisis.
  - Subjects with conditions in which the elevation of blood pressure could be a serious risk (including unstable heart failure, severe cardiovascular disease, recent cerebral injury, increased intracranial pressure / intracranial mass lesion, intracranial bleeding or acute stroke, untreated glaucoma or perforating eye injury) are excluded.
  - An abnormal blood pressure value at screening can be repeated once after 5 minutes of relaxation for subject eligibility. On Day 1 of the double-blind phase prior to randomization, a supine or semi-supine systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg is exclusionary.

DOSAGE AND ADMINISTRATION

Intranasal Study Medication

All intranasal doses of study medication will be self-administered under the direct supervision of the investigator or designee. On Day 1, subjects will be randomized to treatment with either intranasal esketamine 84 mg or intranasal placebo, administered two times per week for 4 weeks. Intranasal treatment sessions should not take place on consecutive days.

Food will be restricted for at least 2 hours before each administration of study medication. Drinking of any fluids will be restricted at least 30 minutes before the first nasal spray on each dosing day. If the subject has nasal congestion on the dosing day, an intranasal decongestant can be used to reduce congestion, or with the exception of the Day 1 dose, the dosing day may be delayed (per the permitted visit window; see the Time and Events Schedule). If an intranasal decongestant is used to reduce congestion, it cannot be used within 1 hour prior to intranasal study drug dosing.

The first dose of study medication will be administered in the ER or other permitted setting that has appropriate staffing to manage acutely suicidal subjects. If the first dose is administered in the ER, it is recommended that the subject not be transferred from the ER to the inpatient psychiatric unit after the postdose assessments (approximately 4 hours in length) are completed. Subjects who have been admitted directly into the inpatient psychiatric unit due to imminent risk for suicide or transferred from a medical unit (following medical stabilization for recent suicide attempt) will receive their first dose of study medication in the inpatient psychiatric unit.

Subjects will remain in the inpatient psychiatry unit for a recommended duration of 5 days, with shorter or longer hospitalizations permitted if clinically warranted per local standard of care. Following discharge from the inpatient psychiatric unit, subsequent visits for the double-blind treatment phase will be conducted twice-weekly at an outpatient psychiatric facility through Day 25.

On all outpatient intranasal dosing days, all subjects must remain at the clinical site until study procedures have been completed and the subject is ready for discharge per clinician's assessment. The minimum time required for postdose monitoring is 1.5 hours. Subjects should be accompanied when released from the clinical study site. Subjects must not drive a car or work with machines for 24 hours after study drug dosing.

On each dosing day: Subjects will self-administer 1 spray into each nostril (ie, a total of 2 sprays using 1 intranasal device) at each of the following 3 time points: t = 0, 5 minutes and 10 minutes; time = 0 is defined as the time of the first 100-µL spray. Subjects will use a separate intranasal device at each of these 3 time points (ie, a total of 3 devices). Sprays to each nostril should be delivered in rapid succession at the scheduled time points.

After the first dose (ie, starting with the Day 4 dose or later), if required due to tolerability issues, a one-time dose reduction to intranasal esketamine 56 mg or intranasal placebo is allowed for subsequent doses. No further dose adjustment is allowed during the double-blind treatment phase. The subject would receive the decreased dose at all remaining dosing days.

Standard of Care Antidepressant Treatment

All subjects will be treated in the context of comprehensive standard clinical care, including hospitalization and the initiation or optimization of antidepressant treatment, which will be determined by the treating physician(s) based on clinical judgment and practice guidelines. The standard of care antidepressant treatment (antidepressant monotherapy or antidepressant plus augmentation therapy) will be initiated or optimized for all subjects at the time of randomization on Day 1. Subjects who are on antidepressant monotherapy from Day 1 should remain on antidepressant monotherapy through the end of double-blind phase (Day 25) whereas subjects who are on antidepressant plus augmentation therapy from Day 1 will remain on antidepressants plus augmentation therapy through the end of double-blind phase (Day 25). Eligible subjects may or may not be receiving antidepressants at the time of study entry. Dose titration/adjustments of newly initiated or optimized standard of care antidepressant treatment should occur during the first 2 weeks of double-blind treatment (ie, by Day 15), with doses remaining stable thereafter through the end of the double-blind phase (Day 25). Subjects who are currently taking a recently initiated antidepressant treatment at screening (initiated <2 weeks prior) may continue taking the antidepressant at the current dose or at an optimized dose (dose adjustment is allowed during the first 2 weeks of double-blind treatment) through the end of the double-blind phase (Day 25), if deemed clinically appropriate by the investigator. During the double-blind treatment phase, the investigator needs to consult with the sponsor's medical monitor in advance if additional changes on antidepressant treatment are clinically indicated. During the follow-up phase, the antidepressant treatment will be managed based on the clinician's judgment.

EFFICACY EVALUATIONS

The primary efficacy evaluation will be the MADRS total score. The assessment will be performed using the Structured Interview Guide for the MADRS.

The other secondary and exploratory efficacy evaluations include the SIBAT, BHS, QLDS, EQ-5D-5L, TSQM-9, and HRUQ.

PHARMACOKINETIC EVALUATIONS

Venous blood samples will be collected for measurement of plasma concentrations of esketamine, noresketamine, and other metabolites if warranted. Plasma collected for pharmacokinetic (PK) evaluation may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period.

BIOMARKER AND PHARMACOGENOMIC (DNA) EVALUATIONS

Blood samples will be collected for exploratory analysis of biomarkers (protein, metabolites, and RNA) related to immune system activity, HPA axis activation, neurotrophic and metabolic factors. Exploratory analyses may be performed for additional biomarkers as well.

A pharmacogenomic blood sample will be collected to allow for pharmacogenomic research, as necessary (where local regulations permit). Subject participation in the pharmacogenomic research is optional.

MEDICAL RESOURCE UTILIZATION

Medical resource utilization data, associated with medical encounters, will be collected using the Healthcare Resource Use Questionnaire (HRUQ). The HRUQ includes information regarding utilization

of healthcare services (including the timing and type of serves), enabling changes in level and quantity of services to be considered as a variable in economic models.

SAFETY EVALUATIONS

Safety evaluations include monitoring and collection of adverse events and concomitant therapies, physical examination, body weight, height, vital signs, 12-lead ECG, pulse oximetry, clinical laboratory tests, and nasal examination.

Although the SIBAT will be an efficacy evaluation, it will also inform the safety evaluation to detect potential effects on suicidal ideation and behavior throughout the study.

The CADSS will be administered to assess treatment-emergent dissociative symptoms, and the MOAA/S will be used to measure treatment-emergent sedation.

STATISTICAL METHODS

Subject Information

The primary efficacy and safety analysis sets are defined below.

- Full analysis set: The full analysis set will include all randomized subjects who have received at least one dose of double-blind study medication and have both a baseline and a post dose evaluation for the MADRS total score.
- Safety analysis set: The safety analysis set will include all randomized subjects who receive at least one dose of double-blind study medication.

Sample Size Determination

The maximum sample size for this study was calculated assuming an effect size of 0.45 for the MADRS total score at 24 hours post first dose (Day 2), a one-sided significance level of 0.025, and a drop-out rate at 24 hours of 5%. Approximately 112 subjects will need to be randomized to each treatment group to achieve 90% power. The effect size used in this calculation was based on results of the ESKETINSUI2001 study where the effect size for the change from baseline to Day 2 was 0.65 (mean difference between treatment groups of -7.2 and a pooled SD of 11.02) for MADRS total score. Given that the ESKETINSUI2001 study was a Phase 2 study carried out in only one country, the maximum sample size for this Phase 3 study was determined using a smaller effect size of 0.45 to allow for greater variability that can be expected for a study conducted globally.

Efficacy Analysis

Primary Estimand

The primary estimand, the main clinical quantity of interest to be estimated in the study, is defined by the following 3 components:

Population: subjects with MDD who are at imminent risk of suicide

Endpoint: change from baseline to 24 hours post first dose (Day 2) in the MADRS total score

Measure of Intervention: the effect of the initially randomized treatment that would have been observed had all subjects remained on their treatment until Day 2 of the double-blind phase.

The primary analysis will be based on the full analysis set and the MADRS total scores collected at Day 2.

Primary Efficacy Endpoint

The primary efficacy variable, change from baseline in MADRS total score at 24 hours post first dose (Day 2), will be analyzed using an analysis of covariance (ANCOVA) model. The model will include factors for treatment, center, standard of care antidepressant treatment (ie, antidepressant monotherapy or an antidepressant plus augmentation therapy), and baseline MADRS total score as a covariate. A point estimate and 95% confidence interval for the treatment difference will be provided. Since subjects are hospitalized at the time of the primary endpoint, it is anticipated that missing data will be infrequent. However, if a subject has a MADRS total score at a time earlier than 24 hours post first dose but does not have the 24 hour value, the earlier value will be used for the primary efficacy analysis. In addition, descriptive statistics (N, mean, standard deviation, median, minimum and maximum) of the primary efficacy variable will be provided by study center.

Secondary Efficacy Endpoints

The analysis of the key secondary efficacy endpoint, change from baseline for CGI-SS-R at 24 hours post first dose (Day 2), will be performed using an ANCOVA model on the ranks of change with factors for treatment, center, standard of care antidepressant treatment (ie, antidepressant monotherapy or an antidepressant plus augmentation therapy) and baseline CGI-SS-R (unranked) as a covariate. The treatment difference will be estimated using the Hodges-Lehmann estimate, which is the median of all possible paired differences for the change from baseline for CGI-SS-R at 24 hours.

The multiplicity with regard to testing multiple endpoints (the primary and the key secondary) will be controlled by a fixed sequence testing procedure, ie, the key secondary hypothesis will be tested only after the null hypothesis for the primary endpoint is rejected.

The secondary efficacy endpoints, proportion of subjects with remission (MADRS total score $\leq$12) and the proportion of subjects achieving resolution of suicidality (CGI-SS-R score of 0 or 1) at each visit during the double-blind phase will be analyzed using a Cochran-Mantel-Haenszel chi-square test adjusting for center and standard of care antidepressant treatment (ie, antidepressant monotherapy or antidepressant plus augmentation therapy). Subjects who discontinue treatment prior to the particular visit of the double-blind phase will not be considered to have remission or resolution of suicidality.

Changes from baseline over time in MADRS total score, BHS, and QLDS total scores will be analyzed based on last observation carried forward (LOCF) data using an ANCOVA model with treatment, center, and standard of care antidepressant treatment (ie, antidepressant monotherapy or an antidepressant plus augmentation therapy) as factors and baseline value as a covariate. Additionally, the change from baseline in MADRS total score at Day 25 will be analyzed using a mixed model for repeated measures (MMRM) analysis with baseline MADRS total score as a covariate, and treatment, center, standard of care antidepressant treatment (ie, antidepressant monotherapy or antidepressant plus augmentation therapy), day, and day-by-treatment interaction as fixed effects, and a random subject effect. Comparison of esketamine versus placebo will be performed using the appropriate contrast. Point estimates and 95% confidence intervals for the treatment differences will be provided. Missing data will be closely monitored and additional sensitivity analyses will be specified in the SAP, if necessary.

Ranks of changes from baseline over time for CGI-SS-R and CGI-SR-I will be analyzed based on LOCF data using an ANCOVA model with treatment, center, and standard of care antidepressant treatment (ie, antidepressant monotherapy or an antidepressant plus augmentation therapy) as factors and baseline value (unranked) as a covariate.

SIBAT Module 5 My Risk, Question 3 (patient reported frequency of suicidal thinking), TSQM-9, dimension scores of EQ-5D-5L data, and health status index will be summarized over time.

Additionally, scores of all efficacy endpoints will be summarized for all visits. Descriptive statistics (N, mean, standard deviation, median, minimum and maximum) will be provided for continuous variables and frequency distributions will be provided for categorical variables.

Pharmacokinetic Analyses

Plasma esketamine and noresketamine concentrations will be listed for all subjects. All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. All subjects and samples excluded from the analysis will be clearly documented in the study report.

Population PK analysis of plasma concentration-time data of esketamine may be performed using nonlinear mixed-effects modeling. Data may be combined with those of other selected studies to support a relevant structural model. Available baseline subject characteristics (demographics, laboratory variables, genotypes, race, etc.) will be tested as potential covariates affecting PK parameters. For the parameter estimates, the standard error and 95% confidence interval will be provided. This will be determined after the population pharmacokinetic modeling of the data is completed. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report.

Pharmacokinetic/Pharmacodynamic Analyses

The relationship between MADRS total score (and possibly selected adverse events and additional pharmacodynamic parameters), and PK metrics of esketamine may be evaluated. The results of the pharmacokinetic/pharmacodynamic analyses may be reported separately.

Biomarker and Pharmacogenetic Analyses

Biomarkers will be tabulated by treatment and summary statistics will be calculated. Posttreatment changes in biomarkers over time will be summarized by treatment group. Associations between baseline levels and changes from baseline in selected biomarkers and clinical endpoints will be explored. Exploratory analyses may include comparison of biomarker measures between the treatment groups and correlation with baseline and change from baseline biomarker values in the efficacy and other measures. Exploratory analyses may be performed for additional biomarkers. In addition, all biomarker data obtained from this study may also be included in an ongoing cross-study analysis to investigate the relationship between depression severity, phenotypes, and biomarkers.

Pharmacogenomic analyses may include candidate gene analyses or genome-wide association analyses in relation to treatment response, non-response, and MDD. Expression analyses may include testing of known messenger RNA/microRNA (mRNA/miRNA) transcripts or transcriptome-wide analysis in relationship to antidepressant treatment response and MDD. Additional exploratory analyses may be performed.

Details of the analysis plan and summary of results from both biomarker and pharmacogenomic analyses will be reported separately.

Medical Resource Utilization Analysis

Medical resource utilization data will be descriptively summarized by treatment group.

Safety Analyses

Safety data will be analyzed for the double-blind phase using the safety analysis set. The safety data from the follow-up phase will be summarized separately.

The verbatim terms used in the electronic case report form (eCRF) by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported adverse events with onset during each phase will be included in the analysis. For each adverse event, the

percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. Subjects who die, who discontinue treatment due to an adverse event, or who experience a serious adverse event will be summarized separately.

The TEAEs of special interest will be examined separately grouped in the following categories: drug abuse, dependence and withdrawal (standardized MedDRA queries [SMQ]), transient dizziness/vertigo, impaired cognition, anxiety, cystitis, and suicidality. The adverse events of special interest will be further listed in the SAP.

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be provided. A listing of subjects with any markedly abnormal laboratory results will also be provided.

The ECG data will be summarized by ECG parameter. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made. All clinically relevant abnormalities in ECG waveform that are changes from the baseline readings will be reported.

Descriptive statistics of temperature, pulse/heart rate, respiratory rate, pulse oximetry measurements, 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 subjects with values beyond clinically important limits will be summarized.

Abnormalities observed during the targeted nasal examinations at screening and post-baseline will be summarized and listed by treatment group.

Sedation data from the MOAA/S and dissociative symptoms data from the CADSS will be summarized descriptively at each scheduled visit by treatment group.

TIME AND EVENTS SCHEDULE

Phase	Screening	Double-blind Treatment																Follow Up								
Visit Number	1	2						3	4[b]	5[b]	6[b]	7[b]	8[b]	9[b]	10[b]	-	-	-	11[b]	12[b]	13[b]	14[a]	15[a]	16[a]	17[a]	18[a]	-
Week		1								2		3		4					4	5	5	6	7	8	10	13	
Day	-[c]	1						2[ff]	4	8	11	15	18	22	25	D/C[u]	DB ET[d]	DB RC[d]	28 RC[ii]	32	35 RC[ii]	39	46	53	67	90/ FU ET[dd]	90 RC[dd]
	-	Pre dose	0 hr	40 min	1 hr	1.5 hr	4 hr[ee]																				
Study Procedures																										
Setting																										
Emergency Room (ER) or other permitted setting [e]	X	X	X	X	X	X	X[f]																			
Inpatient psychiatric unit [g]								X	X																	
Outpatient psychiatric unit										X	X	X	X	X	X	-	-			X		X	X	X	X	X	
Screening/Administrative																										
Informed consent	X																									
Informed consent for optional genetic research samples	X																									
Inclusion/exclusion criteria	X	X																								
Medical history, psychiatric history, and demographics	X																									
Standard of care antidepressants assignment [hh]	X	X																								
Urine pregnancy test for women of childbearing potential [i]	X														X		X									
Urine drug screen [i]	X														X		X									
Mini International Psychiatric Interview (MINI) [j]	X																									
Question B3 and B10 from MINI (current status) [j, k]	X																									
Study Drug Administration																										
Practice session for use of intranasal device		X																								
Randomization			X																							
Study Drug Administration [m] (intranasal esketamine or placebo)			X						X	X	X	X	X	X	X											
Safety Assessments																										
Physical examination	X														X		X								X	
Nasal examination	X														X[h]		X									

Phase	Screening	Double-blind Treatment																Follow Up								
Visit Number	1	2					3	4[b]	5[b]	6[b]	7[b]	8[b]	9[b]	10[b]	-	-	-	11[b]	12[b]	13[b]	14[a]	15[a]	16[a]	17[a]	18[a]	-
Week		1							2		3		4					4	5	5	6	7	8	10	13	
Day	-[c]	1					2[ff]	4	8	11	15	18	22	25	D/C[u]	DB ET[d]	DB RC[d]	28 RC[ii]	32	35 RC[ii]	39	46	53	67	90/ FU ET[dd]	90 RC[dd]
	-	Pre dose	0 hr	40 min	1 hr	1.5 hr	4 hr[ee]																			
Vital signs [n]	X	X[o]		X[o]	X[o]	X[o]			X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X									X	
12-lead ECG	X[p]				X[q]				X[q]					X[q]		X										
Pulse oximetry [r]	X (every 15 min)							X	X	X	X	X	X	X												
Body weight	X													X[h]		X									X	
Height	X																									
Modified Observer's Assessment of Alertness/Sedation (MOAA/S) [j, t]	X (every 15 min)							X	X	X	X	X	X	X												
Clinician Administered Dissociation States Scale (CADSS) [j, s]	X		X		X			X	X	X	X	X	X	X												
Efficacy Assessments																										
Suicide Ideation and Behavior Assessment Tool (SIBAT) [w]	X						X	X	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X	X			X		X	X	X	X	
Montgomery Asberg Depression Rating Scale (MADRS) (Recall: 7 days) [j]	X																					X	X	X	X	X
MADRS (Recall: since last assessment) [j]								X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X	X	X	X	X	X	X					
MADRS (Recall: 4 hours) [j, ee]							X[v,z]							X[v,z]												
MADRS (Recall: 24 hours) [j]							X																			
Beck Hopelessness Scale (BHS) (Recall: Last 7 days) [l]	X								X[h]					X[h]		X						X			X	
Quality of Life in Depression Scale (QLDS) [l]	X						X			X[h]				X[h]		X						X			X	
EQ-5D-5L [l]	X						X			X[h]				X[h]		X						X			X	
Treatment Satisfaction Questionnaire for Medication (TSQM-9) [l]											X[h]			X[h]		X						X			X	
Clinical Laboratory Assessments																										
Hematology, Chemistry	X[x]													X[h]		X										
Urinalysis	X[x]													X[h]		X										

Phase	Screening	Double-blind Treatment																Follow Up								
Visit Number	1	2						3	4[b]	5[b]	6[b]	7[b]	8[b]	9[b]	10[b]	-	-	-	11[b]	12[b]	13[b]	14[a]	15[a]	16[a]	17[a]	18[a]	-
Week		1								2		3		4					4	5	5	6	7	8	10	13	
Day	-[c]	1						2[ff]	4	8	11	15	18	22	25	D/C[u]	DB ET[d]	DB RC[d]	28 RC[ii]	32	35 RC[ii]	39	46	53	67	90/ FU ET[dd]	90 RC[dd]
	-	Pre dose	0 hr	40 min	1 hr	1.5 hr	4 hr[ee]																				
Medical Resource Utilization																										
Health Resource Use Questionnaire (HRUQ) [j]															X	X	X						X		X	
Biomarkers																										
Blood sample collection (serum and plasma biomarkers) [aa]		X[y]						X							X[h, y]		X									
Blood sample collection (RNA biomarkers) [gg]		X						X							X[h]		X									
Pharmacogenomics (DNA/epigenetics) – Optional																										
Blood sample collection [bb]		X						X							X[h]		X									
Pharmacokinetics																										
Blood sample collection [cc]			X						X																	
Ongoing Subject Review																										
Prior and concomitant therapy	*Continuous*																		X			*Continuous*				
Adverse events	*Continuous*																X	X	X	X		*Continuous*				X

Abbreviations: BHS, Beck Hopelessness Scale; CADSS, Clinician Administered Dissociative States Scale; DB, double-blind; D/C, discharge; DNA, deoxyribonucleic acid; ECG, electrocardiogram; EQ-5D-5L, EuroQol-5 dimension- 5-level; ER, emergency room; ET, early termination; FU, follow-up; HRUQ, Health Resource Use Questionnaire; ICF, informed consent form; MADRS, Montgomery-Asberg Depression Rating Scale; MINI, Mini International Neuropsychiatric Interview; MOAA/S, Modified Observer's Assessment of Alertness/Sedation; QLDS, Quality of Life in Depression Scale; RC, remote contact; RNA, ribonucleic acid; SIBAT, Suicide Ideation and Behavior Assessment Tool; SpO_2, oxygen saturation; TSQM-9, Treatment Satisfaction Questionnaire for Medication

Footnotes:

[a] Visit can be performed ±3days.

[b] Visit can be performed ±1 day. Intranasal treatment sessions should not be given on consecutive days.

[c] The subject should be screened (ie, starting with the signing of the informed consent form) within 48 hours prior to intranasal dosing on Day 1 (if possible, the subject should be screened within 24 hours prior to the Day 1 intranasal dose).

[d] Subjects who discontinue from the double-blind treatment phase prior to completion of the Day 25 visit will have an Early Termination (DB ET) visit conducted at the time of discontinuation. For subjects who discontinue from double-blind treatment with reasons other than lost to follow up, death, or withdrawal of consent, Remote Contact (RC) will be implemented 3 days after the last dose of intranasal study medication (if the date of the DB ET visit is less than 3 days after the last dose of intranasal study medication) and on Day 25 for MADRS assessment and adverse event collection. The investigator must ensure the subject is appropriately transitioned/followed for any additional care required.

[e] Not applicable for subjects who have been admitted directly into the inpatient psychiatric unit due to imminent risk for suicide or for medical stabilization (following recent suicide attempt). These subjects will receive their first dose of study medication in the inpatient psychiatric unit. Other permitted setting is a non-ER setting that has appropriate staffing to manage acutely suicidal patients.

[f] For subjects dosed in the ER or other permitted setting, it is recommended that subjects not be transferred from the ER to the inpatient psychiatric unit until after the 4 hour postdose assessments are completed.

[g] Subjects can be admitted directly into the inpatient psychiatric unit due to imminent risk for suicide or for medical stabilization (following recent suicide attempt). These subjects will receive their first dose of study medication in the inpatient psychiatric unit. The recommended duration of inpatient hospitalization is 5 days, with shorter or longer hospitalizations permitted if clinically warranted per local standard of care by the investigator's opinion. Discharge before 5 days must be discussed and approved by the sponsor's medical monitor.

[h] Performed predose.

[i] In addition to the scheduled time points, additional pregnancy and drug screening can be performed at the investigator's discretion during the study.

[j] Clinician-administered assessment.

[k] Subjects will be asked to respond to Questions B3 and B10 of the MINI relative to their current state. The response to B3 must refer to the present, whereas the response to B10 may reflect the past 24 hours. If the screening period is longer than 24 hours, assessment of Questions B3 and B10 of the MINI must be repeated prior to randomization to confirm eligibility.

[l] Subject-completed assessment.

[m] On each dosing day, subjects will self-administer 1 spray into each nostril (ie, 2 sprays per intranasal device) at each of the following 3 time points: t = 0, 5 minutes and 10 minutes, where time = 0 is defined as the time of the first 100-µL spray. After Day 1, a one-time decrease to intranasal esketamine 56 mg or intranasal placebo, in a blinded manner, will be permitted if a subject is unable to tolerate the intranasal esketamine 84 mg or placebo dose assigned at randomization. In this case, the subject would receive the decreased dose on all remaining dosing days. Please see details about study drug administration in Section 6.2.

[n] Blood pressure, heart rate, respiratory rate, and temperature (tympanic recommended).

[o] Blood pressure, heart rate, and respiratory rate at predose and at t = 40 minutes, 1 hour, and 1.5 hours postdose on each dosing day. Temperature at predose only on each dosing day.

[p] At screening, the ECG tracing will be sent to the central ECG laboratory but the investigator or sub-investigator is also required to review the ECG locally to determine subject eligibility.

[q] Performed 1 hour postdose.

[r] On each dosing day, pulse oximetry (SpO_2) will be performed every 15 minutes from predose to 1.5 hour postdose (see Section 9.7 for further guidance on timing of pulse oximetry assessments).

[s] CADSS will be performed on dosing days predose and at 40 minutes and 1.5 hours postdose. If any CADSS items are scored zero at 40 minutes, these items will not be repeated at 1.5 hours postdose.

[t] MOAA/S will be performed every 15 minutes on dosing days from predose to 1.5 hour postdose, or longer, if necessary (see Section 9.7 for further guidance on MOAA/S assessments).

[u] Discharge (D/C) visit is performed on the actual day of discharge from initial hospitalization required at study entry. If the actual day of discharge coincides with another scheduled study visit, all study procedures for the scheduled visit should be completed and duplicate assessments are not required.

[v] MADRS performed at 4 hours postdose.

[w] The SIBAT has both clinician-administered and subject-reported modules; not all modules are completed at every visit. Refer to the SIBAT Time and Events Schedule for an outline of which module(s) will be performed at each scheduled time point.

[x] Samples will be collected for analysis by local laboratory (for eligibility) and central laboratory. If standard of care clinical laboratory tests are performed within 24 hours prior to the screening visit (ie, prior to signing of the ICF) the results for laboratory tests required per protocol at screening can be used for determination of subject eligibility. In this case, after the subject signs the ICF, a sample(s) for the local laboratory is not required, but samples for the central laboratory are still required.

[y] Menstrual cycle information will be collected on these visits.

[z] The sleep item will not be assessed at the 4-hour postdose time point on Day 1 and Day 25. The MADRS scores for the sleep item recorded predose on the same day will be carried forward.

[aa] Approximately 20 mL serum and 10 mL plasma samples will be collected at each time point.

[bb] A 6 mL whole blood sample will be collected at each time point.

[cc] A 2 mL whole blood sample will be collected at each of the following postdose times: 30-50 minutes, 1.5 hour to 2.5 hours, and 4 hours to 12 hours.

[dd] Subjects, who discontinue from the follow-up phase prior to completion of the Day 90 visit, will have an Early Termination (FU ET) visit conducted at the time of discontinuation. For subjects who discontinue with reasons other than lost to follow up, death, or withdrawal of consent, Remote Contact (RC) will be implemented on Day 90 for MADRS assessment and adverse event collection. Subjects who discontinue during the double-blind treatment phase prior to Day 25 will also have a Remote Contact on Day 90 for MADRS assessment and adverse event collection.

[ee] The 4-hour assessments at the Day 1 and Day 25 visit should be performed within ±30 minutes of the 4-hour postdose time point.

[ff] The 24-hour assessments at the Day 2 visit should be performed within ±2 hours of the 24-hour postdose time point.
[gg] A 2.5mL whole blood sample will be collected at each time point.
[hh] The standard of care antidepressant treatment (antidepressant monotherapy or antidepressant plus augmentation therapy) will be determined by the treating physician(s) based on clinical judgment and practice guidelines prior to randomization, and the treatment will be initiated on Day 1. See Section 6.2 for further details.
[ii] Remote contact will be implemented for MADRS assessment and adverse event collection.

SIBAT TIME AND EVENTS SCHEDULE

Phase	Screening	Double-blind Treatment																Follow Up								
Visit Number	1	2						3	4[b]	5[b]	6[b]	7[b]	8[b]	9[b]	10[b]	-	-	-	11[b]	12[b]	13[b]	14[a]	15[a]	16[a]	17[a]	18[a]	-
Week		1						2		3		4							4	5	5	6	7	8	10	13	
Day	-	1						2[j]	4[c]	8[c]	11[c]	15[c]	18[c]	22[c]	25[c]	D/C[d]	DB ET[f]	DB RC[f]	28 RC[g]	32	35 RC[g]	39	46	53	67	90/ FU ET[h]	90 RC[h]
	-	Pre dose	0 hr	40 min	1 hr	1.5 hr	4 hr[i]																				
SIBAT																											
Subject Completed Modules																											
Module 1 About me		X																									
Module 2 My Risk/ Protective Factors		X								X		X			X	X	X								X	
Module 3 My Current Thinking		X					X	X	X	X	X	X	X	X	X	X	X			X		X	X	X	X	X	
Module 4 My Actions										X	X	X	X	X	X	X	X			X		X	X	X	X	X	
Module 5 My Risk		X					X	X	X	X	X	X	X	X	X	X	X			X		X	X	X	X	X	
Clinician Completed Modules																											
Module 6. Clinician Semi-Structured Interview		X					X	X	X	X	X	X	X	X	X	X	X			X		X	X	X	X	X	
Module 7. Clinical Global Impressions [e]		X					X	X	X	X	X	X	X	X	X	X	X			X		X	X	X	X	X	
Module 8. Clinical Judgment of optimal Suicide Management		X						X		X		X			X	X	X			X			X		X	X	

Abbreviations: CGI-SR-I, Clinical Global Impression of Imminent Suicide Risk; CGI-SR-LT, Clinical Global Impression of Long-term Suicide Risk; CGI-SS-R, Clinical Global Impression of Severity of Suicidality – Revised; DB, double-blind; D/C, discharge; ET, early termination; FoST, frequency of suicidal thinking; FU, follow-up; RC, remote contact; SIBAT, Suicide Ideation and Behavior Assessment Tool

Footnotes:

[a] Visit can be performed +/- 3days.

[b] Visit can be performed +/- 1 day. Intranasal treatment sessions should not be given on consecutive days.

[c] The SIBAT modules will be performed predose.

[d] Discharge (D/C) visit is performed at on the actual day of discharge from inpatient hospitalization. If the actual day of discharge coincides with another scheduled study visit, the SIBAT modules will be performed according to the procedures under D/C column and duplicate assessments are not required.

[e] Module 7 includes the Clinical Global Impression of Severity of Suicidality – Revised (CGI-SS-R), Clinical Global Impression of Imminent Suicide Risk (CGI-SR-I), Clinical Global Impression of Long-term Suicide Risk (CGI-SR-LT), and assessment of frequency of suicidal thinking (FoST).

[f] Subjects who discontinue from the double-blind treatment phase prior to completion of the Day 25 visit will have an Early Termination (DB ET) visit conducted at the time of discontinuation. For subjects who discontinue from double-blind treatment with reasons other than lost to follow up, death, or withdrawal of consent, Remote Contact (RC) will be implemented 3 days after the last dose of intranasal study medication (if the date of the DB ET visit is less than 3 days after the last dose of intranasal study medication) and on Day 25 for MADRS assessment and adverse event collection. The investigator must ensure the subject is appropriately transitioned/followed for any additional care required.

[g] Remote contact will be implemented for MADRS assessment and adverse event collection.

[h] Subjects, who discontinue from the follow-up phase prior to completion of the Day 90 visit, will have an Early Termination (FU ET) visit conducted at the time of discontinuation. For subjects who discontinue with reasons other than lost to follow up, death, or withdrawal of consent, Remote Contact (RC) will be implemented on Day 90 for MADRS assessment and adverse event collection. Subjects who discontinue during the double-blind treatment phase prior to Day 25 will also have a Remote Contact on Day 90 for MADRS assessment and adverse event collection.

[i] The 4-hour assessments at the Day 1 visit should be performed within ±30 minutes of the 4-hour postdose time point.

[j] The 24-hour assessments at the Day 2 visit should be performed within ±2 hours of the 24-hour postdose time point.

ABBREVIATIONS

ANCOVA	analysis of covariance
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BDNF	brain-derived neurotrophic factor
BHS	Beck Hopelessness Scale
BUN	blood urea nitrogen
CADSS	Clinician Administered Dissociative States Scale
CGI-SR-I	Clinical Global Impression – Imminent Suicide Risk
CGI-SR-LT	Clinical Global Impression – Long-term Suicide Risk
CGI-SS	Clinical Global Impression – Severity of Suicidality
CGI-SS-R	Clinical Global Impression – Severity of Suicidality - Revised
CGJ-SR	Clinical Global Judgment of Suicide Risk
eCRF	electronic case report form(s)
CYP	hepatic cytochrome P450
DNA	deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders (5th edition)
ECG	electrocardiogram
ECT	electroconvulsive therapy
eDC	electronic data capture
EDTA	ethylenediaminetetraacetic acid
ER	Emergency Room
GCP	Good Clinical Practice
HPA	hypothalamic-pituitary-adrenal
HRUQ	Healthcare Resource Use Questionnaire
ICD-10	International Statistical Classification of Diseases and Related Health Problems - 10th revision
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IM	intramuscular
IRB	Institutional Review Board
ISST	InterSePT Scale for Suicidal Thinking
IV	Intravenous
IWRS	interactive web response system
LC-MS/MS	liquid chromatography/mass spectrometry/mass spectrometry
LSD	lysergic acid diethylamide
MADRS	Montgomery Asberg Depression Rating Scale
MADRS-SI	Montgomery Asberg Depression Rating Scale - Suicidal Thoughts Item
mAMP	methamphetamine
MDD	major depressive disorder
MDMA	3, 4-methylenedioxy-methamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Psychiatric Interview
miRNA	micro ribonucleic acid
MOAA/S	Modified Observer's Assessment of Alertness/Sedation
mRNA	messenger ribonucleic acid
NMDA	*N*-methyl-D-aspartate
PCP	phencyclidine
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PQC	Product Quality Complaint
QTc	corrected QT
QTcB	QT corrected according to Bazett's formula
QTcF	QT corrected according to Fridericia's formula
RNA	ribonucleic acid
SAP	Statistical Analysis Plan

SE	standard error
SIBAT	Suicide Ideation and Behavior Assessment Tool
SMQ	standardized Medical Dictionary for Regulatory Activities queries
SpO_2	arterial oxygen saturation
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TRD	treatment-resistant depression
USP	United States Pharmacopeia
w/v	weight/volume

1. INTRODUCTION

Major depressive disorder (MDD) is the most prevalent mental health condition and the psychiatric diagnosis most commonly associated with suicide. [41,65] Epidemiology studies suggest that nearly 60% of those who die by suicide suffer from affective disorders, and at least one-half of people who complete suicide are depressed at the time of their deaths.[2,13,17,51] Although MDD with imminent risk for suicide is a potentially lethal condition that requires immediate intervention, there is no approved treatment. The current standard of care is hospitalization and treatment with antidepressant medication. However, hospitalization is temporary and not completely effective, and the risk for suicide remains high in the weeks after discharge. As standard antidepressants may take up to 4-6 weeks to exert their full effect[75,79], there is a significant unmet therapeutic need for effective drugs with rapid onset of effect.[24]

Ketamine and esketamine (the *S*-enantiomer of ketamine) are approved and widely used for the induction and maintenance of anesthesia via intramuscular (IM) or intravenous (IV) administration. The anesthetic effects of esketamine are attributed to the blockade of ionotropic *N*-methyl-D-aspartate (NMDA) glutamate receptors.[78] Janssen Research & Development (JRD) is developing intranasal esketamine as an antidepressant therapy. The mechanism of action of esketamine is distinct from conventional monoaminergic antidepressant treatments, and esketamine profoundly affects fast excitatory glutamate transmission, increases brain-derived neurotrophic factor (BDNF) release, and stimulates synaptogenesis.[26] In addition, a higher NMDA receptor binding affinity of esketamine compared to ketamine allows a lower volume of medication to be administered via the non-invasive and rapidly-absorbed intranasal route.

For the most comprehensive nonclinical and clinical information regarding esketamine (JNJ-54135419), refer to the latest version of the Investigator's Brochure for esketamine.[37]

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.

1.1. Background

1.1.1. Nonclinical Studies

Safety Pharmacology

The effects of ketamine on myocardial contractility and blood pressure varied with species and experimental conditions.[37] In these studies, the dog was most predictive of the cardiovascular effects of ketamine in man. In dogs, ketamine produced increases in arterial blood pressure, heart rate and cardiac output as well as a decrease in total peripheral resistance.[43] Results from animal studies suggest that the increase in blood pressure produced by ketamine is due to selective activation of central cardiac stimulating mechanisms leading to an increase in cardiac output.[43]

Toxicology

Repeated-dose Toxicity: Repeated-dose toxicity studies with intranasally administered esketamine were performed in rats for up to 6 months and in dogs for up to 9 months. Intranasal administration of esketamine was well tolerated in these studies. No adverse effects were noted in rats or dogs up to the highest dose tested.[37]

Neurotoxicity: The neurotoxic potential of intranasal esketamine has been investigated in rats in two single-dose studies and one 14-day study. No neuropathological lesions were noted in the esketamine-dosed rats at the highest dose tested in each study.[37]

Reproductive and Developmental Toxicity: In a rat fertility and early embryonic developmental study, no adverse effects of intranasal esketamine on the fertility and reproductive capacities of adult males and females were observed.[37] Rat and rabbit embryo-fetal developmental toxicity studies with intranasally administered racemic ketamine did not reveal evidence of reproductive toxicity. [37] However, when monkey fetuses were exposed in utero to high dose levels of racemic ketamine, neurotoxicity was observed.[37] Intranasal esketamine did not affect pre- and postnatal development in rats; however, high dose levels of racemic ketamine induced neurotoxicity in early postnatal rat pups.[37]

Genotoxicity: In vitro and in vivo genotoxicity studies have been performed with ketamine and esketamine, and the overall weight of evidence demonstrates the absence of significant genotoxic risk.[37]

Abuse potential: The results of self-administration and withdrawal experiments in several animal models suggest that esketamine would have abuse potential in humans. [7,20,21,46,57,83,84]

1.1.2. Clinical Studies

1.1.2.1. Completed and Ongoing Clinical Studies with Intranasal Esketamine

A total of 9 Phase 1 studies with intranasal esketamine have been completed and reported, including 6 studies in healthy younger subjects, 2 studies in healthy elderly and younger subjects, and 1 study in subjects with a history of allergic rhinitis. In total, 263 subjects have been exposed to intranasal esketamine in the completed Phase 1 studies that have been reported.[37] Three additional Phase 1 studies in healthy subjects have been completed but not reported, and a total of 6 Phase 1 studies are ongoing in healthy subjects, subjects with hepatic impairment, and subjects with renal impairment.

One Phase 2 study has been completed in subjects with MDD who are at imminent risk of suicide with 35 subjects exposed to intranasal esketamine.[16] One Phase 2 study has been completed in subjects with treatment-resistant depression (TRD) with 107 subjects exposed to intranasal esketamine.[37] In addition, one Phase 2 study in subjects with TRD is ongoing.

In the clinical development program for intranasal esketamine, 6 Phase 3 clinical studies are ongoing in subjects with TRD: 2 short-term double-blind, randomized, active-controlled studies,

1 maintenance-of-effect study, 2 long-term, open-label studies, and 1 short-term study in elderly subjects with TRD.

Further information about the completed and ongoing studies with esketamine is provided in the Investigator's Brochure.[37]

1.1.2.2. Human Pharmacokinetics and Product Metabolism

Metabolism and Excretion

Ketamine (and esketamine) undergoes extensive metabolism by human hepatic cytochrome P450 (CYP). In humans, *N*-demethylation to the active metabolite norketamine is a major route of metabolism. Norketamine had a half-life in plasma of approximately 5 hours in humans.[31] The major human hepatic cytochromes that catalyze ketamine *N*-demethylation in vitro were CYP2B6 and CYP3A4,[32,68,82] and those that were responsible for the formation of norketamine metabolites included CYP2A6 and CYP2B6.[68] Pharmacokinetic (PK) results after IV administration of racemic ketamine and esketamine to human subjects suggested that inversion of esketamine to arketamine (the R-enantiomer of ketamine) does not occur.[29]

Racemic ketamine and its metabolites have been shown to be predominantly excreted in the urine. An average of 91% of a dose of ketamine administered to healthy subjects was recovered in urine.[18] Less than 3% of an administered dose was excreted in urine as parent drug.[80]

Pharmacokinetics of Intranasal Esketamine

The PK of intranasal esketamine have been characterized in healthy adult subjects (elderly and younger adults) as well as subjects with a history of allergic rhinitis, with TRD[37], and with MDD at imminent risk for suicide. In healthy adult subjects, intranasally-administered esketamine (28 to 112 mg) was rapidly absorbed with measurable concentrations at 7 minutes after the first spray; the plasma esketamine maximum concentration and area under the concentration-time curve increased in a dose-related manner following intranasal administration, and the mean terminal half-life of esketamine ranged from 5.86 to 9.83 hours (ESKETINTRD1001).[37] When administered in healthy adult subjects via the intranasal route, esketamine was rapidly absorbed and had an absolute bioavailability of approximately 48% (ESKTINTRD1009).[37] In a Phase 2 study in subjects with TRD (ESKETINTRD2003), there was a dose-dependent increase in mean plasma esketamine concentrations from subjects in Panel A who were administered 28, 56, or 84 mg doses of intranasal esketamine.[37] Furthermore, the mean esketamine concentrations in plasma samples collected at corresponding timepoints on Days 1, 11, and 25 were similar suggesting that the PK was consistent after repeated intranasal administration.[37] The PK results from subjects with MDD at imminent risk of suicide (ESKETINSUI2001) who received 84 mg doses of intranasal esketamine were consistent with the PK results in healthy adults and those with TRD.

1.1.2.3. Efficacy

Several small clinical studies and case reports suggested that subanesthetic doses of ketamine could improve symptoms of depression within hours even in subjects who responded poorly to conventional antidepressants.[50] Further results from Panel A (conducted in the United States and Belgium) in a Phase 2, 2-panel, double-blind, doubly-randomized, placebo-controlled clinical study in subjects with TRD (ESKETINTRD2003) demonstrated that treatment with intranasal esketamine (28, 56, and 84 mg) rapidly improved clinical symptoms of depression at 2 hours and 24 hours after the first dose as assessed by the change in Montgomery-Asberg Depression Rating Scale (MADRS) total score from baseline.[37] In addition, after 1 week of treatment the analysis showed that all 3 esketamine dose groups were statistically superior to the placebo group using a one-sided significance level of 0.05 (least squares mean differences [SE] between each esketamine group and the placebo group were: -4.2 [2.09], -6.3 [2.07], and -9.0 [2.13] for esketamine 28, 56, and 84 mg, respectively; p=0.021, p=0.001, and p<0.001 for esketamine 28, 56, and 84 mg, respectively) and that there was a significant relationship between esketamine dose and change in MADRS total score (p<0.001).[37] The major secondary analyses of results from Panel A provided preliminary evidence suggesting that improvements in depressive symptoms resulting from esketamine treatment could be sustained with repeated dosing for 74 days, the duration of the study in Panel A.[37] In Panel B (conducted in Japan), subjects were treated with placebo or 14 or 56 mg of intranasal esketamine for up to 25 days. Greater improvements in MADRS total score were observed in the esketamine 56-mg group compared with the placebo group using a one-sided significance level of 0.10 (mean difference [SE]: -3.7 [2.81]; p=0.096), and a dose response was detected during the first week of treatment (p=0.097).[37] Although there was a statistically significant difference between the esketamine 56-mg and placebo groups during the first week of treatment, the results from Panel B must be interpreted with caution due to a significant treatment by baseline MADRS total score interaction during the first week of treatment (p=0.052), where results favored the placebo group for subjects with higher baseline MADRS total scores and the esketamine groups for subjects with lower baseline MADRS total scores.[37]

Several pilot studies in subjects with MDD or bipolar depression also suggested that ketamine may reduce suicidal ideation within hours of administration[25,47,71,72,85]. In addition, three independent randomized, double-blind trials in subjects with MDD suggested that doses of IV ketamine could rapidly decrease suicidal ideation as evaluated by assessments such as the MADRS Suicidal Thoughts Item (MADRS-SI).[5,38,63] Recently, a Phase 2, double-blind, randomized, placebo-controlled, proof-of-concept study (ESKETINSUI2001) evaluated the efficacy and safety of intranasal esketamine for the rapid reduction of the symptoms of MDD, including suicidal ideation. Subjects with a diagnosis of MDD assessed to be at imminent risk for suicide from the United States were randomly assigned to treatment with placebo (n=31) or esketamine 84 mg (n=35) for up to 25 days.[16] All subjects received comprehensive standard of care treatment including initial hospitalization and optimized antidepressant medication. Esketamine 84 mg compared with placebo demonstrated a clinically meaningful and statistically significant reduction of depressive symptoms as assessed by changes from baseline in MADRS total score using a two-sided significance level of 0.20 at 4 hours after the first dose (primary endpoint; mean difference [SE] between esketamine 84 mg and placebo: -5.3 [2.10]; p=0.015)

and at approximately 24 hours after the first dose (mean difference [SE]: -7.2 [2.85]; p=0.015), and esketamine 84 mg demonstrated evidence of a potential therapeutic effect on Day 25 (mean difference [SE]: -4.5 [3.14]; p=0.159).[16] The changes from baseline in suicidal ideation based on the MADRS-SI score also favored esketamine 84 mg; the difference between the esketamine and placebo group was statistically significant at 4 hours after the first dose (p=0.002), and the differences between esketamine and placebo showed evidence of a potential therapeutic effect at approximately 24 hours after the first dose (p=0.129) and on Day 25 (p=0.143).[16] Additionally, changes from baseline in the Clinical Global Judgment of Suicide Risk (CGJ-SR), which summarized the clinician's overall judgment of suicide risk, provided evidence of a potential therapeutic effect of esketamine 84 mg compared with placebo at both 4 hours (p=0.112) and 24 hours (p=0.150) after the first dose.[16] The results from ESKETINSUI2001 support the hypothesis that esketamine, administered intranasally, is an efficacious treatment for the rapid reduction of the symptoms of MDD, including suicidal ideation, in subjects assessed to be at imminent risk for suicide.

1.1.2.4. Safety and Tolerability

Ketamine was first introduced as an anesthetic in 1963 and is considered to have an excellent medical safety profile.[30,45,73,76] The following adverse reactions are listed as very common, common, or frequent occurrences for ketamine and esketamine when administered as an anesthetic: emergence or recovery reactions, elevated blood pressure and pulse rate, stimulation of respiration, nausea, and vomiting.[44,78]

Short-term Use of Intranasal Esketamine in Subjects with TRD

Subjects with TRD in Panel A in Study ESKETINTRD2003, received placebo or 28, 56, or 84 mg of intranasal esketamine, and subjects in Panel B received placebo or 14 or 56 mg of esketamine. All doses of esketamine generally appeared to be tolerated, and no new safety concerns were raised during the study. There were no deaths during the double-blind or open-label treatment phases. There was 1 death due to completed suicide in Panel B during the follow-up phase of the study, 20 days after the subject received the last dose of study medication.[37] A total of 4 non-fatal serious adverse events (SAEs) occurred in 3 subjects during the study; oesophagitis (during placebo treatment), ectopic pregnancy (during esketamine treatment, leading to treatment withdrawal), general physical health deterioration (follow-up phase) and confusional state (follow-up phase).[37] The investigator assessed the SAE of confusional state as probably related to study medication and SAEs of esophagitis, ectopic pregnancy, and general physical health deterioration, and completed suicide as not related to study medication. In total, 4 subjects experienced treatment-emergent adverse events (TEAEs) which led to withdrawal of study medication while receiving esketamine treatment (ectopic pregnancy [described above], syncope, headache, and dissociative disorder).[37] The investigator assessed the events of headache and dissociative disorder as very likely related to study medication. The investigator considered the event of syncope possibly related to the study medication, and the sponsor considered the event of syncope not related to the study medication based on the short half-life of esketamine and the onset of the event of syncope.

In Panels A and B combined, the common TEAEs (≥10% the total esketamine or placebo groups) that occurred more frequently in the total esketamine group compared with the placebo group during the double-blind phase were: dizziness, headache, dissociation, nausea, feeling abnormal, and hypoaesthesia.[19] A majority of subjects in Panels A and B experienced elevations in blood pressure measurements after receiving esketamine doses; the maximum elevations from predose in blood pressure measurements on each dosing day were observed in most cases within 1 hour post dose, with the majority returning within the normal range by 2 hours postdose.[19] The blood pressure changes observed did not appear to attenuate over time with multiple doses. A majority of subjects in the esketamine treatment groups in Panels A and B experienced an increase in dissociative symptoms after dosing as assessed using the Clinician Administered Dissociative States Scale (CADSS). Dissociative symptoms peaked at approximately 40 minutes after dosing and typically resolved by 2 hours after dosing.[19] The magnitude of postdose dissociative symptoms decreased over time with repeated consecutive doses for all esketamine doses.

Short-term Use of Intranasal Esketamine in Subjects with MDD at Imminent Risk for Suicide

In the Phase 2 study in subjects with MDD at imminent risk for suicide (ESKETINSUI2001), the TEAEs reported by esketamine-treated subjects were consistent with the safety profile of esketamine observed in earlier studies. Esketamine 84 mg was generally tolerated, and no new safety signals emerged in this population. There were no deaths during the study. There were 4 SAEs in the double-blind phase, all in the esketamine 84 mg group.[16] Three of these events were related to re-hospitalization of subjects with re-emergence of suicidal ideation (n=2) or depression (n=1) in subjects who had improved and had been discharged from the hospital. In all 3 instances, the subjects recovered and completed both the double-blind and follow-up phases. One subject experienced an event of increased agitation, and the study medication was withdrawn. With the exception of re-emergence of depressive symptoms, which was considered possibly related to study medication, none of the other SAEs were considered to be related to study medication by the investigator. During the follow-up phase, 5 subjects in the placebo group experienced SAEs, including suicidal ideation (n=1) and attempted suicide (n=3) and cellulitis (n=1), compared with only 1 subject in the esketamine group, who experienced suicidal ideation. One subject in the placebo group and 5 subjects in the esketamine 84 mg group discontinued from the double-blind phase due to TEAEs.[16] Events leading to discontinuation in the esketamine group were dizziness, dysgeusia, ventricular extrasystole, nausea, and dyspnea, which were considered by the investigator to be probably or very likely related to study drug; and aggression and agitation, which were considered to be doubtfully and not related to study drug, respectively. In total, 3 of 35 subjects in the esketamine group had dose reductions from 84 mg to 56 mg for intolerance.[16]

The most common (≥20%) individual TEAEs in the esketamine 84 mg group were nausea, dizziness, dysgeusia, headache, and dissociation and vomiting.[16] A majority of subjects in the esketamine group experienced elevations in blood pressure measurements after dosing. The maximum increases in blood pressure occurred in the esketamine treated subjects at approximately 40 minutes postdose.[16] A greater proportion of subjects in the esketamine group

reported dissociative symptoms as assessed by the CADSS compared with the placebo group. The dissociative symptoms observed in the esketamine group had an onset shortly after the start of the dose and generally resolved within 2 hours postdose.[16] The dissociative symptoms attenuated with repeated dosing.

Adverse Events Associated with Chronic Use of Ketamine

Much of the literature on chronic ketamine use comes from data gathered from illegal use, rather than clinical studies. Several studies have examined cognitive function in ketamine users, [23,58,60,64]; overall, infrequent use did not appear to be associated with long-term cognitive impairment.[64] The most robust findings were that frequent ketamine users (more than 5 times a week) exhibited impairments in both short- and long-term memory.[60] Although dosages varied, the dosages reported by ketamine users in this study were much higher than the dosages of ketamine or equivalent doses of esketamine intended for use in treating MDD. The memory impairments were not found in ex-users who had been abstinent for at least a year, thus impairments may be reversible.[61]

Ketamine-induced ulcerative cystitis is also an identified complication.[59] The most common symptoms are frequency and urgency of urination, dysuria, urge incontinence, and occasionally painful hematuria. Most cases were in near-daily recreational ketamine users; the majority of cases resolved after stopping ketamine use, and one-third remained static. The ketamine dose, dosing frequency, and duration of chronic ketamine use at which cystitis may develop are not known. Compared with the doses and dosing frequency of esketamine proposed in this study, the equivalent ketamine dose in published reports of interstitial cystitis and bladder-related symptoms was typically much higher; ketamine was dosed more frequently, and often there was concomitant use of other substances.

Abuse Liability, Dependence and Withdrawal

There are reports of ketamine dependence in the literature but no large-scale studies. [35,39,56,59,66] One study found that ketamine users and ex-users expressed concerns about ketamine addiction, and the majority of frequent users reported using the drug without stopping until supplies ran out, so compulsive patterns of behavior are a concern.[62] A few published reports describe craving and somatic and psychological aspects of anxiety as symptoms of withdrawal from ketamine; however, a specific ketamine withdrawal syndrome has not yet been described.[22,48,59]

1.2. Overall Rationale for the Study

The current study is being conducted to evaluate the efficacy and safety of intranasal esketamine in addition to comprehensive standard of care in subjects with MDD who are at imminent risk for suicide as a pivotal Phase 3 study in support of regulatory agency requirements for registration of intranasal esketamine.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

2.1.1. Objectives

Primary Objective

The primary objective is to evaluate the efficacy of intranasal esketamine 84 mg compared with intranasal placebo in addition to comprehensive standard of care in reducing the symptoms of MDD, including suicidal ideation, in subjects who are assessed to be at imminent risk for suicide, as measured by the change from baseline on the Montgomery-Asberg Depression Rating Scale (MADRS) total score at 24 hours post first dose.

Key Secondary Objective

The key secondary objective is to assess the efficacy of intranasal esketamine compared with intranasal placebo in reducing severity of suicidality as measured by the clinical global impression of severity of suicidality revised version (CGI-SS-R) at 24 hours post first dose.

Other Secondary Objectives

The other secondary objectives are:

- To evaluate the efficacy of intranasal esketamine compared with intranasal placebo in remission of MDD (defined as MADRS total score ≤12) at 4 hours and 24 hours post first dose, and through the end of the double-blind treatment phase (Day 25).
- To evaluate the efficacy of intranasal esketamine compared with intranasal placebo in reducing symptoms of MDD as assessed by the MADRS total score at 4 hours post first dose on Day 1, and through the end of the double-blind treatment phase (Day 25).
- To assess the efficacy of intranasal esketamine compared with intranasal placebo in reducing severity of suicidality as measured by the CGI-SS-R at 4 hours post first dose on Day 1, and through the end of the double-blind treatment phase (Day 25).
- To assess the efficacy of intranasal esketamine compared with intranasal placebo in achieving resolution of suicidality as measured by the score of 0 (normal, not at all suicidal) or 1 (questionably suicidal) of the CGI-SS-R at 4 hours and 24 hours post first dose, and through the end of the double-blind treatment phase (Day 25).
- To assess the efficacy of intranasal esketamine compared with intranasal placebo in reducing imminent suicide risk as measured by the clinical global impression of imminent suicide risk (CGI-SR-I) at 4 hours and 24 hours post first dose, and through the end of the double-blind treatment phase (Day 25).
- To assess the impact of intranasal esketamine compared with intranasal placebo on the following patient-relevant concepts through the end of the double-blind treatment phase (Day 25)
  - Hopelessness as measured by Beck Hopelessness Scale (BHS)

  - Health related quality of life and health status, using the European Quality of Life (EuroQol) Group, 5-Dimension, 5-Level (EQ-5D-5L)
  - Health related quality of life using the Quality of Life in Depression Scale (QLDS)
  - Treatment satisfaction using the Treatment Satisfaction Questionnaire for Medication (TSQM-9)
  - Patient-reported suicidality using the Suicidal Ideation and Behaviors Assessment Tool (SIBAT), including Module 5 My Risk, Question 3 (patient-reported frequency of suicidal thinking)
- To assess the safety and tolerability of intranasal esketamine during the double-blind treatment phase and the follow-up phase, with special attention given to the following assessments:
  - Potential effects on suicidal ideation and behavior using the SIBAT
  - On dosing days:
    - Effect on heart rate, blood pressure, respiratory rate, and blood oxygen saturation
    - Effect on alertness and sedation using the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale
    - Treatment-emergent dissociative symptoms using the Clinician Administered Dissociative States Scale (CADSS)
- To assess the pharmacokinetics of intranasal esketamine.

Exploratory Objectives

The exploratory objectives are:

- To evaluate the efficacy of intranasal esketamine compared with intranasal placebo in reducing symptoms of MDD as assessed by the MADRS total score and remission rate through the end of the follow-up phase (Day 90).
- To assess the efficacy of intranasal esketamine compared with intranasal placebo in reducing severity of suicidality as measured by the CGI-SS-R through the end of the follow-up phase (Day 90).
- To assess the efficacy of intranasal esketamine compared with intranasal placebo in reducing imminent suicide risk as measured by the CGI-SR-I through the end of the follow-up phase (Day 90).
- To assess the impact of intranasal esketamine compared with intranasal placebo through the end of the follow-up phase (Day 90) on the following patient-relevant concepts:
  - Hopelessness (BHS)
  - Health related quality of life and health status (EQ-5D-5L)
  - Health related quality of life (QLDS)
  - Subject treatment satisfaction (TSQM-9)

- To assess the effect of intranasal esketamine compared with intranasal placebo on the SIBAT Module 3 My Current Thinking through the double-blind treatment (Day 25) and follow-up (Day 90) phases.
- To assess medical resource utilization as measured by the Healthcare Resource Use Questionnaire (HRUQ) of intranasal esketamine compared with intranasal placebo through the end of the follow-up phase (Day 90), including 30-day and 60-day readmission, and emergency room visits related to MDD and suicidality.
- To evaluate whether pretreatment concentrations or post-treatment change in MDD-related biomarkers (eg, hypothalamic-pituitary-adrenal [HPA] axis function, immune system activation, growth factors, metabolic markers) correlate with clinical response or non-response as measured by the MADRS, following intranasal administration of esketamine.

2.1.2. Endpoints

The primary efficacy endpoint will be the change from baseline (Day 1, predose) to 24 hours post first dose in depressive symptoms, as measured by the MADRS total score.

The key secondary efficacy endpoint will be the change from baseline (Day 1, predose) at 24 hours post first dose in severity of suicidality, as measured by the CGI-SS-R.

The other secondary endpoints are:

- MADRS
  - Remission rate (MADRS ≤12) at 4 hours and 24 hours post first dose, and through the end of the double-blind treatment phase (Day 25)
  - Change from baseline of MADRS total score at 4 hours post first dose and through the end of the double-blind treatment phase (Day 25)
- CGI-SS-R
  - Change from baseline at 4 hours post first dose and through the end of the double-blind treatment phase (Day 25).
  - Proportion of subjects achieving resolution of suicidality (CGI-SS-R score of 0 or 1) at 4 hours and 24 hours post first dose, and through the end of the double-blind treatment phase (Day 25)
- CGI-SR-I: Change from baseline at 4 hours and 24 hours post first dose, and through the end of the double-blind treatment phase (Day 25)
- BHS: Change from baseline through the end of the double-blind treatment phase (Day 25)
- EQ-5D-5L: Change from baseline through the end of the double-blind treatment phase (Day 25)
- QLDS: Change from baseline through the end of the double-blind treatment phase (Day 25)
- TSQM-9: Scores through the end of the double-blind treatment phase (Day 25)
- SIBAT: Change from baseline in Module 5 My Risk, Question 3 (patient-reported frequency of suicidal thinking), through the end of the double-blind treatment phase (Day 25)

- Pharmacokinetics: Plasma esketamine and noresketamine concentrations will be summarized; plasma concentrations of esketamine (and noresketamine concentrations, if warranted) will be included in a population analysis
- Safety endpoints will be evaluated throughout the study:
  - Monitoring of treatment emergent adverse events (TEAEs)
  - Clinical laboratory tests, physical examination, nasal examination, 12-lead electrocardiogram (ECG), and vital signs
  - SIBAT
  - On dosing days: MOAA/S, CADSS, and pulse oximetry

The exploratory endpoints include:

- Change from baseline in MADRS, CGI-SS-R, CGI-SR-I, BHS, QLDS, and EQ-5D-5L through the end of the follow-up phase (Day 90)
- TSQM-9 scores, medical resource utilization, and biomarkers through the end of the follow-up phase (Day 90)
- SIBAT: Change from baseline in Module 3 My Current Thinking through the end of the double-blind (Day 25) and follow-up (Day 90) phases

Refer to Section 9, Study Evaluations for evaluations related to endpoints.

2.2. Hypothesis

The primary hypothesis is that, in addition to comprehensive standard of care, intranasal esketamine 84 mg is superior to intranasal placebo in rapidly reducing the symptoms of MDD, including suicidal ideation, as assessed by the change from baseline in the MADRS total score at 24 hours post first dose in subjects who are assessed to be at imminent risk for suicide.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a randomized, double-blind, placebo-controlled, multicenter study. A target of 224 male and female subjects, 18 to 64 years of age, with MDD presenting to an emergency room (ER) or other permitted setting and assessed to be at imminent risk for suicide will be enrolled in this study.

The study will consist of a screening evaluation performed within 48 hours prior to the Day 1 intranasal dose (if possible, screening should occur within 24 hours prior to the Day 1 intranasal dose), immediately followed by a 25-day double-blind treatment phase (Day 1 to 25), and a 65-day follow-up phase (Day 26 to Day 90). The total study duration for each subject will be approximately 13 weeks.

On Day 1 of the double-blind treatment phase, approximately 224 subjects will be randomized in a 1:1 ratio to 1 of 2 treatments: intranasal esketamine 84 mg (n = 112) or intranasal placebo (n = 112), administered two times per week for 4 weeks (Days 1, 4, 8, 11, 15, 18, 22, and 25).

Randomization will be stratified by study center and by the physician's assessment of the subject's need of standard of care antidepressant treatment (ie, antidepressant monotherapy or an antidepressant plus augmentation therapy); the standard of care will be determined prior to randomization on Day 1.

The first dose of study medication will be administered in the ER or other permitted setting, including the inpatient psychiatric unit. All subjects will be treated in the context of comprehensive standard clinical care, including hospitalization and the initiation or optimization of antidepressant treatment, which will be determined by the treating physician(s). The standard of care antidepressant treatment will be initiated or optimized for all subjects on Day 1.

After the first dose (ie, starting with the Day 4 dose or later), a one-time dose reduction to intranasal esketamine 56 mg or intranasal placebo is allowed if a subject is unable to tolerate the intranasal esketamine 84 mg or placebo dose assigned at randomization. No further dose adjustment is allowed during the double-blind treatment phase.

Dose titration/adjustments of newly initiated or optimized standard of care antidepressant treatment should occur during the first 2 weeks of double-blind treatment (ie, by Day 15), with doses remaining stable thereafter through the end of the double-blind phase (Day 25). During the follow-up phase, the antidepressant treatment will be managed based on clinician's judgment.

Subjects will remain in the inpatient psychiatry unit for a recommended duration of 5 days, with shorter or longer hospitalizations permitted if clinically warranted per local standard of care. Discharge before 5 days must be discussed and approved by the sponsor's medical monitor. Following discharge from the inpatient psychiatric unit, subsequent visits for the double-blind treatment phase will be conducted twice-weekly at an outpatient psychiatric facility through Day 25. During the follow-up phase, subjects will be monitored twice weekly for the first two weeks (Days 28, 32, 35, and 39) after study drug treatment. Subjects will then be followed up weekly for the next two weeks (Days 46 and 53) and every two weeks for the rest of the follow-up period (Days 67 and 90).

Efficacy, safety, pharmacokinetic, biomarker, and pharmacogenomic evaluations will be performed as described in the Time and Events Schedule.

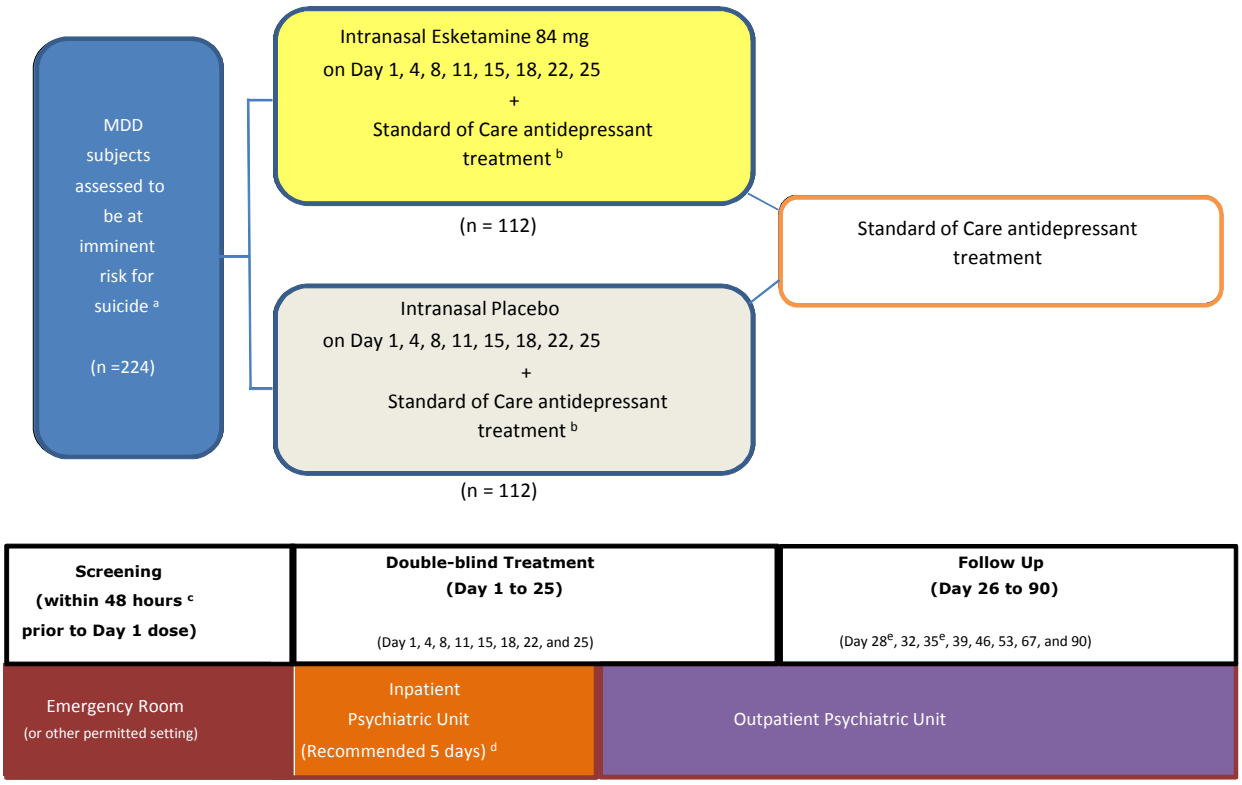
- The primary efficacy evaluation is the MADRS, the key secondary evaluation is CGI-SS-R, and other efficacy evaluations include the SIBAT, BHS, EQ-5D-5L, QLDS, and TSQM-9.
- Safety evaluations include monitoring and collection of adverse events and concomitant therapies, physical examination, nasal examination, body weight, height, vital signs, 12-lead ECG, pulse oximetry, respiratory rate, clinical laboratory tests, SIBAT, MOAA/S, and CADSS.
- Blood samples will be collected for measurement of plasma concentrations of esketamine, noresketamine, and other metabolites if warranted.
- Blood samples will be collected for biomarker evaluations.

- Pharmacogenomic blood samples will be collected from subjects who consent separately to this component of the study (where local regulations permit). Subject participation in pharmacogenomic research is optional.

An Independent Data Monitoring Committee (IDMC) will be commissioned for this study. Refer to Section 11.9, Data Monitoring Committee, for details.

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

Figure 1: Schematic Overview of the Study



[a] Randomization will be stratified by study center and by the physician's assessment of the subject's need of standard of care antidepressant treatment (ie, antidepressant monotherapy or an antidepressant plus augmentation therapy); the standard of care will be determined prior to randomization on Day 1.
[b] Standard of care antidepressant treatment will be initiated or optimized on Day 1.
[c] If possible, screening should be performed within 24 hours prior the Day 1 intranasal dose.
[d] Discharge before 5 days must be discussed and approved by the sponsor's medical monitor.
[e] Remote contact

3.2. Study Design Rationale

3.2.1. Study Population

This study will enroll adult subjects (18 to 64 years) with MDD presenting with suicidal ideation who are assessed to be at imminent risk for suicide. Subjects must meet Diagnostic and Statistical Manual of Mental Disorders - 5th edition (DSM-5) criteria for MDD (without psychosis), based on diagnostic assessment with the Mini International Psychiatric Interview (MINI), and subjects must have a MADRS total score >28 at baseline. By selecting for subjects with a MADRS total score of >28 (representing moderate to severe depression), the study may reduce placebo response and enhance signal detection.

Enrolled subjects must also present with suicidal ideation with intent, operationalized by affirmative responses to MINI questions B3 (*Think about harming/hurting/injuring yourself or about suicide?*) and B10 (*Intend to act on thoughts of killing yourself?*). This generally corresponds with the level of severity of suicidal ideation that appears to predict suicidal behavior over the short term.[69] Additionally, in the physician's opinion, acute psychiatric hospitalization of the subject must be clinically warranted due to the subject's imminent risk of suicide. By selecting for subjects with this degree of suicide risk, the possibility of a favorable benefit-risk balance for the experimental treatment is enhanced.

The age range of 18 to 64 years was selected as this Phase 3 study is designed to confirm the efficacy and safety of esketamine in subjects with MDD presenting with suicidal ideation using 84 mg, the dose anticipated to offer the most rapid and sustained benefit in adults. As higher systemic bioavailability of intranasal esketamine has been previously observed in an elderly population (≥65 years) (Studies ESKETINTRD1003 and ESKETINTRD1012[37]) and the efficacy and safety of esketamine in the elderly population with MDD is being further evaluated in other studies, elderly adult subjects will not be enrolled in this study.

Subjects with a recent history (<6 months) of moderate or severe substance or alcohol use disorders will be excluded to ensure the subject's depression is not attributed to substance or alcohol use (ie, substance-induced depressive disorder). Subjects with a current diagnosis of bipolar or related disorders will be excluded to allow accurate assessment of efficacy and/or safety data of the study drug in the context of MDD.

3.2.2. Treatment and Study Duration

Patients with MDD with suicidal thoughts and behaviors are at risk for increased suicidality both in the first several days after initiating treatment with a standard antidepressant[40] and post-hospitalization.[12,79] Therefore, the dosing regimen in this study includes administration of esketamine twice weekly for 4 weeks (Days 1, 4, 8, 11, 15, 18, 22, and 25). This duration of repeated dosing is consistent with the timeframe in which standard antidepressants take to exert their action, and will allow for the evaluation of depression and assessment of suicide risk during this period of increased vulnerability. The same dosing regimen and duration of treatment was used in the Phase 2 study ESKETINSUI2001.

While Study ESKETINSUI2001 demonstrated a rapid onset of effect for esketamine in reducing the symptoms of depression and suicidality, it also suggested that continued dosing through Day 25 provided an additional therapeutic advantage. Indeed, esketamine showed greater improvement compared to placebo on the MADRS total score and on the MADRS-SI at the double-blind endpoint (Day 25).[16] This result was further supported by response rates (at least 50% improvement in MADRS total score from baseline) and remission rates (MADRS total score ≤12) on Day 25, 4 hours post dose. At that timepoint, 20 of 24 (83%) esketamine subjects, compared to 15 of 24 (63%) placebo subjects, were considered responders; similarly, 16 of 24 (67%) esketamine subjects, compared to 12 of 24 (50%) placebo subjects were considered remitters.[16] The improvements continued throughout the posttreatment follow-up phase; at

Day 81, remission rates were 63% in the esketamine group compared with 50% in the placebo group.[16]

The duration of follow-up in this study covers the period of greatest risk for recurrent suicidality post initial attempt and/or hospitalization.[12,15] Specifically, the follow-up after the 25-day treatment period is through Day 90 and will allow for the exploration of the continued effects of esketamine on depression and suicidal symptoms. No intranasal study medication will be administered during the follow-up phase. Subjects will be monitored twice weekly for the first two weeks (Days 28, 32, 35, and 39) after study drug treatment. Subjects will then be followed up weekly for the next two weeks (Days 46 and 53) and every two weeks for the rest of the follow-up period (Days 67 and 90). The MADRS and CGI-SS-R will be completed at each of these visits. Additionally, throughout the follow-up period, suicide attempts, hospital re-admissions for suicidality, and ER visits will be assessed.

The short-term treatment course of esketamine in subjects with MDD at imminent risk for suicide is expected to provide antidepressant efficacy during the interval needed for the newly initiated or optimized oral antidepressants to become effective.

3.2.3. Control, Randomization and Blinding

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 treatment.

Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Randomization will be stratified by study center and by the physician's assessment of the subject's need of standard of care antidepressant treatment (ie, antidepressant monotherapy or an antidepressant plus augmentation therapy); the standard of care will be determined prior to randomization on Day 1. This stratification is aimed at balancing treatment groups within the standard of care antidepressant treatment to be initiated or optimized on Day 1, as antidepressant monotherapy and antidepressant plus augmentation therapy may be differentially effective. A similar stratification approach was used successfully in Study ESKETINSUI2001.

Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints. Administration of esketamine, however, is associated with a number of transient adverse events, including sedation, dissociative symptoms, and elevation of blood pressure. To minimize the risk of unblinding the treatment assignment, different raters will perform efficacy and safety assessments; clinicians who perform the MADRS and SIBAT assessments will be different from those who evaluate vital signs, MOAA/S, CADSS, and adverse events. Raters for the MADRS and SIBAT assessments will not be allowed to access or to review subject safety records; therefore, they will not provide clinical care for subjects. Clinical care of subjects will be performed by clinicians at the study site who are not MADRS and SIBAT raters.

3.2.4. Dose

The currently available nonclinical safety studies support chronic intranasal administration of esketamine in human subjects up to a dose of 84 mg/day.[37] The treatment groups in the double-blind treatment phase of this study are esketamine 84 mg or placebo. The esketamine dose may be reduced at any time after the first dose to 56 mg for subsequent doses if a subject is unable to tolerate 84 mg. The same dosing regimen was used in the Phase 2 study ESKETINSUI2001.

The rationale for this dose selection is based on the fact that MDD with imminent risk for suicide is a psychiatric emergency requiring rapid and robust efficacy, and for which titration to an effective dose is not warranted. Study treatment will initially be administered in a hospital setting where any adverse effects can be closely monitored and managed. Finally, a course of treatment of esketamine for MDD with imminent risk for suicide is limited to 4 weeks.

Given the benefit-risk assessment of treatment for a life-threatening condition, the 84 mg dose of esketamine (with an option to reduce to the 56 mg dose) was selected to provide the greatest opportunity for rapid onset of efficacy and longer durability of activity, with acceptable tolerability, in the context of a psychiatric emergency.

Efficacy Findings Supporting the 84-mg Dose

Results from the Phase 2 placebo-controlled study ESKETINTSUI2001 provided evidence of efficacy of the esketamine 84 mg dose in MDD with imminent risk for suicide. At 4 hours and 24 hours after the first dose and at the double-blind endpoint (Day 25), esketamine 84 mg demonstrated a rapid and statistically significant reduction in symptoms of depression (based on MADRS total score) and suicidal ideation (based on the MADRS-SI score) compared to placebo (refer to Section 1.1.2.3 for details).Additionally, esketamine demonstrated evidence for a potential therapeutic effect based on the CGJ-SR, which summarized clinician overall judgment of suicide risk as derived from the SIBAT, at both 4 hours and 24 hours after the first dose.

Further support for the efficacy of the esketamine 84 mg dose comes from Panel A of the Phase 2 study ESKETINTRD2003 conducted in subjects with TRD; statistically significant reductions in the MADRS total score were observed in all esketamine groups (28, 56, 84 mg) compared with the placebo group after the first week of treatment, with a significant dose-response relationship detected (refer to Section 1.1.2.3 for details).[37] In addition, for those subjects in Panel A who received the same esketamine treatment for both periods and completed the double-blind phase, the greatest decrease in MADRS total score was seen with the 84-mg dose, followed by the 56-mg dose, whereas the 28 mg dose had the smallest decrease.[37]

Safety and Tolerability

The dosing regimen in this study has a provision for reducing the esketamine dose to 56 mg after Day 1 for subsequent doses if a subject is unable to tolerate the assigned esketamine 84 mg dose.

In ESKETINSUI2001, more subjects in the esketamine 84 mg group than in the placebo group received all 8 scheduled doses of the study medication, and mean treatment durations were similar in the esketamine 84 mg group and in the placebo group. Furthermore, only 3 of the

35 subjects included in the safety analysis set had esketamine dose reductions from 84 mg to 56 mg for intolerance. The most common (≥20%) TEAEs in the esketamine 84 mg group during the double-blind phase were nausea, dizziness, dysgeusia, headache, dissociation, and vomiting. The most common TEAE in the placebo group was headache. Dissociative symptoms, as measured on the CADSS, and transient blood pressure increases observed in the esketamine group were consistent with prior studies.

There were no deaths during Study ESKETINSUI2001. There were 4 SAEs in the double-blind phase, all in the esketamine 84 mg group. Three of these events were related to re-hospitalization of subjects with re-emergence of suicidal ideation (n=2) or depression (n=1) in subjects who had improved and had been discharged from the hospital. In all 3 instances, the subjects recovered and completed both the double-blind and follow-up phases. One subject experienced an event of increased agitation, and the study medication was withdrawn. Six subjects experienced an SAE in the follow-up phase (5 in the placebo group and 1 in the esketamine 84 mg group; see Section 1.1.2.4 for further details). The SAEs in the placebo group included 3 suicide attempts (non-fatal), 1 subject who experienced suicidal ideation, and 1 subject with cellulitis. The SAE in the subject from the esketamine group was suicidal ideation.

Six subjects (1 in the placebo group and 5 in the esketamine 84 mg group) discontinued from the double-blind phase due to TEAEs. In the esketamine group, events resulting in discontinuation were dizziness, dysgeusia, ventricular extrasystole, nausea and dyspnea, which were considered by the investigator to be probably or very likely related to study drug; and aggression and agitation, which were considered to be doubtfully and not related to study drug, respectively.

Overall, the safety profile of esketamine 84 mg in Study ESKETINSUI2001 was consistent with that observed in previous clinical studies of intranasal esketamine. No new safety signals were identified.

3.2.5. Efficacy Measures

3.2.5.1. Montgomery-Asberg Depression Rating Scale (MADRS)

The primary outcome measure in this study will be the MADRS (see Section 9.2.1). The MADRS is considered the gold standard to measure antidepressant treatment response and is acceptable to the regulatory health authorities for use as a primary endpoint to determine symptomatic improvement. Further, the MADRS is sensitive to rapid changes in depression symptoms and suicidal thoughts, and has been included as a key outcome parameter in published studies of ketamine for depression and suicidal ideation[5,25,47,63,70,71] as well as in the sponsor's Phase 2 studies of esketamine in MDD with imminent risk for suicide (ESKETINSUI2001) and in TRD (ESKETINTRD2003 and the Phase 3 studies of esketamine in TRD).

This study is primarily aimed at evaluating the rapid reduction of symptoms of MDD, including suicidal ideation, in subjects who are assessed to be at imminent risk for suicide. Accordingly, the primary efficacy endpoint is the change from baseline (Day 1 predose) in the MADRS total score at 24 hours post first dose. Although therapeutic activity is observed with esketamine as early as 4 hours after administration, it appears that the full benefit is evident after 24 hours, and

evaluation of the primary efficacy endpoint at 24 hours after the first dose is expected to reflect the timeframe needed for esketamine to exert its full antidepressant effect. This timepoint is relevant to current clinical practice as patients at imminent risk for suicide are typically hospitalized for at least 24 hours.

The MADRS also will be used to evaluate secondary objectives assessing the change from baseline in MADRS total score at 4 hours post first dose and through the end of the double-blind treatment phase and the remission rate at 4 hours and 24 hours post first dose and through the end of the double-blind treatment phase. In addition, the MADRS will be used to evaluate the exploratory objective assessing the change from baseline in MADRS total score and the remission rate through the end of the follow-up phase (Day 90).

3.2.5.2. Suicide Ideation and Behavior Assessment Tool (SIBAT)

The development of treatments with the potential for rapid onset of efficacy as measured by diminished severity of suicidal thinking and reduced clinical perception of risk for suicide has driven the need for scales that can reliably measure these attributes. However, these requirements correspond with specific deficits in existing suicide assessment scales. To address these unmet needs, a new instrument, the SIBAT, has been developed by a team of experts in suicide and psychometrics. The SIBAT is a suicide assessment tool that captures suicidal ideation and behavior(s) as reported by patients and reviewed by clinicians permitting efficient collection and documentation of clinical impression of severity of suicidality and imminent and long-term suicide risk and treatment plans (see Section 9.2.2).

The SIBAT is computerized and organized into 8 modules with branching logic to allow for efficient, comprehensive, and flexible data collection from a broad base of patients who may have a wide variety of demographic, cultural and demographic backgrounds. The 8 modules of the SIBAT are divided into patient-reported (Modules 1-5) and clinician-rated (Modules 6-8) sections. This modular structure allows for customization, and the administration of specific modules can be adjusted to meet clinical needs. Responses less susceptible to change (eg, demographics, medical history) are segregated into modules distinct from those responses more likely to fluctuate over shorter time intervals (eg, current suicidal ideation). In general, the patient-reported modules document information regarding the severity of suicidal ideation and risk and protective factors associated with suicide risk and specific suicidal behaviors. Information from the patient-reported modules, plus a brief semi-structured clinician interview in Module 6, represent a comprehensive profile for assessment of the Clinical Global Impressions in Module 7, which includes the Clinical Global Impression of Severity of Suicidality – Revised (CGI-SS-R), the Clinical Global Impression of Imminent Suicide Risk (CGI-SR-I), the Clinical Global Impression of Long-Term Suicide Risk, and assessment of the frequency of suicidal thinking. An assessment of the Clinical Global Judgment of Optimal Suicide Management is included in Module 8.

The SIBAT builds on prior work used to develop scales which are available for assessing suicidality; for example, the InterSePT Scale for Suicidal Thinking (ISST),[49] a 12-item instrument designed for the assessment of current suicidal ideation in patients with schizophrenia and schizoaffective disorders, and the Clinical Global Impression of Severity of Suicidality (CGI-SS). Module 7 (Clinical Global Impressions) of the SIBAT includes a revised version of the CGI-SS (CGI-SS-R), which will be used to evaluate the key secondary objective in this study (further details are provided below), as well as a Clinical Global Impression of Imminent Suicide Risk (CGI-SR-I), which will be used to evaluate secondary and exploratory objectives (further details are provided below). In addition, Question 3 (patient- reported frequency of suicidal thinking) in Module 5 (My Risk) from the SIBAT will be used to evaluate the secondary objective assessing patient-reported suicidality through the end of the double-blind treatment phase.

Formal testing of inter- and intra-rater reliability and assessments of construct validity and internal consistency are being conducted on the SIBAT.

Clinical Global Impression of Severity of Suicidality – Revised (CGI-SS-R)

The CGI-SS was initially created for the International Suicide Prevention Trial (InterSePT), a large-scale, long-term prospective study that evaluated the potential of clozapine and olanzapine to reduce suicidal behaviors in subjects with schizophrenia or schizoaffective disorder who are known to be at high risk for suicide. [1,49,53] The CGI-SS was derived from the Clinical Global Impression Severity Scale (CGI-S), a global rating scale that gives an overall measure of the severity of a patient's illness. The CGI-SS provided an index to quantify an expert's impression of severity of suicidality that helped to confirm the validity ISST.

A revised version of the CGI-SS (CGI-SS-R) will be used in this study (see Section 9.2.2). This revision is aligned with the standard CGI-S with which all clinicians are familiar, and has more severity levels than the original version, allowing for greater sensitivity.

The CGI-SS-R, assessed at 24 hours post initial dosing, will be used as the key secondary endpoint in this study. In addition, the CGI-SS-R will be used to evaluate secondary objectives assessing:

- Change in severity of suicidality at 4 hours postdose on Day 1 and through the end of the double-blind treatment phase
- Resolution of suicidality as measured by the score of 0 (normal, not at all suicidal) or 1 (questionably suicidal) of the CGI-SS-R at 4 hours postdose on Day 1, 24 hours postdose on Day 2, and through the end of the double-blind treatment phase

and exploratory objectives assessing:

- Change in severity of suicidality through the end of the follow-up phase

Clinical Global Impression of Imminent Suicide Risk (CGI-SR-I)

The CGI-SR-I is a scale summarizing the clinician's best assessment of the likelihood that the subject will attempt suicide in the next 7 days (see Section 9.2.2).

The CGI-SR-I will be used to evaluate secondary objectives assessing:

- Change in imminent suicide risk at 4 hours postdose on Day 1, 24 hours postdose on Day 2, and through the end of the double-blind treatment phase

and exploratory objectives assessing:

- Change in imminent suicide risk through the end of the follow-up phase

3.2.5.3. Beck Hopelessness Scale (BHS)

The Beck Hopelessness Scale (BHS) is a self-reported measure to assess the level of a subject's negative expectations or pessimism regarding the future, and as such, is an important future predictor of suicide. Further information about the BHS is provided in Section 9.2.3.

3.2.5.4. European Quality of Life (EuroQol) Group, 5-Dimension, 5-Level (EQ-5D-5L)

The EQ-5D-5L is included as a standardized subject-completed instrument for use as a measure of health-related quality of life and health status.[27,28] Further information about the EQ-5D-5L is provided in Section 9.2.4.

3.2.5.5. Quality of Life in Depression Scale (QLDS)

The QLDS is a disease-specific patient-reported outcome designed to assess health related quality of life in patients with MDD.[34,52,77] Further information about the QLDS is provided in Section 9.2.5.

3.2.5.6. Treatment Satisfaction Questionnaire for Medication (TSQM-9)

The TSQM-9 is a 9-item generic patient reported outcome instrument to assess patients' satisfaction with medication.[4] It is derived from the longer TSQM Version 1.4[11] and covers domains of effectiveness, convenience and global satisfaction. Further information about the TSQM-9 is provided in Section 9.2.6.

3.2.6. Safety Evaluations

Physical examination, nasal examination, body weight, vital signs (including measurement of blood pressure, heart rate, respiratory rate, and temperature), 12-lead ECG, pulse oximetry, clinical laboratory tests (hematology, chemistry, and urinalysis), pregnancy testing (for women of childbearing potential), urine drug screen, and evaluation of TEAEs and concomitant therapies will be performed during the study per the Time and Events Schedule to monitor subject safety.

The TEAEs of special interest will be examined separately grouped in the following categories: drug abuse, dependence and withdrawal, transient dizziness/vertigo, impaired cognition, anxiety, cystitis, and suicidality. The adverse events of special interest will be further listed in the Statistical Analysis Plan (SAP).

Given the potential for treatment-emergent transient elevation in systolic and diastolic blood pressure, heart rate and blood pressure will be monitored throughout the study and at multiple

time points on dosing days. Specific guidance to be followed on intranasal dosing days is provided in Section 6.1.1.

The MOAA/S will be administered to assess the severity and duration of any sedation, and the CADSS will be administered to assess treatment-emergent dissociative symptoms. Although the SIBAT will be an efficacy evaluation, it will also be used to inform safety evaluation to detect any worsening of suicidal ideation and behavior throughout the study.

On all outpatient intranasal dosing days, all subjects must remain at the clinical site until study procedures have been completed and the subject is ready for discharge per clinician's assessment. The minimum time required for postdose monitoring is 1.5 hours. Subjects should be accompanied when released from the clinical study site. Subjects must not drive a car or work with machines for 24 hours after receiving study drug.

A list of prohibited therapies is provided in Attachment 1 for general guidance for the investigator; however, this list is not all-inclusive.

3.2.7. Pharmacokinetic Assessments

Blood samples will be collected for measurement of plasma concentrations of esketamine, noresketamine, and other metabolites if warranted.

3.2.8. Biomarker, Pharmacogenomic (DNA), and Expression (RNA) Evaluations

Blood samples may be collected for the analysis of one or more candidate genes and/or the analysis of genetic and epigenetic markers as well as RNA expression markers. In addition, blood samples will be collected for the exploratory analysis of biomarkers related to immune system activity, HPA axis activation, neurotrophic and metabolic factors.

It is recognized that genetic variation can be an important contributory factor to interindividual differences in drug distribution and response and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain interindividual 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 to allow the identification of genetic and/or epigenetic factors that may influence the pharmacokinetics (PK), pharmacodynamics (PD), efficacy, safety, or tolerability of esketamine and to identify genetic factors associated with MDD and suicidality. Specifically, genes and epigenetic changes in genes known to be in pathways relevant to depression (HPA axis, inflammation, growth factors, monoamine transporters, ion channels, circadian rhythm) will be evaluated. Expression analyses may include testing of known messenger RNA/microRNA (mRNA/miRNA) transcripts or transcriptome-wide analysis in relationship to antidepressant treatment response and MDD.

Increasingly, it is recognized that psychiatric disorders may be associated with altered immune/metabolic activation patterns. Blood samples will be collected to explore biomarkers related to immune system activity, HPA axis activation, and neurotropic factors (including but not limited to growth factors, inflammation, or endocrine markers). Biomarker samples (plasma,

serum, and RNA) will be collected to evaluate the mechanism of action of esketamine or help to explain interindividual variability in clinical outcomes or may help to identify population subgroups that respond differently to a drug. In addition, biomarker samples may be combined with samples collected from other sources to understand the biomarker correlates of suicidal behavior including but not limited to high ideation state versus low ideation state versus no ideation and to understand the MDD disease mechanism.

The DNA, RNA, protein, and metabolic biomarker samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

3.2.9. Medical Resource Utilization

Treatment of subjects with MDD at immediate risk of suicide with esketamine versus placebo may result in lower utilization of services (ie, outpatient visits, ER visits or hospitalization) as assessed using the Heath Resource Use Questionnaire (HRUQ). The HRUQ includes information regarding utilization of healthcare services, including the timing of services, enabling changes in level and quantity of services to be considered as a variable in economic models.

4. SUBJECT POPULATION

Screening for eligible subjects should be performed within 48 hours prior to the first administration of intranasal study drug (if possible, screening should occur within 24 hours prior to the first administration of intranasal study drug).

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

4.1. Inclusion Criteria

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

1. Subject must be a man or woman, 18 to 64 years of age, inclusive.

2. Subject must meet Diagnostic and Statistical Manual of Mental Disorders (5th edition) (DSM-5) diagnostic criteria for MDD, without psychotic features, based upon clinical assessment and confirmed by the MINI.

3. Subjects must have current suicidal ideation with intent, confirmed by a “Yes” response to Question B3 [Think (even momentarily) about harming or of hurting or of injuring yourself: with at least some intent or awareness that you might die as a result; or think about suicide (ie, about killing yourself)?] AND Question B10 [Intend to act on thoughts of killing yourself?] obtained from the MINI. Note: the response to B3 must refer to the present, whereas the response to B10 may reflect the past 24 hours. If the screening period is longer than 24 hours, assessment of B3 and B10 of MINI must be repeated prior to randomization to confirm eligibility.

4. In the physician's opinion, acute psychiatric hospitalization is clinically warranted due to subject's imminent risk of suicide.

5. Subject has a MADRS total score of >28 predose on Day 1.

6. As part of standard of care treatment, subject agrees to be hospitalized voluntarily for a recommended period of 5 days after randomization (may be shorter or longer if clinically warranted in the investigator's opinion) and take prescribed non-investigational antidepressant therapy(ies) for at least the duration of the double-blind treatment phase (Day 25).

7. Subject is comfortable with self-administration of intranasal medication and able to follow instructions provided.

8. Subject must be medically stable on the basis of physical examination, medical history, vital signs, and 12-lead ECG performed at screening. If there are abnormalities, the subject may be included only if the investigator judges the abnormalities to be not clinically significant. This determination must be recorded in the subject's source documents and initialed by the investigator.

   Note: Subjects recovering from a recent suicide attempt may be eligible provided they are medically stable.

9. Subject must be medically stable on the basis of clinical laboratory tests performed by the local laboratory at screening. If the results of the serum chemistry panel, hematology, or urinalysis are outside the normal reference ranges, the subject may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant. This determination must be recorded in the subject's source documents and initialed by the investigator.

   - Incidental exclusionary laboratory values ("incidental" refers to duplicate results from a separate blood sample analyzed at the central laboratory that become available after the subject has satisfied the inclusion and exclusion criteria based on the local laboratory values) will be handled on a case-by-case basis to determine if the subject should be withdrawn from the study.

10. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for subject participating in clinical studies.

    Before randomization, a woman must be either:

    a. Not of childbearing potential defined as:

       - postmenopausal (>45 years of age with amenorrhea for at least 12 months), permanently sterilized (eg, bilateral tubal occlusion/ligation procedures, hysterectomy, bilateral salpingectomy, bilateral oophorectomy); or otherwise be incapable of pregnancy

b. Of childbearing potential and

- practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly)

  Examples of highly effective contraceptives include
  - user-independent methods:
    implantable progestogen-only hormone contraception associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); vasectomized partner; sexual abstinence (s*exual 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 drug. 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 subject.*)
  - user-dependent methods:
    combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, and transdermal; progestogen-only hormone contraception associated with inhibition of ovulation: oral and injectable

  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 subjects participating in clinical studies.

- agrees to use a highly effective method throughout the study and for at least 6 weeks after the last dose of study drug.

Note: If the childbearing potential changes after start of the study 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.

11. A woman of childbearing potential must have a negative urine pregnancy test at screening.

12. During the study (ie, from Day 1 of the double-blind phase) and for a minimum of 1 spermatogenesis cycle (defined as approximately 90 days) after receiving the last dose of study drug, a man who is sexually active with a woman of childbearing potential

- must be practicing a highly effective method of contraception with his female partner from those listed above (see examples of highly effective methods of contraception provided for female subjects).
- must use a condom if his partner is pregnant.
- must agree not to donate sperm.

Note: If the childbearing potential changes after start of the study, a female partner of a male study subject must begin a highly effective method of birth control, as described above.

13. Subject must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

14. Each subject must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and is willing to participate in the study.

    Note: Subjects with acute alcohol intoxication should not be screened (but can be screened once sober).

15. Each subject must sign a separate informed consent form if he or she agrees to provide an optional DNA sample for research (where local regulations permit). Refusal to give consent for the optional DNA research sample does not exclude a subject from participation in the study.

4.2. Exclusion Criteria

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

1. Subject has a current DSM-5 diagnosis of bipolar (or related disorders), antisocial personality disorder, or obsessive compulsive disorder.

2. Subject currently meets DSM-5 criteria for borderline personality disorder.

   – Subjects not meeting full DSM-5 criteria for borderline personality disorder but exhibiting recurrent suicidal gestures, threats, or self-mutilating behaviors should also be excluded.

3. Subject has a current clinical diagnosis of autism, dementia, or intellectual disability.

4. Subject has a current or prior DSM-5 diagnosis of a psychotic disorder, or MDD with psychotic features.

5. Criterion modified per Amendment 1

   5.1. Subject meets the DSM-5 severity criteria for moderate or severe substance or alcohol use disorder (except for nicotine or caffeine) within the 6 months before screening.

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

6. Criterion modified per Amendment 1

6.1. Subject has any of the following conditions:

- a history or current signs and symptoms of liver or renal insufficiency
- clinically significant cardiac (including unstable coronary artery disease and congestive heart failure, tachyarrhythmias and recent myocardial infarction) or vascular, pulmonary, gastrointestinal, endocrine (including uncontrolled hyperthyroidism), neurologic (including current or past history of seizures except uncomplicated childhood febrile seizures with no sequelae), hematologic, rheumatologic, or metabolic (including severe dehydration/hypovolemia) disease.

7. Criterion modified per Amendment 1

7.1. Subject has uncontrolled hypertension (systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg) despite diet, exercise or a stable dose of anti-hypertensive treatment for at least 2 weeks at screening; or any past history of hypertensive crisis.

- Subjects with conditions in which the elevation of blood pressure could be a serious risk (including unstable heart failure, severe cardiovascular disease, recent cerebral injury, increased intracranial pressure / intracranial mass lesion, intracranial bleeding or acute stroke, untreated glaucoma or perforating eye injury) are excluded.
- An abnormal blood pressure value at screening can be repeated once after 5 minutes of relaxation for subject eligibility. On Day 1 of the double-blind phase prior to randomization, a supine or semi-supine systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg is exclusionary.

8. Criterion modified per Amendment 1

8.1. Subject has a positive urine test result(s) for phencyclidine (PCP), cocaine, or amphetamines (inclusive of amphetamine, methamphetamine [mAMP], and 3, 4-methylenedioxy-methamphetamine [MDMA]) at screening.

- Subjects who have a positive test due to the appropriate use of prescribed opiates, benzodiazepines, or barbiturates may be eligible for study participation per clinician judgment. In addition, subjects who have a positive test for opiates, benzodiazepines, or barbiturates used without a prescription, may be considered eligible per clinician judgment and in consultation with the sponsor's medical monitor. Subjects known to be using heroin should be excluded from the study.
- Subjects who have a positive test due to opiates, benzodiazepines, or barbiturates taken in a suicide attempt (eg, overdose) may be eligible for study participation per clinician judgment and in consultation with the sponsor's medical monitor.

8.2 Criterion modified per Amendment 2

- Subjects, who have a positive test result at screening due to prescribed psychostimulants (eg. amphetamine, methylphenidate) that are permitted during the study in accordance with Attachment 1, are eligible for study participation.

9. Subject has a history of malignancy within 5 years before screening (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 to have minimal risk of recurrence).

10. Subject has any anatomical or medical condition that, per the investigator's clinical judgment based on assessment, may impede delivery or absorption of intranasal study drug.

11. Subject has known allergies, hypersensitivity, intolerance or contraindications to esketamine or ketamine or its excipients (refer to Investigator's Brochure for esketamine[37], Summary of Product Characteristics[42,45,78], US prescribing information[43,44]).

12. Subject has taken any disallowed therapy(ies) as noted in Section 8, Prestudy and Concomitant Therapy, and Attachment 1.

13. Criterion modified per Amendment 1

    13.1 Subject has received an investigational drug (including esketamine, ketamine, or investigational vaccines) or used an invasive investigational medical device within 60 days before the planned first dose of study drug or is currently enrolled in an investigational study or was previously enrolled in this study or the Sponsor's other studies in this population, 54135419SUI3001 and ESKETINSUI2001.

14. Subject is a woman who is pregnant, breast-feeding, or planning to become pregnant while enrolled in this study or within 3 months after the last dose of study drug.

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

16. Subject 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.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. Refer to Section 4.1, Inclusion Criteria, for information regarding contraception/birth control requirements and sperm donation restrictions.

2. On all outpatient intranasal dosing days, all subjects must remain at the clinical site until study procedures have been completed and the subject is ready for discharge per clinician's assessment. The minimum time required for postdose monitoring is 1.5 hours. Subjects should be accompanied when released from the clinical study site. Subjects must not drive a car or work with machines for 24 hours after study drug dosing.

3. Refer to Section 8, Prestudy and Concomitant Therapy and Attachment 1 (Prohibited Therapies) for information regarding prohibited therapies.

4. Subjects may not receive electroconvulsive therapy (ECT) during the study. ECT non-responders at imminent risk for suicide may be included in the study. If an investigator were to enroll a subject currently receiving ECT, the investigator would have to document why it is clinically appropriate to discontinue the ECT treatments, and to ensure that treatment is not changed for the purpose of making the subject eligible.

5. Food will be restricted for at least 2 hours before each administration of study medication.

6. Drinking of any fluids will be restricted at least 30 minutes before the first nasal spray on each dosing day.

7. Subjects should refrain from using alcohol within 24 hours before and after each intranasal treatment session. If a subject appears intoxicated, dosing should not occur (delayed per the permitted visit window; see the Time and Events Schedule).

8. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation and Randomization

Central randomization will be implemented in this study. Subjects will be randomly assigned to 1 of 2 treatment groups in a 1:1 ratio 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 center and by the physician's assessment of the subject's need of standard of care antidepressant treatment (ie, antidepressant monotherapy or an antidepressant plus augmentation therapy); the standard of care will be determined prior to randomization on Day 1. The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and

matching study drug kits for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject.

Blinding

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 subject.

Data that may potentially unblind the treatment assignment (eg, study drug plasma concentrations, treatment allocation) 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. To minimize the risk of unblinding the treatment assignment during the study, different raters will perform efficacy and safety assessments. Clinicians who perform MADRS and SIBAT will be different than those who evaluate vital signs, MOAA/S, CADSS, and adverse events. Raters for the MADRS and SIBAT assessment will not be allowed to access or to review subject safety records; therefore, they will not provide clinical care for subjects. Clinical care of subjects will be performed by clinicians at the study site who are not MADRS and CGI-SS-R/SIBAT raters. Adherence to this procedure will be monitored and enforced during the study.

Under normal circumstances, the blind should not be broken until all subjects have completed the study and the database is finalized. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may in an emergency determine the identity of the treatment by contacting the IWRS. 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 in the appropriate section of the electronic case report form (eCRF), and in the source document. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner.

Subjects who have had their treatment assignment unblinded should continue to return for scheduled early termination and follow-up contacts and visits.

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

To maintain the blinding of intranasal study medication, the esketamine and placebo intranasal devices will be indistinguishable. Please refer to Section 14 (Study Drug Information) for information on the physical characteristics of the study drugs and devices.

6. DOSAGE AND ADMINISTRATION

6.1. Intranasal Study Drug

All intranasal doses of study medication will be self-administered under the direct supervision of the investigator or designee. Instructions for use of the device will be provided as a separate document (see Section 15, Study-specific Materials). Details regarding study drug administration will be recorded in the source documents and the eCRF. On all intranasal treatment session days, a site staff member with training in cardiopulmonary resuscitation (eg, Basic Life Support course or equivalent course) that is up to date per local regulations must be present with the subject during the intranasal treatment session and the postdose observation period. In addition, equipment for supportive ventilation and resuscitation needs to be present. A physical description of the study drugs is provided in Section 14.1.

On Day 1, subjects will be randomized to treatment with either intranasal esketamine 84 mg or intranasal placebo, administered two times per week for 4 weeks. Intranasal treatment sessions should not take place on consecutive days.

Food will be restricted for at least 2 hours before each administration of study medication. Drinking of any fluids will be restricted at least 30 minutes before the first nasal spray on each dosing day. If the subject has nasal congestion on the dosing day, an intranasal decongestant can be used to reduce congestion, or with the exception of the Day 1 dose, the dosing day may be delayed (per the permitted visit window; see the Time and Events Schedule). If an intranasal decongestant is used to reduce congestion, it cannot be used within 1 hour prior to intranasal study drug dosing (see Attachment 1 for allowed intranasal decongestant).

The first dose of study medication will be administered in the ER or other permitted setting that has appropriate staffing to manage acutely suicidal subjects. If the first dose is administered in the ER, it is recommended that the subject not be transferred from the ER to the inpatient psychiatric unit after the 4-hour postdose assessments are completed. Subjects who have been admitted directly into the inpatient psychiatric unit due to imminent risk for suicide or transferred from a medical unit (following medical stabilization for recent suicide attempt) will receive their first dose of study medication in the inpatient psychiatric unit.

Subjects will remain in the inpatient psychiatry unit for a recommended duration of 5 days, with shorter or longer hospitalizations permitted if clinically warranted per local standard of care. Following discharge from the inpatient psychiatric unit, subsequent visits for the double-blind treatment phase will be conducted twice-weekly at an outpatient psychiatric facility through Day 25.

On all outpatient intranasal dosing days, all subjects must remain at the clinical site until study procedures have been completed and the subject is ready for discharge per clinician's assessment. The minimum time required for postdose monitoring is 1.5 hours. Subjects should be accompanied when released from the clinical study site. Subjects must not drive a car or work with machines for 24 hours after study drug dosing. Subjects should refrain from using alcohol within 24 hours before and after each intranasal treatment session. If a subject appears

intoxicated, dosing should not occur (delayed per the permitted visit window; see the Time and Events Schedule).

On each dosing day: Subjects will self-administer 1 spray into each nostril (ie, a total of 2 sprays using 1 intranasal device) at each of the following 3 time points: t = 0, 5 minutes and 10 minutes; time = 0 is defined as the time of the first 100-µL spray. Subjects will use a separate intranasal device at each of these 3 time points (ie, a total of 3 devices). Sprays to each nostril should be delivered in rapid succession at the scheduled time points. Table 1 describes how esketamine 84 mg or placebo will be administered in the double-blind treatment phase.

Table 1: Dose Administration of Esketamine 84 mg or Placebo

	Time of Intranasal Device Administration		
Intranasal Treatment	**0** [a]	**5 minutes**	**10 minutes**
Intranasal device [b]	1st	2nd	3rd
Placebo	1 spray of placebo to each nostril	1 spray of placebo to each nostril	1 spray of placebo to each nostril
Esketamine 84 mg	1 spray of esketamine to each nostril	1 spray of esketamine to each nostril	1 spray of esketamine to each nostril

[a] Time 0 is defined as the time of administration of the first intranasal spray to one nostril from the first intranasal device.
[b] One device will be used at each time point. Each individual intranasal device contains 2 sprays. The intranasal devices containing esketamine deliver 14 mg per spray, for a total of 28 mg per individual device (ie, 2 sprays).

After the first dose (ie, starting with the Day 4 dose or later), if required due to tolerability issues, a one-time dose reduction to intranasal esketamine 56 mg or intranasal placebo is allowed for subsequent doses. No further dose adjustment is allowed during the double-blind treatment phase. The subject would receive the decreased dose at all remaining dosing days.

Table 2 describes how esketamine 56 mg or placebo will be administered in the double-blind treatment phase.

Table 2: Dose Administration of Esketamine 56 mg or Placebo

	Time of Intranasal Device Administration		
Intranasal Treatment	**0** [a]	**5 minutes**	**10 minutes**
Intranasal device [b]	1st	2nd	3rd
Placebo	1 spray of placebo to each nostril	1 spray of placebo to each nostril	1 spray of placebo to each nostril
Esketamine 56 mg	1 spray of esketamine to each nostril	1 spray of esketamine to each nostril	1 spray of placebo to each nostril

[a] Time 0 is defined as the time of administration of the first intranasal spray to one nostril from the first intranasal device.
[b] One device will be used at each time point. Each individual intranasal device contains 2 sprays. The intranasal devices containing esketamine deliver 14 mg per spray, for a total of 28 mg per individual device (ie, 2 sprays).

6.1.1. Guidance on Blood Pressure Monitoring on Intranasal Treatment Session Days

Given the potential for treatment emergent transient elevation in systolic and diastolic blood pressure, the guidance shown in Table 3 should be followed on intranasal dosing days.

Table 3: Guidance for Blood Pressure Monitoring

Timing of blood pressure measurement	Thresholds for elevated blood pressure that require further guidance	Guidance for dosing, blood pressure monitoring, or follow-up assessment
Predose on Day 1	Refer to exclusion criterion #7 (Section 4.2)	• Refer to exclusion criterion #7 (Section 4.2).
Predose on any dosing day after Day 1	SBP: >140 mmHg and/or DBP: >90 mmHg	• Blood pressure measurement should be repeated after the subject rests in a supine or semi-supine position to confirm measurement. • If SBP and/or DBP remain higher than thresholds, dosing should be postponed and rescheduled on the following day or within the given visit window. • If blood pressure elevation persists at the next visit, the subject will be scheduled for a consultation by cardiologist, other specialist, or primary care physician prior to further dosing.
At any postdose timepoint on any dosing day	SBP: ≥180 mmHg but <200 mmHg and/or DBP: ≥110 mmHg but <120 mmHg	• Further intranasal dosing should be interrupted and the subject should be referred to a cardiologist, other specialist, or primary care physician for a follow-up assessment. • After the follow-up assessment, if recommended by the referring doctor and considered appropriate according to the clinical judgment for the subject to continue in the study, the subject may continue with intranasal dosing if the predose blood pressure at the next scheduled visit is within the acceptable range (see above).
At any postdose timepoint on any dosing day	SBP: ≥200 mmHg and/or DBP: ≥120 mmHg	• Subject must discontinue from further dosing. • Subject should be referred to a cardiologist, other specialist, or primary care physician for a follow-up assessment.
At 90 minutes postdose on any dosing day	SBP: ≥160 mmHg and/or DBP: ≥100 mmHg	• Blood pressure assessments should continue every 30 minutes until: o SBP is <160 mmHg and DBP is <100 mmHg, or o In the investigator's clinical judgment, the subject is clinically stable and can be discharged from the study site, or o The subject is referred for appropriate medical care, if clinically indicated.
At 120 minutes postdose on any dosing day	SBP: ≥180 mmHg and/or DBP: ≥120 mmHg	• The subject should be referred for immediate medical treatment.

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure

6.2. Standard of Care Antidepressant Treatment

All subjects will be treated in the context of comprehensive standard clinical care, including hospitalization and the initiation or optimization of antidepressant treatment, which will be determined by the treating physician(s) based on clinical judgment and practice guidelines. The standard of care antidepressant treatment (antidepressant monotherapy or antidepressant plus augmentation therapy) will be initiated or optimized for all subjects at the time of randomization on Day 1. Subjects who are on antidepressant monotherapy from Day 1 should remain on antidepressant monotherapy through the end of double-blind phase (Day 25) whereas subjects who are on antidepressant plus augmentation therapy from Day 1 will remain on antidepressants plus augmentation therapy through the end of double-blind phase (Day 25). Eligible subjects may or may not be receiving antidepressants at the time of study entry. Dose titration/adjustments of newly initiated or optimized standard of care antidepressant treatment should occur during the first 2 weeks of double-blind treatment (ie, by Day 15), with doses remaining stable thereafter through the end of the double-blind phase (Day 25). Subjects who are currently taking a recently initiated antidepressant treatment at screening (initiated <2 weeks prior) may continue taking the antidepressant at the current dose or at an optimized dose (dose adjustment is allowed during the first 2 weeks of double-blind treatment) through the end of the double-blind phase (Day 25), if deemed clinically appropriate by the investigator. During the double-blind treatment phase, the investigator needs to consult with the sponsor's medical monitor in advance if additional changes on antidepressant treatment are clinically indicated. During the follow-up phase, the antidepressant treatment will be managed based on the clinician's judgment.

7. TREATMENT COMPLIANCE

All doses of study medication will be self-administered under the direct supervision of the investigator or designee.

The investigator or designated study-site personnel will maintain a log of all study drug dispensed and returned. Drug supplies for each subject will be inventoried and accounted for throughout the study.

8. PRESTUDY AND CONCOMITANT THERAPY

Prestudy therapies administered up to 30 days before first dose of study drug should be recorded at screening. Concomitant therapies must be recorded throughout the study beginning with start of the first dose of study drug through the final visit. Concomitant therapies should also be recorded beyond this time only in conjunction with new or worsening adverse events, including serious adverse events that meet the criteria outlined in Section 12.3.2., Serious Adverse Events.

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) different from the study drug must be recorded in the eCRF. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a subject into the study.

A list of prohibited therapies is provided in Attachment 1 as general guidance for the investigator; please note, however, this list is not all inclusive. Please contact the study team to discuss any questions or concerns regarding any specific concomitant therapies for a subject. Subjects must also adhere to the list of prohibitions and restrictions provided in Section 4.3.

Subjects may not receive ECT during the study. ECT non-responders at imminent risk for suicide may be included in the study. If an investigator were to enroll a subject currently receiving ECT, the investigator would have to document why it is clinically appropriate to discontinue the ECT treatments, and to ensure that treatment is not changed for the purpose of making the subject eligible.

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

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule summarizes the frequency and timing of efficacy, PK, biomarker, pharmacogenomic/epigenetic, medical resource utilization, and safety measurements applicable to this study.

If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the sequence provided by the sponsor (see Section 9.1.3). Actual dates and times of assessments will be recorded in the source documentation and eCRF.

Additional 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 subject's participation in the study.

Additional drug tests may be performed as determined necessary by the investigator or required by local regulation.

Medical resource utilization data will be collected. Refer to Section 9.6, Medical Resource Utilization for details.

The total blood volume to be collected from each subject will be approximately 141 mL (see Table 4).

Table 4: Approximate Volume of Blood to be Collected From Each Subject

Type of Sample	Volume (mL) per sample	Number of Samples per Subject	Total Volume of Blood (mL)[a]
Screening Phase			
Serum chemistry	2.5	2 (1 local, 1 central) [b]	5
Hematology	2	2 (1 local, 1 central) [b]	4
Approximate total blood volume for screening phase			9
Double-Blind Treatment Phase			
Serum chemistry	2.5	1	2.5
Hematology	2	1	2
Pharmacokinetic evaluation	2	6	12
Blood for biomarker evaluation	30 [c]	3	90
Blood for RNA biomarker evaluation	2.5	3	7.5
Approximate total blood volume for double-blind treatment phase with biomarker samples			114
Pharmacogenomic/epigenetic evaluation [d]	6	3	18
Approximate total blood volume for double-blind treatment phase with biomarker and pharmacogenomic/epigenetic samples			132
Approximate total blood volume for study			**141 mL**

[a] Calculated as number of samples multiplied by amount of blood per sample.
[b] At screening, 2 samples will be collected for analysis – 1 sample each for the local laboratory (to have results prior to Day 1 dose) and the central laboratory (see Section 9.7 for further details).
[c] Blood volume for biomarker samples represents volume of several tubes combined.
[d] Blood sample(s) will be collected only from subjects who have consented to provide an optional sample for genetic research.

Note: If desired, an indwelling intravenous cannula may be used for blood sample collection.

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

9.1.2. Screening Phase

Prior to conducting any study procedure, the investigator (or designated study personnel) will review and explain the written ICF to each potential subject with MDD presenting to an ER or other permitted setting and assessed to be at imminent risk for suicide.

After signing the ICF, potential subjects will be screened under close supervision within 48 hours of intranasal dosing on Day 1 to determine eligibility for study participation (if possible, potential subjects should be screened within 24 hours of intranasal dosing on Day 1). Subjects who have recently attempted suicide and are currently hospitalized for medical stabilization and continue to be at imminent risk for suicide, or subjects who have been admitted directly into the inpatient psychiatric unit due to imminent risk for suicide, may also be screened to determine eligibility.

Subjects must meet DSM-5 diagnostic criteria for MDD, without psychotic features, based upon clinical assessment and confirmed by the MINI. In addition, the subject must have a MADRS total score of >28 predose on Day 1, and in the physician's opinion, acute psychiatric hospitalization is clinically warranted due to the subject's imminent risk of suicide. Refer to Section 4 (Subject Population) for all inclusion and exclusion criteria that will be used to

determine subject eligibility. Eligible subjects may or may not be receiving antidepressants at the time of study entry.

Refer to the Time and Events Schedule for a complete list of study procedures that will be performed at screening.

The clinician-administered assessments at screening can be performed in the order preferred by the clinical site: MINI, Question B3 and B10 from MINI (current status). If the screening phase is longer than 24 hours, Question B3 and B10 from MINI (current status) must be repeated prior to randomization to confirm eligibility.

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure (which may include contact for follow-up of safety).

9.1.3. Double-Blind Treatment Phase

Following completion of all required screening procedures and confirmation of subject eligibility, subjects will enter the double-blind treatment phase.

On Day 1 of the double-blind treatment phase, approximately 224 subjects will be randomly assigned to 1 of 2 treatment groups in a 1:1 ratio (approximately 112 subjects per group): intranasal esketamine 84 mg or intranasal placebo. Study drug will be administered two times per week for 4 weeks (Days 1, 4, 8, 11, 15, 18, 22, and 25). Intranasal treatment sessions should not take place on consecutive days.

Subjects will be admitted to and receive the first dose of study medication in the ER or other permitted setting; for example, subjects who have been admitted directly into the inpatient psychiatric unit due to imminent risk for suicide or transferred from a medical unit (following medical stabilization for recent suicide attempt) will receive their first dose of study medication in the inpatient psychiatric unit. If the first dose is administered in the ER, it is recommended that subjects not be transferred from the ER to the inpatient psychiatric unit until after the postdose assessments are completed (approximately 4 hours after study drug administration). Prior to the first intranasal dose on Day 1, subjects will practice spraying (into the air, not intranasally) a demonstration intranasal device that is filled with placebo solution. All subjects will self-administer the study medication under the direct supervision of the investigator or designee (Refer to Section 6, Dosage and Administration).

All subjects will be treated in the context of comprehensive standard clinical care, including hospitalization and the initiation or optimization of antidepressant treatment (antidepressant monotherapy or antidepressant plus augmentation therapy). On Day 1, all subjects will begin standard of care treatment and will continue, at least, this treatment through the duration of the double-blind treatment phase. The standard of care will be determined by the treating physician(s) based on clinical judgment and local practice at the time of randomization on Day 1. Any changes to the standard of care treatment, that is different from what was planned at the time of randomization, should be clearly documented including the reason for the change.

The 4-hour assessments at the Day 1 visit should be performed within ±30 minutes of the 4-hour postdose time point. The 24-hour assessments at the Day 2 visit should be performed ±2 hours of the 24-hour postdose time point.

Subjects will remain in the inpatient psychiatry unit for a recommended duration of 5 days, with shorter or longer hospitalizations permitted if clinically warranted per local standard of care. The discharge decision will be made based upon the investigator's judgment that the subject is no longer imminently suicidal and meets standard discharge criteria per local practice. Discharge before 5 days must be discussed and approved by the sponsor's medical monitor. The investigator must discuss the need for continued hospitalization beyond 10 days and thereafter on a weekly basis with the sponsor's medical monitor. Following discharge from the inpatient psychiatric unit, subsequent visits for the double-blind treatment phase will be conducted twice-weekly at an outpatient psychiatric facility through Day 25.

Dose titration/adjustments of newly initiated or optimized standard of care antidepressant treatment should occur during the first 2 weeks of double-blind treatment (ie, by Day 15), with doses remaining stable thereafter through the end of the double-blind phase (Day 25). Subjects who are currently taking a recently initiated antidepressant treatment at screening (initiated <2 weeks prior) may continue taking the antidepressant at the current dose or at an optimized dose (dose adjustment is allowed during the first 2 weeks of double-blind treatment) through the end of the double-blind phase (Day 25), if deemed clinically appropriate by the investigator. The investigator needs to consult with the sponsor's medical monitor in advance if additional changes to antidepressant treatment are clinically indicated.

On all outpatient intranasal dosing days, all subjects must remain at the clinical site until study procedures have been completed and the subject is ready for discharge per clinician's assessment. The minimum time required for postdose monitoring is 1.5 hours. Subjects should be accompanied when released from the clinical study site. Subjects must not drive a car or work with machines for 24 hours after study drug dose administration.

Efficacy, safety, pharmacokinetic, biomarker, pharmacogenomics, and medical resource utilization evaluations will be performed as described in the Time and Events Schedule. When multiple patient-reported outcomes and clinician-administered assessments are scheduled for the predose time point it is recommended they be performed in the following sequence:

- SIBAT
- MADRS
- Patient-reported outcomes: BHS, QLDS, EQ-5D-5L, and TSQM-9

Clinicians who perform the MADRS and SIBAT assessments will be different from those who evaluate vital signs, MOAA/S, CADSS, and adverse events.

Subjects and site staff will complete the clinician-administered assessments and patient-reported outcomes using an electronic tablet device provided for this study or using a paper version (refer to Section 15, Study-Specific Materials).

Early Withdrawal

Subjects who discontinue from the double-blind treatment phase prior to completion of the Day 25 visit will have an Early Termination visit conducted at the time of discontinuation. Subjects who discontinue with reasons other than withdrawal of consent, lost to follow up, or death will be contacted remotely at 3 days after the last dose of intranasal study medication (if the date of the Early Termination visit is less than 3 days after the last dose of intranasal study medication), on Day 25, and on Day 90 for MADRS assessment and adverse event collection. For information obtained via telephone contact, written documentation of the communication must be available for review in the source documents. During telephone contact visits with the subject by site personnel, adverse event information will be obtained, and MADRS assessment will be performed by appropriately qualified staff. In addition, the investigator must ensure the subject is appropriately transitioned/followed for any additional care required.

9.1.4. Posttreatment Phase (Follow-Up)

During the follow-up phase, subjects will be monitored twice weekly for the first two weeks (Days 28, 32, 35, and 39) after study drug treatment. Subjects will then be followed up weekly for the next two weeks (Days 46 and 53) and every two weeks for the rest of the follow-up period (Days 67 and 90).

During the follow-up phase, the antidepressant treatment will be managed based on the clinician's judgment.

Efficacy, safety, and medical resource utilization evaluations will be performed as described in the Time and Events Schedule. When multiple patient-reported outcomes and clinician-administered assessments are scheduled for the same time point it is recommended they be performed in the following sequence:

- SIBAT
- MADRS
- Patient-reported outcomes: BHS, QLDS, EQ-5D-5L, and TSQM-9

Clinicians who perform the MADRS and SIBAT assessments will be different from those who evaluate vital signs, and adverse events.

Subjects and site staff will complete the clinician-administered assessments and patient-reported outcomes electronically using a device provided for this study or using a paper version (refer to Section 15, Study-Specific Materials).

Any clinically significant abnormalities persisting at the end of the study will be followed by the investigator until resolution or until a clinically stable endpoint is reached. All adverse events and special reporting situations, whether serious or non-serious, will be reported until completion of the subject's last study-related procedure (which may include contact for follow-up of safety).

Early Withdrawal

Subjects who discontinue from the follow-up phase prior to completion of the Day 90 visit will have an Early Termination visit conducted at the time of discontinuation. Subjects who discontinue with reasons other than withdrawal of consent, lost to follow up, or death will be contacted remotely on Day 90 for MADRS assessment and adverse event collection. For information obtained via telephone contact, written documentation of the communication must be available for review in the source documents. During telephone contact visits with the subject by site personnel, adverse event information will be obtained, and MADRS assessment will be performed by appropriately qualified staff. In addition, the investigator must ensure the subject is appropriately transitioned/followed for any additional care required.

9.2. Efficacy Evaluations

9.2.1. Montgomery-Asberg Depression Rating Scale

The primary efficacy evaluation will be the MADRS total score. The MADRS will be performed using the Structured Interview Guide for the Montgomery Asberg Depression Rating Scale.[81]

The MADRS is a clinician-rated scale designed to be used in subjects with MDD to measure depression severity and detect changes due to antidepressant treatment.[54,55] The test 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, interest level, pessimistic thoughts, and suicidal thoughts. The test exhibits high inter-rater reliability.

The typical recall period for the MADRS is 7 days. In this study, the MADRS will also be administered using a since last assessment recall, a 4-hour recall on Day 1 and Day 25 postdose, and a 24-hour recall on Day 2. For the MADRS performed at 4 hours postdose on Days 1 and 25, the MADRS scores for the sleep item recorded predose on the same day will be carried forward.

Whenever possible, all efforts should be made to use the same raters for the MADRS at each site to assess the same subjects throughout the study. If this is not possible, review of the appropriate prior assessments and communication with prior raters should be conducted as needed.

9.2.2. Suicide Ideation and Behavior Assessment Tool

The SIBAT has two major divisions: a patient-rated section and a clinician-rated section. The patient-rated section has modules of demographics and suicide history, risk/protective factors, suicidal thinking, suicide behavior, and suicide risk. The information generated in this section will be summarized and used to support the clinical decision-making of the second section. The clinician-rated section has modules for semi-structured interview, clinical global impressions of current severity of suicidality and imminent suicide risk, clinical global impression of long-term suicide risk, and clinical judgment of optimal suicide management.

The SIBAT will be provided in an electronic format for use by the subject and study staff during the study. Refer to the SIBAT Time and Events Schedule for an outline of which modules will be performed at each scheduled time point.

One module of the SIBAT includes a revised version of the Clinical Global Impression – Severity of Suicidality. The CGI-SS-R rating is scored on a 7-point scale from 0 (normal, not at all suicidal) to 6 (among the most extremely suicidal patients) and will be based on the totality of information available to the clinician, including information from the SIBAT. The CGI-SS-R summarizes the clinician's overall impression of severity of suicidality and will be used to assess the key secondary endpoint in this study (see Section 2.1.2). This rating operates like numerous other CGI-severity scales that have been used in other psychiatric studies. These instruments have shown clinical validity and sensitivity to change.

The CGI-SR-I summarizes the clinician's best assessment of the likelihood that a patient will attempt suicide in the next 7 days.

Whenever possible, all efforts should be made to use the same raters for the SIBAT at each site to assess the same subjects throughout the study. If this is not possible, review of the appropriate prior assessments and communication with prior raters should be conducted as needed.

9.2.3. Beck Hopelessness Scale

The BHS is a self-reported measure to assess one's level of negative expectations or pessimism regarding the future. It consists of 20 true-false items that examine the respondent's attitude over the past week by either endorsing a pessimistic statement or denying an optimistic statement; 9 are keyed false and 11 are keyed true. These items fall within 3 domains: (1) feelings about the future; (2) loss of motivation; and (3) future expectations. For every statement, each response is assigned a score of 0 or 1. The total BHS score is a sum of item responses and can range from 0 to 20, with a higher score representing a higher level of hopelessness. Total scores that range from 0 to 3 are considered within the normal range, scores 4 to 8 identify mild hopelessness, scores 9 to 14 identify moderate hopelessness, and scores greater than 14 identify severe hopelessness.

BHS scores of ≥9 have been found to be predictive of eventual suicide in depressed suicide ideators who were followed for 5-10 years after discharge from a hospital.[8] Among a group of 72 subjects with single-episode MDD, the scale was found to have a high degree of internal consistency (0.92); the same value of internal consistency was found among a group of 134 subjects with recurrent-episode MDD.[9] Among a group of hospitalized MDD subjects, the scale showed a relatively high correlation with clinical ratings of hopelessness and other self-administered measures of hopelessness. Test-retest scores of 0.69 and 0.66 have been reported.[9] The scale has been found to have concurrent and discriminant validity among subjects with MDD.[9] Further, the scale was found to be sensitive to change in the subject's state of depression over time.[10] The measure is designed for use in adults aged 17 to 80 years and takes 5 to 10 minutes to complete. A scoring manual and scoring platform is available from the licensee holder.

The BHS will be administered using a recall period of the last 7 days.

9.2.4. EuroQol 5-Dimension 5-Level

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome, primarily designed for self-completion by respondents. It consists of the EQ-5D-5L descriptive system and the EQ visual analogue scale (EQ-VAS). The EQ-5D-5L descriptive system comprises the following 5 dimensions: Mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each of the 5 dimensions is divided into 5 levels of perceived problems (Level 1 indicating no problem, Level 2 indicating slight problems, Level 3 indicating moderate problems, Level 4 indicating severe problems, and Level 5 indicating extreme problems).[27,28]

The subject selects an answer for each of the 5 dimensions considering the response that best matches his or her health "today." The descriptive system can be represented as a health state. The EQ-VAS self-rating records the respondent's own assessment of his or her overall health status at the time of completion, on a scale of 0 to 100.

The time taken to complete the questionnaire varies with age, health status, and setting but is likely to be approximately 1 minute.

9.2.5. Quality of Life in Depression Scale

The QLDS is a disease specific patient-reported outcome designed to assess health related quality of life in patients with MDD, ie, it captures the impact of depression and its treatment from the patient's perspective.[34,52,77] The instrument has a recall period of "at the moment", contains 34-items with "yes"/"no" or "true"/"not true" response options and takes approximately 5-10 minutes to complete. The score range is from 0 (good quality of life) to 34 (very poor quality of life). It has been shown to have acceptable psychometric properties and sensitivity to change.

9.2.6. Treatment Satisfaction Questionnaires for Medication

The Treatment Satisfaction Questionnaire for Medication (TSQM-9)[4] is a 9-item generic patient reported outcome instrument to assess patients' satisfaction with medication. It is derived from the longer TSQM Version 1.4[11] and covers domains of effectiveness, convenience and global satisfaction. The instrument is scored by domain with scores ranging from 0-100 where a lower score indicates lower satisfaction. The recall period is "the last 2-3 weeks". It takes approximately 5 minutes to complete.

9.3. Pharmacokinetics

Whole blood samples will be used to evaluate the PK of esketamine. Plasma collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these plasma samples. Subject confidentiality will be maintained.

9.3.1. Evaluations

Venous blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of esketamine, noresketamine, and other metabolites if warranted at the time points specified in the Time and Events Schedule. The exact dates and times and pharmacokinetic blood sampling must be recorded.

9.3.2. Analytical Procedures

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

If required, some plasma samples may be analyzed to document the presence of 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.

9.3.3. Pharmacokinetic Parameters

The plasma concentration-time data of esketamine (and noresketamine, if warranted) will be analyzed using population PK modeling. If conducted, the results of population PK analyses may be reported separately.

9.4. Pharmacokinetic/Pharmacodynamic Evaluations

The relationship between MADRS total score (and possibly selected adverse events and additional pharmacodynamic parameters), and PK metrics of esketamine may be evaluated. The results of such analyses may be reported separately.

9.5. Biomarker and Pharmacogenomic (DNA) Evaluations

Biomarker Evaluations

Blood samples will be collected as indicated in the Time and Events Schedule for exploratory analysis of biomarkers (protein, metabolites, and RNA) related to immune system activity, HPA axis activation, neurotrophic and metabolic factors. Exploratory analyses may be performed for additional biomarkers as well. Results may be presented in a separate biomarkers report.

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 on Day 1 (predose) and Day 25 when blood samples for biomarker analysis are collected.

Pharmacogenomic Evaluations

Subject participation in pharmacogenomic/epigenetic evaluations is optional. A whole blood sample for DNA analyses will be collected from all subjects who provide consent for pharmacogenomic research at the time points indicated in the Time and Events Schedule.

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

DNA 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 and epigenetic markers throughout the genome (as appropriate) in relation to esketamine or MDD clinical endpoints.

9.6. Medical Resource Utilization

Medical resource utilization data, associated with medical encounters, will be collected using the Healthcare Resource Use Questionnaire (HRUQ) on an ongoing basis whenever an encounter occurs and will be reviewed as indicated in the Time and Events Schedule. The HRUQ includes information regarding utilization of healthcare services (including the timing and type of serves), enabling changes in level and quantity of services to be considered as a variable in economic models.

9.7. Safety Evaluations

Details regarding the Independent Data Monitoring Committee are provided in Section 11.9.

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

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 endpoint is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Time and Events Schedule:

Adverse Events

Adverse events will be reported by the subject for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

The TEAEs of special interest will be examined separately (refer to Sections 3.2.6 and 11.8 for further details).

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology and a random urine sample for urinalysis will be collected. 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 eCRF. The laboratory reports must be filed with the source documents.

A local laboratory will be used at screening to ensure results are available in enough time to determine subject eligibility. If standard of care clinical laboratory tests are performed within 24 hours prior to the screening visit (ie, signing of the ICF), results for those laboratory tests

required per protocol at screening can be used for determination of subject eligibility. In this situation, following signing of the ICF, sample(s) for the local laboratory are not required, but sample(s) must be obtained and sent to the central laboratory (see below). A local laboratory can also be used in any instance where safety follow up is time-critical and the central laboratory results are not expected to be available before actions need to be taken for safety reasons.

A central laboratory will be used at screening and during the study.

The following tests will be performed:

- Hematology Panel

  -hemoglobin
  -hematocrit
  -red blood cell (RBC) count
  -white blood cell (WBC) count with differential
  -platelet count

- Serum Chemistry Panel

  -sodium
  -potassium
  -chloride
  -bicarbonate
  -blood urea nitrogen (BUN)
  -creatinine
  -glucose
  -aspartate aminotransferase (AST)
  -alanine aminotransferase (ALT)
  -gamma-glutamyltransferase (GGT)
  -total bilirubin
  -alkaline phosphatase
  -creatine phosphokinase (CPK)
  -lactic acid dehydrogenase (LDH)
  -uric acid
  -calcium
  - phosphate
  -albumin
  -total protein

- Urinalysis

  Dipstick
  -specific gravity
  -pH
  -glucose
  -protein
  -blood
  -ketones
  -bilirubin
  -urobilinogen
  -nitrite
  -leukocyte esterase

  Sediment (if dipstick result is abnormal)
  -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.

Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, and urobilinogen will be determined using a dipstick. Red blood cells, white blood cells, epithelial cells, crystals, casts, and bacteria will be measured using flow cytometry. If there is discordance between the dipstick results and the flow cytometric results, the sediment will be examined microscopically.

The following additional clinical laboratory assessments will be performed on-site:

- Urine Pregnancy Testing (for women of childbearing potential only)
- Urine Drug Screen - barbiturates, opiates, cocaine, PCP, amphetamines, and benzodiazepines

Electrocardiogram (ECG)

A single, 12-lead ECG will be performed at each time point specified in the Time and Events Schedule.

During the collection of ECGs, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine or semi-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 sub-investigator is required to review all ECGs at the study visit to assess for any potential safety concerns or evidence exclusionary conditions prior to dosing.

At screening, the ECG tracing will be sent to the central ECG laboratory but the investigator or sub-investigator is also required to review the ECG locally to determine subject eligibility.

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

Vital signs will be performed per the Time and Events Schedule. Blood pressure and pulse/heart rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

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 monitoring, please see Guidance on Blood Pressure Monitoring on Intranasal Treatment Session Days (Section 6.1.1).

Tympanic temperature is recommended. The method used for obtaining temperature should be documented.

Physical Examination, Body Weight, and Height

Physical examinations and measurement of body weight and height will be performed per the Time and Events Schedule.

Nasal Examination

Targeted nasal examinations (including the upper respiratory tract/throat) will be conducted per the Time and Events Schedule. The objective of the examination at screening is to rule out any subjects with anatomical or medical conditions that may impede drug delivery or absorption.

Subsequent examination will consist of a visual inspection of the nostrils, nasal mucosa, and throat for nasal erythema, rhinorrhea, rhinitis, capillary/blood vessel disruption and epistaxis and will be graded as follows: none, mild, moderate, or severe.

Dosing Day Assessments

Pulse Oximetry

Pulse oximetry will be used to measure arterial oxygen saturation (SpO_2). On each dosing day, the device will be attached to the finger, toe, or ear, and SpO_2 will be monitored and documented every 15 minutes from predose to 1.5 hours postdose. If oxygen saturation levels are <93% at any time during the 1.5 hour postdose interval, pulse oximetry will be recorded every 5 minutes until levels return to ≥93% or until the subject is referred for appropriate medical care, if clinically indicated.

Modified Observer's Assessment of Alertness/Sedation (MOAA/S)

The MOAA/S will be used to measure treatment-emergent sedation with correlation to levels of sedation defined by the American Society of Anesthesiologists (ASA) continuum.[67] The MOAA/S scores range from 0 (no response to painful stimulus; ASA continuum = general anesthesia) to 5 (readily responds to name spoken in normal tone [awake]; ASA continuum = minimal sedation).

On each intranasal dosing day, the MOAA/S will be performed every 15 minutes from predose to 1.5 hours postdose.

If the score is ≤3 at any time during the 90 minute postdose interval, the MOAA/S will be performed every 5 minutes until a score of 4 is reached (at which point a frequency of every 15 minutes can be resumed until t = 90 minutes postdose).

If a subject does not have a score of at least 5 at t = 90 minutes postdose, the subject should continue to be monitored. For subjects with a score of 4, the assessment should be repeated every 15 minutes. And for subjects with a score of ≤3, the assessment should be repeated every 5 minutes until the score returns to 5 or the subject is referred for appropriate medical care, if clinically indicated.

Clinician-Administered Dissociative States Scale (CADSS)

The CADSS is an instrument for the measurement of present-state dissociative symptoms[14] and will be administered to assess treatment-emergent dissociative symptoms. On each dosing day, the CADSS will be performed predose, and at 40 minutes and 1.5 hours postdose.

The CADSS consists of 23 subjective items, divided into 3 components: depersonalization (items 3 to 7, 20, and 23), derealization (items 1, 2, 8 to 13, 16 to 19, and 21) and amnesia (items 14, 15, and 22). The subject's responses are coded on a 5-point scale (from 0=not at all to 4=extremely). The CADSS has excellent inter-rater reliability and internal consistency.

If any CADSS items are scored zero at 40 minutes, these items will not need to be repeated at 1.5 hours postdose.

9.8. Other Evaluations

Mini-International Neuropsychiatric Interview (MINI)

The MINI is a short, structured diagnostic interview developed for the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) psychiatric disorders. It has an administration time of approximately 15 to 30 minutes and provides an accurate structured psychiatric interview for multicenter clinical trials. The MINI is used to confirm the diagnosis of MDD with current suicidal ideation and to determine if there are other psychiatric conditions present.

Questions B3 and B10 from the MINI

Current suicidal ideation with intent will be evaluated at screening using Question B3 (*Think [even momentarily] about harming or of hurting or of injuring yourself: with at least some intent or awareness that you might die as a result; or think about suicide [ie, about killing yourself]*?) and Question B10 (*Intend to act on thoughts of killing yourself?*) from the MINI. Subjects will be asked to answer these questions (Yes or No) relative to their current status. The response to B3 must refer to the present, whereas the response to B10 may reflect the past 24 hours. If the screening phase is longer than 24 hours, Question B3 and B10 from MINI (current status) must be repeated prior to randomization to confirm eligibility.

9.9. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or 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 (USP) (or equivalent) and charged with a volume equal to the dead space volume of the lock.

Refer to the Time and Events Schedule 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.

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY TREATMENT/ WITHDRAWAL FROM THE STUDY

10.1. Completion

A subject will be considered to have completed treatment if he or she has completed assessments up to and including Day 25 of the double-blind treatment phase. Subjects who prematurely discontinue study treatment for any reason before completion of the double-blind phase will not be considered to have completed the study treatment.

A subject will be considered to have completed the study if he or she has completed assessments up to and including Day 90.

10.2. Discontinuation of Study Treatment/Withdrawal From the Study

Discontinuation of Study Treatment During the Double-blind Phase

A subject will not be automatically withdrawn from the study if he or she has to discontinue treatment before the end of the double-blind treatment phase.

A subject's study treatment will be discontinued for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Death
- Lack of efficacy, per the investigator's judgment
- The investigator believes that for safety reasons or tolerability reasons (eg, adverse event or worsening of underlying condition) it is in the best interest of the subject to discontinue study treatment
- The subject becomes pregnant during the double-blind treatment phase
- Blind is broken
- Violation of protocol procedures, per the investigator's judgment and in consultation with the sponsor
- Change in the in-patient hospitalization status from voluntary to involuntary as a result of a judicial or other legal administrative order

If a subject discontinues study treatment for any reason other than lost to follow up, death, or withdrawal of consent before the end of the double-blind treatment phase, an Early Termination visit will be conducted at the time of discontinuation and the subject will be contacted remotely at 3 days after the last dose of intranasal study medication (if the date of the Early Termination visit is less than 3 days after the last dose of intranasal study medication), on Day 25 and on Day 90 for MADRS assessment and adverse event collection. No further planned assessments will be conducted. In addition, the investigator must ensure the subject is appropriately transitioned and/or followed for any additional care required.

Withdrawal From the Study During the Follow-up Phase

A subject will be withdrawn from the study during the follow-up phase for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Death
- Violation of protocol procedures, per the investigator's judgment and in consultation with the sponsor

If a subject withdraws from the study after the double-blind phase but before the end of the follow-up phase for reasons other than lost to follow up, death, or withdrawal of consent, an Early Termination visit will be conducted at the time of discontinuation and the subject will be contacted remotely on Day 90 for MADRS assessment and adverse event collection. No further planned assessments will be conducted. In addition, the investigator must ensure the subject is appropriately transitioned and/or followed for any additional care required.

If a subject is lost to follow up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. This should include at least 3 telephone calls, certified letters, email requests, etc. To ensure access to follow-up subjects, the study sites should attempt to obtain both primary and secondary telephone contact numbers (eg, home, work, and mobile phone numbers) as well as other contact information (eg, email addresses) from subjects before randomization. In addition, the study site should emphasize the importance of follow-up information to the subject before randomization. The measures taken to follow up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced.

Withdrawal of Consent

Every effort will be made in the study to ensure withdrawal of consent is not selected as a reason for discontinuation when in fact the subject withdrew for an identifiable reason (eg, due to an adverse event or lack of efficacy).

Subjects who wish to withdraw from the study should be asked if they are agreeable to continue to an Early Termination visit and to be contacted remotely to collect follow-up information at 3 days after the last dose of intranasal study medication (if the subject discontinued during the double-blind phase and the date of the Early Termination visit is less than 3 days after the last dose of intranasal study medication), on Day 25 (if the subject discontinued during the double-blind phase) and on Day 90. Subjects who are not agreeable to remote follow-up contact will be withdrawn from the study as "withdrawal of consent." Subjects who no longer wish to take study drug but agree to provide follow-up information will be withdrawn from the double-blind phase with the reason noted as "Other" and will specify the reason why.

For a subject who withdraws consent, it is recommended that the subject withdraw consent in writing; if the subject refuses or is physically unavailable, the study site should document and sign the reason for the subject's failure to withdraw consent in writing and maintain it with the subject's source records.

The investigator will be responsible for making all required notifications to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

10.3. Withdrawal From the Use of Research Samples

A subject who withdraws from the study will have the following options regarding the optional research sample:

- The collected sample will be retained and used in accordance with the subject's original separate informed consent for optional research samples.
- The subject may withdraw consent for optional research sample, in which case the sample 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 optional 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 sample has been destroyed.

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

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

Withdrawal From the Use of Samples in Future Research

The subject may withdraw consent for use of samples for research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). 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 and in the separate ICF for optional research samples.

11. STATISTICAL METHODS

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 SAP.

11.1. Subject Information

The primary efficacy and safety analysis sets are defined below.

- Full analysis set: The full analysis set will include all randomized subjects who have received at least one dose of double-blind study medication and have both a baseline and a post dose evaluation for the MADRS total score.

- Safety analysis set: The safety analysis set will include all randomized subjects who receive at least one dose of double-blind study medication.

11.2. Sample Size Determination

The maximum sample size for this study was calculated assuming an effect size of 0.45 for the MADRS total score at 24 hours post first dose (Day 2), a one-sided significance level of 0.025, and a drop-out rate at 24 hours of 5%. Approximately 112 subjects will need to be randomized to each treatment group to achieve 90% power. The effect size used in this calculation was based on results of the ESKETINSUI2001 study where the effect size for the change from baseline to Day 2 was 0.65 (mean difference between treatment groups of -7.2 and a pooled SD of 11.02) for MADRS total score. Given that the ESKETINSUI2001 study was a Phase 2 study carried out in only one country, the maximum sample size for this Phase 3 study was determined using a smaller effect size of 0.45 to allow for greater variability that can be expected for a study conducted globally.

11.3. Efficacy Analyses

Primary Estimand

The primary estimand, the main clinical quantity of interest to be estimated in the study, is defined by the following 3 components:

- Population: subjects with MDD who are at imminent risk of suicide
- Endpoint: change from baseline to 24 hours post first dose (Day 2) in the MADRS total score
- Measure of Intervention: the effect of the initially randomized treatment that would have been observed had all subjects remained on their treatment until Day 2 of the double-blind phase.

The primary analysis will be based on the full analysis set and the MADRS total scores collected at Day 2.

Primary Efficacy Endpoint

The primary efficacy variable, change from baseline in MADRS total score at 24 hours post first dose (Day 2), will be analyzed using an analysis of covariance (ANCOVA) model. The model will include factors for treatment, center, standard of care antidepressant treatment (ie, antidepressant monotherapy or an antidepressant plus augmentation therapy), and baseline MADRS total score as a covariate. A point estimate and 95% confidence interval for the treatment difference will be provided. Since subjects are hospitalized at the time of the primary endpoint, it is anticipated that missing data will be infrequent. However, if a subject has a MADRS total score at a time earlier than 24 hours post first dose but does not have the 24 hour value, the earlier value will be used for the primary efficacy analysis. In addition, descriptive statistics (N, mean, standard deviation, median, minimum and maximum) of the primary efficacy variable will be provided by study center.

Secondary Efficacy Endpoints

The analysis of the key secondary efficacy endpoint, change from baseline for CGI-SS-R at 24 hours post first dose (Day 2), will be performed using an ANCOVA model on the ranks of change with factors for treatment, center, standard of care antidepressant treatment (ie, antidepressant monotherapy or an antidepressant plus augmentation therapy) and baseline CGI-SS-R (unranked) as a covariate. The treatment difference will be estimated using the Hodges-Lehmann estimate, which is the median of all possible paired differences for the change from baseline for CGI-SS-R at 24 hours.

The multiplicity with regard to testing multiple endpoints (the primary and the key secondary) will be controlled by a fixed sequence testing procedure, ie, the key secondary hypothesis will be tested only after the null hypothesis for the primary endpoint is rejected.

The secondary efficacy endpoints, proportion of subjects with remission (MADRS total score ≤12) and the proportion of subjects achieving resolution of suicidality (CGI-SS-R score of 0 or 1) at each visit during the double-blind phase will be analyzed using a Cochran-Mantel-Haenszel chi-square test adjusting for center and standard of care antidepressant treatment (ie, antidepressant monotherapy or antidepressant plus augmentation therapy). Subjects who discontinue treatment prior to the particular visit of the double-blind phase will not be considered to have remission or resolution of suicidality.

Changes from baseline over time in MADRS total score, BHS, and QLDS total scores will be analyzed based on last observation carried forward (LOCF) data using an ANCOVA model with treatment, center, and standard of care antidepressant treatment (ie, antidepressant monotherapy or an antidepressant plus augmentation therapy) as factors and baseline value as a covariate. Additionally, the change from baseline in MADRS total score at Day 25 will be analyzed using a mixed model for repeated measures (MMRM) analysis with baseline MADRS total score as a covariate, and treatment, center, standard of care antidepressant treatment (ie, antidepressant monotherapy or antidepressant plus augmentation therapy), day, and day-by-treatment interaction as fixed effects, and a random subject effect. Comparison of esketamine versus placebo will be performed using the appropriate contrast. Point estimates and 95% confidence intervals for the treatment differences will be provided. Missing data will be closely monitored and additional sensitivity analyses will be specified in the SAP, if necessary.

Ranks of changes from baseline over time for CGI-SS-R and CGI-SR-I will be analyzed based on LOCF data using an ANCOVA model with treatment, center, and standard of care antidepressant treatment (ie, antidepressant monotherapy or an antidepressant plus augmentation therapy) as factors and baseline value (unranked) as a covariate.

SIBAT Module 5 My Risk, Question 3 (patient reported frequency of suicidal thinking), TSQM-9, dimension scores of EQ-5D-5L data, and health status index will be summarized over time.

Additionally, scores of all efficacy endpoints will be summarized for all visits. Descriptive statistics (N, mean, standard deviation, median, minimum and maximum) will be provided for continuous variables and frequency distributions will be provided for categorical variables.

Details regarding the other secondary and exploratory analyses will be provided in the Statistical Analysis Plan.

11.4. Pharmacokinetic Analyses

Plasma esketamine and noresketamine concentrations will be listed for all subjects. All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. All subjects and samples excluded from the analysis will be clearly documented in the study report.

Population PK analysis of plasma concentration-time data of esketamine may be performed using nonlinear mixed-effects modeling. Data may be combined with those of other selected studies to support a relevant structural model. Available baseline subject characteristics (demographics, laboratory variables, genotypes, race, etc.) will be tested as potential covariates affecting PK parameters. For the parameter estimates, the standard error and 95% confidence interval will be provided. This will be determined after the population pharmacokinetic modeling of the data is completed. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report.

11.5. Pharmacokinetic/Pharmacodynamic Analyses

The relationship between MADRS total score (and possibly selected adverse events and additional pharmacodynamic parameters), and PK metrics of esketamine may be evaluated. The results of the PK/PD analyses may be reported separately.

11.6. Biomarker and Pharmacogenomic Analyses

Biomarkers will be tabulated by treatment and summary statistics will be calculated. Posttreatment changes in biomarkers over time will be summarized by treatment group. Associations between baseline levels and changes from baseline in selected biomarkers and clinical endpoints will be explored. Exploratory analyses may include comparison of biomarker measures between the treatment groups and correlation with baseline and change from baseline biomarker values in the efficacy and other measures. Exploratory analyses may be performed for additional biomarkers. In addition, all biomarker data obtained from this study may also be included in an ongoing cross-study analysis to investigate the relationship between depression severity, phenotypes, and biomarkers.

Pharmacogenomic analyses may include candidate gene analyses or genome-wide association analyses in relation to treatment response, non-response, and MDD. Expression analyses may include testing of known mRNA/miRNA transcripts or transcriptome-wide analysis in relationship to antidepressant treatment response and MDD. Additional exploratory analyses may be performed.

Details of the analysis plan and summary of results from both biomarker and pharmacogenomic analyses will be reported separately.

11.7. Medical Resource Utilization Analyses

Medical resource utilization data will be descriptively summarized by treatment group.

11.8. Safety Analyses

Safety data will be analyzed for the double-blind phase using the safety analysis set. The safety data from the follow-up phase will be summarized separately.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported adverse events with onset during each 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 subjects 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 (refer to Section 3.2.6 for further details); adverse events of special interest will be further listed in the SAP. Subjects who die, who discontinue treatment due to an adverse event, or who experience a serious adverse event will be summarized separately.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Markedly abnormal results (specified in the SAP) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be provided. A listing of subjects with any markedly abnormal laboratory results will also be provided.

Electrocardiogram (ECG)

The effects on cardiovascular variables will be evaluated by means of descriptive statistics and frequency tabulations. These tables will include observed values and changes from baseline values.

Electrocardiogram data will be summarized by ECG parameter. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

The ECG variables that will be analyzed are heart rate, PR interval, QRS interval, QT interval, and corrected QT (QTc) interval using the following correction methods: QT corrected according to Bazett's formula (QTcB), QT corrected according to Fridericia's formula (QTcF). [6,33,36,74]

Descriptive statistics of QTc intervals and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with QTc interval >450 milliseconds,

>480 milliseconds, or >500 milliseconds will be summarized, as will the percentage of subjects with QTc interval increases from baseline >30 milliseconds or >60 milliseconds.

All clinically relevant abnormalities in ECG waveform that are changes from the baseline readings will be reported (eg, changes in T-wave morphology or the occurrence of U-waves.

Vital Signs, Pulse Oximetry and Body Weight

Descriptive statistics of temperature, pulse/heart rate, respiratory rate, pulse oximetry measurements, 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 subjects with values beyond clinically important limits will be summarized.

Nasal Examination

Abnormalities observed during the targeted nasal examinations at screening and post-baseline will be summarized and listed by treatment group.

MOAA/S and CADSS

Sedation data from the MOAA/S and dissociative symptoms data from the CADSS will be summarized descriptively at each scheduled visit by treatment group.

11.9. Independent Data Monitoring Committee

An external Independent Data Monitoring Committee will be established to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study. The committee will meet every 6 months to review safety data. After the reviews, the IDMC will make recommendations regarding the continuation of the study. The details will be provided in a separate IDMC charter.

The IDMC will consist of at least one medical expert in the relevant therapeutic area and at least one statistician. The IDMC responsibilities, authorities, and procedures will be documented in its charter.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, 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.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. 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 Section 12.3.1, All Adverse Events, 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 subject 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 subject 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 drug 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 Investigator's Brochure.

Adverse Event Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2, Attribution Definitions.

12.1.2. Attribution Definitions

Not Related

An adverse event that is not related to the use of the drug.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. 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 subject (eg, laboratory abnormalities).

12.2. Special Reporting Situations

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

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Accidental or occupational exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)
- Exposure to a sponsor study drug from breastfeeding

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

12.3. Procedures

12.3.1. All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure, which may include contact for follow-up of safety, with the exception of pregnancy which will be reported up to 6 weeks after the last dose of study medication (females) or 90 days after the last dose of study medication (partners of male subjects). Serious adverse events, including those spontaneously reported to the investigator from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure, 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.

All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments. Anticipated events will be recorded and reported as described in Attachment 2.

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the eCRF. 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 eCRF 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.

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 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.

For all studies with an outpatient phase, including open-label studies, the subject 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 subject 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 staff only)
- Site number
- Subject number
- Any other information that is required to do an emergency breaking of the blind

12.3.2. 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, which must be completed and signed 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 made by facsimile (fax).

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject'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 drug or to factors unrelated to study conduct

- It becomes unlikely that any additional information can be obtained (subject 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 subject's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Inpatient hospitalizations that extend beyond the protocol-recommended 5 days (not due to adverse event, ie, clinical worsening)
- 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 eCRF). 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 subject in a study from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure, whether or not the event is expected or associated with the study drug, is considered a serious adverse event.

12.3.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects 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 subject who becomes pregnant during the study must promptly discontinue further study treatment.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported as noted above.

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

12.4. 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.

13. 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 subjects, 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.

13.1. 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 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. 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.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

The esketamine supplied for this study is available as a clear, colorless intranasal solution of esketamine hydrochloride (16.14% weight/volume [w/v]; equivalent to 14% w/v of esketamine base) in a nasal spray pump. The solution will consist of 161.4 mg/mL esketamine hydrochloride (equivalent to 140 mg of esketamine base) formulated in 0.12 mg/mL EDTA and 1.5 mg/mL citric acid at pH of 4.5. It is provided in a nasal spray pump, which delivers 16.14 mg esketamine hydrochloride (14 mg esketamine base) per 100 µL spray. Each individual nasal spray pump (device) contains a total of 28 mg (ie, 2 sprays).

The placebo solution will be provided as a clear, colorless intranasal solution of water for injection with a bittering agent (denatonium benzoate [Bitrex®] at a final concentration of 0.001 mg/mL) added to simulate the taste of the intranasal solution with active drug. The placebo solution will be provided in matching nasal spray pump devices. Benzalkonium chloride is added as a preservative at a concentration of 0.3 mg/mL. Each individual nasal spray pump (device) contains 2 sprays.

Study drug will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a list of excipients.[37]

14.2. Packaging

Study drug (ie, intranasal esketamine and placebo solution) will be supplied by the sponsor in a bi-dose nasal spray device. The devices will contain 230 µL (of which ~30 µL is the residual volume). Each device delivers 16.14 mg esketamine hydrochloride (14 mg esketamine base) or 0.1 µg of denatonium benzoate per 100 µL spray.

Each nasal spray device will be individually packaged in a blister tray and subsequently put into a carton box. Each carton box constitutes a non-child-resistant subject kit, labeled with a unique medication kit number.

Device for Practicing Intranasal Study Drug Administration

The demonstration intranasal device will also be supplied by the sponsor and will contain placebo solution. Subjects will practice spraying into the air and will not spray intranasally.

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements.

14.4. Preparation, Handling, and Storage

Study drug will be stored at the study site in a secure area with restricted access until dispensed to the subjects.

All study drug must be stored at controlled temperatures as indicated on the product specific labeling.

Refer to the pharmacy manual/study site investigational product and procedures manual for additional guidance on study drug preparation, handling, and storage.

14.5. Drug Accountability

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

Study drug 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 under appropriate environmental conditions. Unused study drug, and study drug returned by the subject, 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 drug, or used returned study drug for destruction, will be documented on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator's Brochure for esketamine
- Pharmacy manual/study site investigational product and procedures manual
- Study medication “Instructions for Use” documents for subject and clinical site staff
- Practice/demonstration intranasal devices and ancillary supplies
- Central laboratory manual and materials
- ECG manuals and materials
- Clinician-administered and subject-completed/patient-reported outcome assessments
  - Paper versions if applicable
  - Electronic devices and associated materials
- IWRS Manual
- Electronic data capture (eDC) manual
- Information for clinician regarding dosing, switching, and augmenting antidepressant treatments
- Guidance for minimum requirements for site staff and equipment on dosing days
- Study awareness and support materials (ie, to facilitate subject identification and retention)

Any updates to these documents that occur during the study will also be provided.

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Clinical Study in Subjects with MDD Assessed to be at Imminent Risk of Suicide

Major depressive disorder is the most prevalent mental health condition and the psychiatric diagnosis most commonly associated with suicide.[41,65]Epidemiology studies suggest that nearly

60% of those who die by suicide suffer from affective disorders, and at least one-half of people who complete suicide are depressed at the time of their deaths.[2,13,17,51]

There is no approved treatment for patients with MDD assessed to be at imminent risk for suicide. The current standard of care is hospitalization and initiation or optimization of treatment with antidepressant medication.

Pilot studies in subjects with MDD or bipolar depression suggest that ketamine may have a significant effect on reducing suicidal ideation within hours of administration.[25,47,71,72,85] Furthermore, a Phase 2 study (ESKETINSUI2001) recently completed by the sponsor suggested that intranasal esketamine rapidly reduced symptoms of depression and suicidality in subjects with MDD at imminent risk for suicide and that intranasal esketamine was tolerated in this population.

Selection of Subjects

The primary aim of the study is to evaluate the efficacy of intranasal esketamine for the rapid reduction of the symptoms of major depressive disorder, including suicidal ideation, in subjects assessed to be at imminent risk for suicide. Thus, the study cannot be completed in healthy subjects or depressed patients who are not at imminent risk for suicide.

While a patient's decisional capacity can be impacted by severe depression and suicidality, this becomes an ethical concern when the patient refuses medically necessary treatment. However, the subjects in this trial will be providing voluntary consent to participate in the study of a potentially efficacious treatment, given in the context of standard of care treatment (ie, hospitalization and antidepressant treatment). Subjects may participate in the study only if they have adequate capacity to give consent and after fully understanding the potential risks, benefits, and potential adverse events of the study. Determination of a subject's decisional capacity will be made by the study investigator. Thus, ethical concerns regarding subjects' decision to participate are minimal.

Justification for Using Placebo

Assessment of the potential efficacy of a new compound for the treatment of major depression requires adequate and well-controlled clinical studies. As there are no approved treatments for the rapid reduction of symptoms of MDD, including suicidal ideation, a placebo controlled study conducted in the context of comprehensive standard of care treatment (ie, acute psychiatric hospitalization, the initiation of optimization standard of care antidepressant treatment, and close outpatient follow up) is ethically appropriate. Subjects will remain hospitalized for a recommended period of 5 days, which is consistent with the typical length of stay for MDD patients who are hospitalized due to imminent risk of suicide, and may stay shorter or longer if clinically warranted.

Precautions to Ensure Subject Safety in the Study

Subjects 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. Determination of

capacity will be made by the study investigator. Subjects may discontinue the study at any time. The probability of receiving placebo and the concept of random assignment will be explained to the subject. Potential disadvantages and adverse events of participating in the study and alternative treatment options will be discussed.

Importantly, the study will be conducted in the context of standard clinical care, including hospitalization the initiation or optimization of antidepressant treatment, and close outpatient follow up. Subjects will remain hospitalized for a recommended period of 5 days, which is consistent with the typical length of stay for MDD patients who are hospitalized due to imminent risk of suicide, and may stay longer if clinically warranted. Subjects will receive standard of care antidepressant treatment beginning on Day 1.

For subjects who do not respond during the study and are not willing or able to receive additional study drug treatment, clinical care will be arranged between the study investigator and or their physician.

Compensation for any procedure will be fair per local standards and approved by the IECs/IRBs for participating sites in order to not offer any undue incentive to participate in the study.

The investigator will ensure that subjects who withdraw from the study prior to completion are appropriately followed and/or transitioned for any additional care required.

Only qualified and experienced investigators will participate in the study.

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects 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 subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study and will be less than a Red Cross blood donation.[3]

16.2. Regulatory Ethics Compliance

16.2.1. 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 subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of

study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. 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 subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects 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 subjects
- 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 subjects, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and subject 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.

Approval for the collection of optional samples for research and for the corresponding ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda

- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

16.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. 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 subject 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 subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects 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 subject will receive for the treatment of his or her disease. Finally, they will be told that the investigator will maintain a subject 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 subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorizing such access, which includes permission to obtain information about his or her survival status. It

also denotes that the subject agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The subject 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 subject's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

Subjects will be asked for consent to provide optional samples for research (where local regulations permit). After informed consent for the study is appropriately obtained, the subject will be asked to sign and personally date a separate ICF indicating agreement to participate in the optional research component. Refusal to participate in the optional research will not result in ineligibility for the study. A copy of this signed ICF will be given to the subject.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects 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 subjects confidential.

The informed consent obtained from the subject 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 subject 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, biomarker, and PK research is not conducted under standards appropriate for the return of data to subjects. 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 subjects 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.

16.2.5. 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 depression, to understand differential drug responders, and to develop tests/assays related to esketamine and depression. 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. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.3, Withdrawal From the Use of Samples in Future Research.

16.2.6. 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 16.1, Study-Specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. 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 subjects, 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) involves 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 eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. 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.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug 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, subject 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 subject:

- 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

17.3. Subject Identification, Enrollment, and Screening Logs

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

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

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: subject 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; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug 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 minimum source documentation requirements for Section 4.1, Inclusion Criteria and Section 4.2, 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 subject interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An electronic source 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 the electronic source system is utilized, references made to the eCRF in the protocol include the electronic source system but information collected through the electronic source system may not be limited to that found in the eCRF. Data in this system may be considered source documentation.

17.5. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each subject in electronic format. All eCRF 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 eCRF are accurate and correct.

Electronic data capture (eDC) will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an eCRF, and transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the study site. The electronic file will be considered to be the eCRF.

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

All subjective measurements (eg, scale information or other questionnaires) should be completed by the same individual who made the initial baseline determinations whenever possible.

The investigator must verify that all data entries in the eCRFs are accurate and correct. All eCRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. If corrections to a eCRF are needed after the initial entry into the eCRF, 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.

17.6. 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, 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 eCRF completion will be provided and reviewed with study-site personnel before the start of the study.

The sponsor will review eCRF 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.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each subject, 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.

17.8. Monitoring

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 data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records); a sample may be reviewed. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF 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.

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The study is considered completed with the last study assessment for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. 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 subjects by the investigator
- Discontinuation of further study drug development

17.10. 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. Subject 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.

17.11. Use of Information and Publication

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. 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 subject 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 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 substudy 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 12 months of the availability of the final data (tables, listings, graphs), 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 Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

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.

REFERENCES

1. Alphs L, Anand R, Islam MZ, et al. The international suicide prevention trial (InterSePT): rationale and design of a trial comparing the relative ability of clozapine and olanzapine to reduce suicidal behavior in schizophrenia and schizoaffective patients. Schizophr Bull. 2004;30 (3):577-586.
2. American Association of Suicidology. Depression and suicide risk 2014. http://www.suicidology.org/Portals/14/docs/Resources/FactSheets/2011/DepressionSuicide2014.pdf (accessed 7 September 2016).
3. American Red Cross. Blood Facts and Statistics. http://www.redcrossblood.org/learn-about-blood/blood-facts-and-statistics (accessed 7 December 2016).
4. Atkinson MJ, Sinha A, Hass SL, et al. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. Health Qual Life Outcomes. 2004 Feb 26;2(1):12.
5. Ballard ED, Luckenbaugh DA, Richards EM, et al. Assessing measures of suicidal ideation in clinical trials with a rapid-acting antidepressant. J Psychiatr Res. 2015;68:68-73.
6. Bazett HC. An analysis of the time-relationship of electrocardiograms. Heart. 1920;7:353-380.
7. Beardsley PM, Balster RL. Behavioral dependence upon phencyclidine and ketamine in the rat. J Pharmacol Exp Ther. 1987;242:203-211.
8. Beck AT, Steer RA, Kovacs M, Garrison B. Hopelessness and eventual suicide: a 10-year prospective study of patients hospitalized with suicidal ideation. Am J Psychiatry. 1985;142(5):559-563.
9. Beck AT, Steer RA. Beck Hopelessness Scale Manual. 1993 Edition.
10. Beck AT, Weissman A, Lester D, Trexler L. The measurement of pessimism: the hopelessness scale. J Consult Clin Psychol. 1974; 42: 861-5.
11. Bharmal M, Payne K, Atkinson MJ, Desrosiers MP, Morisky DE, Gemmen E. Validation of an abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) among patients on antihypertensive medications. Health Qual Life Outcomes. 2009;7:36.
12. Bickley H, Hunt IM, Windfuhr K, Shaw J, Appleby L, Kapur N. Suicide within two weeks of discharge from psychiatric inpatient care: a case-control study. Psychiatr Serv. 2013;64(7):653-659.
13. Borges G, Nock MK, Haro Abad JM, et al. Twelve-month prevalence of and risk factors for suicide attempts in the World Health Organization World Mental Health Surveys. J Clin Psychiatry. 2010 Dec; 71(12):1617-1628.
14. Bremner JD, Krystal JH, Putnam FW, Southwick SM, Marmar C, Charney DS, Mazure CM. Measurement of dissociative states with the Clinician-Administered Dissociative States Scale (CADSS). J Trauma Stress. 1998;11(1):125-136.
15. Brent DA, Greenhill LL, Compton S, et al. The Treatment of Adolescent Suicide Attempters study (TASA): predictors of suicidal events in an open treatment trial. J Am Acad Child Adolesc Psychiatry. 2009;48(10):987-996.
16. Briefing Book, JNJ-54135419-AAC (esketamine hydrochloride). Esketamine for Rapid Reduction of Symptoms of Major Depressive Disorder, including Suicidality, in Patients who are Assessed to be at Imminent Risk for Suicide (25 Aug 2016).
17. Cavanagh JT, Carson AJ, Sharpe M, Lawrie SM. Psychological autopsy studies of suicide: a systematic review. Psychol Med. 2003 Apr; 33(3):395-405. Addendum in: Psychol Med. 2003 Jul; 33(5):947.
18. Chang T, Savory A, Albin M, Goulet R, Glasko AJ. Metabolic disposition of tritium-labelled ketamine (Ketalar®, CI-581) in normal human subjects. Clin Res. 1970;18:597.
19. Clinical Study Report ESKETINTRD2003. A Double-Blind, Doubly-Randomized, Placebo-Controlled Study of Intranasal Esketamine in an Adaptive Treatment Protocol to Assess Safety and Efficacy in Treatment-Resistant Depression (29 Apr 2016).

20. Collins GT, Woods JH. Drug and reinforcement history as determinants of the response-maintaining effects of quinpirole in the rat. J Pharmacol Exp Ther. 2007;323:599-605.

21. Collins RJ, Weeks JR, Cooper MM, Good PI, Russell RR. Prediction of abuse liability of drugs using IV self-administration by rats. Psychopharmacology. 1984;82:6-13.

22. Critchlow DG. A case of ketamine dependence with discontinuation symptoms. Addiction. 2006;101:1212-1213.

23. Curran HV, Morgan C. Cognitive, dissociative and psychotogenic effects of ketamine in recreational users on the night of drug use and 3 days later. Addiction. 2000;95:575-590.

24. Deisenhammer EA, Ing CM, Strauss R, Kemmler G, Hinterhuber H, Weiss EM. The duration of the suicidal process: how much time is left for intervention between consideration and accomplishment of a suicide attempt? J Clin Psychiatry. 2009; 70(1):19-24.

25. DiazGranados N, Ibrahim LA, Brutsche NE, et al. Rapid resolution of suicidal ideation after a single infusion of an *N*-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. J Clin Psychiatry. 2010; 7 1(12):1605-1611.

26. Duman RS, Aghajanian GK. Synaptic dysfunction in depression: potential therapeutic targets. Science. 2012;338:68-72.

27. EuroQol Group. About EQ-5D. http://www.euroqol.org/about-eq-5d.html (accessed 15 September 2016).

28. EuroQol Group. EQ-5D-5L User Guide: basic information on how to use the EQ-5D-5L instrument. Version 2.1; Apr 2015. http://www.euroqol.org/fileadmin/user_upload/Documenten/PDF/Folders_Flyers/EQ-5D-5L_UserGuide_2015.pdf (accessed 15 September 2016).

29. Geisslinger G, Hering W, Thomann P, Knoll R, Kamp H-D, Brune K. Pharmacokinetics and pharmacodynamics of ketamine enantiomers in surgical patients using a stereoselective analytical method. Br J Anaesth. 1993;70:666-671.

30. Haas DA, Harper DG. Ketamine: a review of its pharmacologic properties and use in ambulatory anesthesia. Anesth Prog. 1992;39:61-68.

31. Hagelberg NM, Peltoniemi MA, Saari TI, et al. Clarithromycin, a potent inhibitor of CYP3A, greatly increases exposure to oral S-ketamine. Eur J Pain. 2010;14:625-629.

32. Hijazi Y, Boulieu R. Contribution of CYP3A4, CYP2B6, and CYP2C9 isoforms to *N*-demethylation of ketamine in human liver microsomes. Drug Metab Dispos. 2002;30:853-858.

33. Hodges M, Salerno D, Erlien D. Bazett's QT correction reviewed: evidence that a linear QT correction for heart rate is better. J Am Coll Cardiol. 1983;1:694.

34. Hunt SM, McKenna SP. The QLDS: a scale for the measurement of quality of life in depression. Health Policy. 1992 Oct;22(3):307-319.

35. Hurt PH, Ritchie EC. A case of ketamine dependence. Am J Psychiatry. 1994;151:779.

36. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonized Tripartite Guideline E14: Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. ICH 12 May 2005.

37. Investigator's Brochure, JNJ-54135419-AAC (esketamine hydrochloride) (29 Feb 2016).

38. Ionescu DF, Swee MB, Pavone KJ, et al. Rapid and Sustained Reductions in Current Suicidal Ideation Following Repeated Doses of Intravenous Ketamine: Secondary Analysis of an Open-Label Study. J Clin Psychiatry. 2016 Jun;77(6):e719-725.

39. Jansen KL. Ketamine--can chronic use impair memory? Int J Addict. 1990;25:133-139.

40. Jick H, Kaye JA, Jick SS. Antidepressants and the risk of suicidal behaviors. JAMA. 2004;292:338-343.

41. Kessler RC, Berglund P, Borges G, et al. Trends in suicide ideation, plans, gestures, and attempts in the United States, 1990-1992 to 2001-2003. JAMA. 2005 May 25; 293(20):2487-2495.

42. Ketalar 10 mg/mL solution for injection/infusion: Summary of Product Characteristics; Aug 2014. Pfizer Healthcare Ireland, Dublin, Ireland.

43. Ketalar® (ketamine hydrochloride injection, USP) [United States Prescribing Information]. JHP Pharmaceuticals, LLC; March 2012.

44. Ketamine HCl Injection: US Prescribing Information; Mar 2012. JHP Pharmaceuticals, LLC. Rochester, Minnesota, USA.

45. Ketanest-S [Summary of Product Characteristics]. Ankeveen, Netherlands: Eurocept BV; 2011.

46. Koffarnus MN, Hall A, Winger G. Individual differences in rhesus monkeys' demand for drugs of abuse. Addict Biol. 2011;17:887-896.

47. Larkin GL, Beautrais AL. A preliminary naturalistic study of low-dose ketamine for depression and suicide ideation in the emergency department. Int J Neuropsychopharmacol. 2011; 14 (8):1127-1131.

48. Lim DK. Ketamine associated psychedelic effects and dependence. Singapore Med J. 2003;44:31-34.

49. Lindenmayer JP, Czobor P, Alphs L, et al. InterSePT Study Group. The InterSePT Scale for Suicidal Thinking reliability and validity. Schizophr Res. 2003; 63:161-170.

50. Mathew SJ, Shah A, Lapidus K, et al. Ketamine for treatment-resistant unipolar depression: current evidence. CNS Drugs. 2012; 26 (3):189-204.

51. McAuliffe CM. Suicidal ideation as an articulation of intent: A Focus for Suicide Prevention? Archives of Suicide Research, 2002; 6:325-338.

52. McKenna SP, Hunt SM. A new measure of quality of life in depression: testing the reliability and construct validity of the QLDS. Health Policy. 1992 Oct;22(3):321-330.

53. Meltzer HY, Alphs L, Green AI, et al. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). Arch Gen Psychiatry. 2003;60(1):82-91. Erratum in: Arch Gen Psychiatry. 2003;60 (7):735.

54. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979;134:382-389.

55. Montgomery SA. Clinically relevant effect sizes in depression. Eur Neuropsychopharmacology. 1994;(4)283-284.

56. Moore NN, Bostwick JM. Ketamine dependence in anesthesia providers. Psychosomatics. 1999;40:356-359.

57. Moreton JE, Meisch RA, Stark L, Thompson T. Ketamine self-administration by rhesus monkey. J Pharmacol Exp Ther. 1977;203:303-309.

58. Morgan CJ, Muetzelfeldt L, Curran HV. Ketamine use, cognition and psychological wellbeing: a comparison of frequent, infrequent and ex-users with polydrug and non-using controls. Addiction. 2009;104:77-87.

59. Morgan CJA, Curran HV, Independent Scientific Committee on Drugs. Ketamine use: a review. Addiction. 2012;107:27-38.

60. Morgan CJA, Curran HV. Acute and chronic effects of ketamine upon human memory: a review. Psychopharmacology. 2006;188:408-424.

61. Morgan CJA, Muetzelfeldt L, Curran HV. Consequences of chronic ketamine self-administration upon neurocognitive function and psychological wellbeing: a 1-year longitudinal study. Addiction. 2010;105:121-133.

62. Muetzelfeldt L, Kamboj SK, Rees H, Taylor J, Morgan CJ, Curran HV. Journey through the K-hole: phenomenological aspects of ketamine use. Drug Alcohol Depend. 2008;95:219-229.

63. Murrough JW, Soleimani L, deWilde KE, et al. Ketamine for rapid reduction of suicide ideation: a randomized controlled trial. Psychol Med. 2015 (16);3571-3580.

64. Narendran R, Frankle WG, Keefe R, et al. Altered prefrontal dopaminergic function in chronic recreational ketamine users. Am J Psychiatry. 2005;162:2352-2359.

65. National Institute for Health and Clinical Excellence (NICE) Depression in adults: recognition and management. Clinical Guideline 90. National Collaborating Centre for Mental Health, London: October 2009. https://www.nice.org.uk/guidance/CG90 (accessed 16 September 2016).

66. Pal HR, Berry N, Kumar R, Ray R. Ketamine dependence. Anaesth Intensive Care. 2002;30:382-384.

67. Pambianco DJ, Vargo JJ, Pruitt RE, Hardi R, Martin JF. Computer-assisted personalized sedation for upper endoscopy and colonoscopy: a comparative, multicenter randomized study. Gastrointest Endosc. 2011;73(4):765-772.

68. Portmann S, Kwan HY, Theurillat R, Schmitz A, Mevissen M, Thormann W. Enantioselective capillary electrophoresis for identification and characterization of human cytochrome P450 enzymes which metabolize ketamine and norketamine in vitro. J Chromatogr A. 2010;1217:7942-7948.

69. Posner, K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale (C-SSRS): Internal Validity and Internal Consistency Findings From Three Multi-Site Studies With Adolescents and Adults, Am J Psychiatry 2011;168:1266-1277.

70. Price RB, Iosifescu DV, Murrough JW, et al. Effects of ketamine on explicit and implicit suicidal cognition: a randomized controlled trial in treatment-resistant depression. Depress Anxiety. 2014 Apr;31(4):335-343.

71. Price RB, Nock MK, Charney DS, Mathew SJ. Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. Biol Psychiatry. 2009; 66:522-526.

72. Rasmussen KG, Lineberry TW, Galardy CW, et al. Serial infusions of low-dose ketamine for major depression. J Psychopharmacol. 2013 May; 27(5):444-450.

73. Reich DL, Silvay G. Ketamine: an update on the first twenty-five years of clinical experience. Can J Anaesth. 1989;36:186-197.

74. Sagie A, Larson MG, Goldberg RJ, Bengston JR, Levy D. An improved method for adjusting the QT interval for heart rate (the Framingham Heart Study). Am J Cardiol. 1992;70:797-801.

75. Simon GE, Savarino J. Suicide attempts among patients starting depression treatment with medications or psychotherapy. Am J Pyschiatry. 2007; 164:1029-1034.

76. Sinner B, Graf BM. Ketamine. In: Schüttler J, Schwilden H, eds. Modern Anesthetics: Handbook of Experimental Pharmacology. Berlin: Springer-Verlag; 2008;182:313-333.

77. Tuynman-Qua H, de Jonghe F, McKenna SP. Quality of Life in Depression Scale (QLDS). Development, reliability, validity, responsiveness and application. European Psychiatry. 1997;12:199-202

78. Vesierra® [Summary of Product Characteristics]. Sandwich, Kent, United Kingdom: Pfizer Limited; 2014.

79. Wasserman D, Rihmer Z, Rujescu D, et al. The European Psychiatric Association (EPA) guidance on suicide treatment and prevention. Eur Psychiatry. 2012;27: 129-141.

80. Wieber J, Gugler R, Hengstmann JH, Dengler HJ. Pharmacokinetics of ketamine in man. Anaesthesist. 1975;24:260-263.

81. Williams JB, Kobak KA. Development and reliability of a structured interview guide for the Montgomery Asberg Depression Rating Scale (SIGMA). Br J Psychiatry. 2008 Jan;192:52-58.

82. Yanagihara Y, Kariya S, Ohtani M, et al. Involvement of CYP2B6 in *N*-demethylation of ketamine in human liver microsomes. Drug Metab Dispos. 2001;29:887-890.

83. Young AM, Herling S, Winger GD, Woods JH. Comparison of discriminative and reinforcing effects of ketamine and related compounds in the rhesus monkey. NIDA Res Monogr. 1981;34:173-179.

84. Young AM, Woods JH. Maintenance of behavior by ketamine and related compounds in rhesus monkeys with different self-administration histories. J Pharmacol Exp Ther. 1981,218:720-727.

85. Zarate C, Brutsche NE, Ibrahim L, et al. Replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial. Biol Psychiatry. 2012;71: 939-946.

Attachment 1: Prohibited Therapies

The table below is intended for general guidance, please contact the study team to discuss any questions or concerns regarding any specific concomitant therapies for a subject.

The pharmacotherapies listed below are permitted (Y) or excluded (N) due to potential impact on efficacy evaluation and/or subject safety or because they are indicated for exclusionary conditions.

Except where specifically noted in the protocol, the prohibited therapies listed in this table are prohibited from screening until at least 1 day (24 hours) after the last dose of intranasal study medication.

Drug Class	Episodic Use (PRN)	Continuous Use	Comments
ADHD medications (eg, atomoxetine, guanfacine)	N	Y	See also "Psychostimulants" row
Amantadine	N	N	
Anorexiants (eg, phenteramine)	N	N	
Anticonvulsants	N	N	Subjects with seizures are excluded. Anticonvulsants used for other indications may be allowed (eg, valproate for migraine, lamotrigine for mood disorder). Approval for use can be discussed on a case-by-case basis with the sponsor's medical monitor.
Antidepressants (*except* monoamine oxidase inhibitors)	N	Y	While continuous use of tricyclic antidepressants (TCAs) is not prohibited, given the target population (patients at imminent risk for suicide) and the known risk of lethality in TCA overdose, caution should be used if they are prescribed. Episodic use (PRN) of trazodone is permitted but should not be used within 8 hours prior to the start of each intranasal study drug administration.
Antidepressants: Monoamine oxidase inhibitors	N	N	Prohibited within the past 2 weeks prior to intranasal study drug administration on Day 1 and are not permitted throughout the study.
Antipsychotics	Y (for sleep only)	Y	Use of antipsychotics (except clozapine) for treatment of depression is not excluded. It would be excluded if being used for psychotic symptoms. Episodic use (PRN) of antipsychotics (except clozapine) for sleep is permitted but should not be used within 8 hours prior to the start of each intranasal study drug administration.
Benzodiazepines (at dosages equal to or less than the equivalent of 6 mg/day lorazepam)	Y	Y	Prohibited within 8 hours prior to the start of each intranasal study drug administration. Additionally, no benzodiazepines should be used within 4 hours after the first intranasal study administration on Day 1 and within 8 hours of Day 2 assessments.
Chloral hydrate	N	N	
Clonidine	Y	Y	Prohibited within 8 hours prior to the start of each intranasal study drug administration.

Drug Class	Episodic Use (PRN)	Continuous Use	Comments
Corticosteriods	Y	N	Inhaled, intranasal, topical, and ophthalmic steroids are not prohibited. Intermittent IM/IV corticosteroids are permitted (chronic use prohibited). Episodic or continuous oral use can be discussed on a case-by-case basis with sponsor's medical monitor.
Cough/Cold/Allergy preparations (except those containing dextromethorphan)	Y	Y	Intranasally-administered decongestants (vasoconstrictors) should not be used from 1 hour prior to each intranasal study medication administration. Pseudoephedrine- containing products should not be used within 12 hours prior to an intranasal treatment session.
Dextromethorphan	N	N	
DHEA	Y	Y	
Diphenhydramine	Y	N	PRN use is permitted, but should not be used within 8 hours prior to the start of each intranasal study drug administration.
Hypnotics (Non-benzodiazepine only)	Y	Y	Do not use within 8 hours prior to the start of each intranasal study drug administration.
Ketanserin	N	N	
Lithium	N	Y	Patients with bipolar disorder (ie, lithium use for bipolar disorder) are excluded. Lithium use for another indication (eg, augmentation treatment for treatment-resistant depression) is permitted.
Methyldopa	N	N	
Metyrosine	N	N	
Opioids	Y	Y	Prescription opioid medication(s) can be continued, per clinician's judgment
Non-vitamin K antagonist oral anticoagulation agents (eg, dabigatran, rivaroxaban, apixaban)	N	N	
Psychostimulants (eg, amphetamines, methylphenidate, and modafinil, armodafinil)	N	Y	The use of amphetamines (including prescribed amphetamines) can be continued but must not be taken within 12 hours prior to the intranasal treatment session or for 2 hours after the intranasal treatment session.
Reserpine	N	N	
Scopolamine	N	N	
St. John's Wort	N	N	
Thyroid hormone supplement	N	Y	Subjects needing supplements must be on a stable thyroid supplement dose for at least 4 weeks prior to Day 1 of the double-blind treatment phase.
Warfarin	N	N	

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; DHEA, dehydroepiandrosterone ; IM, intramuscular; IV, intravenous; PRN, episodic use; TCA, tricyclic antidepressant

Attachment 2: Anticipated Events

Anticipated Event

An anticipated event is an adverse event (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease related) or background regimen.

For the purposes of this study the following events will be considered anticipated events[37] for esketamine and major depressive disorder (MDD) (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

Reporting of Anticipated Events

All adverse events will be recorded in the eCRF regardless of whether considered to be anticipated events and will be reported to the sponsor as described in Section 12.3.1, All Adverse Events. Any anticipated event that meets serious adverse event criteria will be reported to the sponsor as described in Section 12.3.2, Serious Adverse Events. These anticipated events are exempt from expedited reporting as individual single cases to Health Authorities. However if based on an aggregate review, it is determined that an anticipated event is possibly related to study drug, the sponsor will report these events in an expedited manner.

Anticipated Event Review Committee (ARC)

An Anticipated Event Review Committee (ARC) will be established to perform reviews of pre-specified anticipated events at an aggregate level. The ARC is a safety committee within the sponsor's organization that is independent of the sponsor's study team. The ARC will meet to aid in the recommendation to the sponsor's study team as to whether there is a reasonable possibility that an anticipated event is related to the study drug.

Statistical Analysis

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate Anticipated Events Safety Monitoring Plan (ASMP).

INVESTIGATOR AGREEMENT

JNJ54135419 (esketamine)
Clinical Protocol 54135419SUI3002 Amendment 2

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 drug, 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): Carla Canuso, MD

Institution: Janssen Research & Development

Signature: [redacted] Date: Feb 1, 2018
(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.

120

Status: Approved, Date: 31 January 2018