Janssen Research & Development *

Clinical Protocol

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

Protocol ESKETINSUI2002; Phase 2b
AMENDMENT 4

JNJ-54135419 (esketamine)

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen 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: 2016-004422-42

Status: Approved
Date: 22 November 2020
Prepared by: Janssen Research & Development
EDMS number: EDMS-ERI-132382053, 5.0

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

TABLE OF CONTENTS

LIST OF ATTACHMENTS

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

FIGURES

PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	30 January 2017
Amendment 1	28 April 2017
Amendment 2	14 June 2017
Amendment 3	20 November 2018
Amendment 4	01 December 2020

Amendments below are listed beginning with the most recent amendment.

Amendment 4 (01 December 2020)

The overall reason for the amendment: The overall reason for the amendment is to update the text related to statistical methods on sample size determination and multiple testing procedure. The multiple testing procedure has been modified to improve power while controlling the overall Type I error rate when comparing the individual doses with psychoactive placebo.

Applicable Section(s)	Description of Change(s)
Rationale: Text for sample size determination and multiple testing procedure was updated to improve power while controlling the overall Type 1 error rate when comparing the individual doses with psychoactive placebo.	
Synopsis, Sample Size Determination; Section 11.2. Sample Size Determination	Text was revised as follows: The sample size for this study was calculated assuming an effect size of 0.65 between any dose of esketamine and psychoactive placebo for the change from baseline at 24 hours postdose for the CDRS-R total score and a ~~1~~ **2**-sided significance level of ~~0.025~~ **0.05**. A total of 145 subjects will be randomized in this study. Using a 1:1:1:2 randomization ratio (esketamine 28 mg: esketamine 56 mg: esketamine 84 mg: psychoactive placebo), approximately 58 subjects will need to be randomized to psychoactive placebo and 29 subjects will need to be randomized to each esketamine treatment group to achieve ~~80% power for the comparison of each esketamine dose~~ **94% power for the comparison of the pooled doses of esketamine 56 mg and esketamine 84 mg versus psychoactive placebo and 92% power for at least one of the 2 esketamine higher doses (56-mg and 84-mg)** versus psychoactive placebo. The effect size of 0.65 is based on results from study ESKETINSUI2001 (mean difference between treatment groups of -7.2 and a pooled SD of 11.02) for MADRS total score.
Rationale: A pooled sequential multiple testing strategy will be implemented to control Type 1 error.	
Synopsis, Primary Efficacy Analysis; Section 11.3. Efficacy Analysis	Text was revised as follows: ~~As the primary analysis, each dose will be compared to psychoactive placebo using the appropriate contrast at a 1-sided significance level of 0.025. A fixed sequence test procedure will be applied where the 84-mg dose will be tested first and the 56-mg dose will be tested only if the 84-mg dose is shown to be significant.~~ **A pooled sequential multiple testing procedure will be implemented to control for Type 1 error. The esketamine 56-mg and 84-mg treatment groups will be pooled and compared with psychoactive placebo at a 2-sided significance level of 0.05. If this comparison achieves statistical significance in favor of esketamine, the 56-mg dose and the 84-mg dose will each be simultaneously tested versus psychoactive placebo at the 2-sided significance level of 0.05 based on the closed testing procedure. The 28-mg dose will be tested only if both the individual doses of 56 mg and 84 mg are shown to be significant.**

Applicable Section(s)	Description of Change(s)
Rationale: An additional database lock (DBL) and analysis of efficacy and safety will be performed when the last subject completes the double-blind Day 25 visit. This analysis will enable selection of a dose for the planned Phase 3 trial, facilitating Phase 3 trial design and preparation as early as possible. Database locks will also be performed at Days 81 and 200 (study completion)	
Synopsis, Other Objectives Section 2.1.1. Objective Other Objective	Text was revised as follows: • To evaluate the safety and tolerability of intranasal esketamine at specified times through the initial **25 day double-blind treatment period (Day 25), the** 8-week post-treatment follow-up (Day 81) and 6-month post-treatment follow-up, with special attention given to the following assessments: – Effects on suicidal ideation and behavior using the SIBAT – Effects on cognitive function as measured by the Cogstate computerized cognitive battery
Section 5. TREATMENT ALLOCATION AND BLINDING Blinding	In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed. However, an analysis is planned after the last subject completes the Day **25** ~~81~~ visit. Randomization codes will be disclosed to the sponsor in order to plan for Phase 3 studies.
Section 11. STATISTICAL METHODS	An analysis of efficacy and safety will be performed after the last subject completes the ~~8 week Post Treatment Follow up phase (Day 81)~~ **25-day Double-blind Treatment Period (Day 25)**. This analysis will enable selection of a dose for the planned Phase 3 trial, facilitating Phase 3 trial design and preparation. **Database locks will also be performed after the last subject completes the Day 81 Visit and Day 200 Visit, respectively.**

Amendment 3 (20 November 2018)

Overall reasons for the amendment: The protocol was modified to 1) streamline the assessment schedule (number, type and timing of study visits and visit windows) to reduce burden for subjects who discontinue the study; 2) update Attachment 1 (Prohibited and Permitted Concomitant Medications) with new guidelines; 3) add blood pressure withdrawal criteria and clarify blood pressure exclusion criteria and guidance; 4) include changes to biomarker and pharmacogenomic assessments; and 5) update consent/assent language to reflect the pediatric study population requirements.

Applicable Section(s)	Description of Change(s)
Rationale: Blood Pressure (BP) exclusionary criterion was updated to include information for both Screening (Day -1) and Day 1. Attachment 2 "Weight Chart" was replaced by a "Stature Chart" as the "Weight Chart" was erroneously included and stature is needed to determine the appropriate criteria for individual subject BP thresholds. Titles for Attachments 2 and 3 were revised accordingly, and Attachment 4 was added to include guidance for postdose BP withdrawal values. Language was updated for clarity.	
Synopsis Key Exclusion Criteria	Exclusion criterion was modified as follows: On Day -1 (screening) or Day 1 of the double-blind phase prior to randomization, a supine or semi-supine SBP and/or DBP $\geq$ the 95th percentile for sex, age and height is exclusionary. Subjects who fall below the 5th or above the 95th percentile for their age, sex, and height should be evaluated using the parameters for the 5th or 95th percentile. Note that subjects whose SBP and/or DBP values are $\geq$ the 95th percentile for sex, age and height may be reevaluated with a repeated measure once after 5 minutes of rest to assess eligibility.

Applicable Section(s)	Description of Change(s)
Section 4.2. Exclusion Criteria	Exclusion criterion 7 was revised as follows: Criterion modified per Amendment 3 7.2. On Day -1 (screening) or Day 1 of the double-blind phase prior to randomization, a supine or semi-supine SBP and/or DBP ≥ the 95th percentile for sex, age and height is exclusionary. Subjects who fall below the 5th or above the 95th percentile for their age, sex, and height should be evaluated using the parameters for the 5th or 95th percentile. Note that subjects whose SBP and/or DBP values are ≥ the 95th percentile for sex, age and height may be reevaluated with a repeated measure once after 5 minutes of rest to assess eligibility.
Section 6.3. Guidance on Blood Pressure Monitoring on Study Medication Dosing Days	Text was revised to reflect the new titles of Attachments 2 and 3, and to add information for a new attachment (Attachment 4): Attachment 2 (Growth Charts: Stature-for-Age Percentiles for Use in Blood Pressure Assessments) and Attachment 3 (95th Percentile Blood Pressure Levels For Sex by Age and Height) will be used to determine the 95th percentile for both the systolic (SBP) and diastolic blood pressures (DBP) by sex, age and height percentile (refer to Attachment 3 for instructions). On any dosing day, if either the postdose SBP or DBP levels are equal to or greater than the sex, age and height values in Attachment 4 (Postdose Blood Pressure: Withdrawal Criteria Levels for Sex by Age and Height), the blood pressure should be repeated after the subject rests for at least 5 minutes (ie, sitting or supine). If the values are still equal to or greater than the sex, age and height values in Attachment 4, the subject should be withdrawn from the study and appropriate follow-up clinical care should be initiated.
Rationale: Withdrawal criteria were updated to include 1) additional therapies that are excluded during the study, and 2) to include the withdrawal of subjects whose postdose withdrawal values for systolic and/or diastolic blood pressure exceeds individual thresholds that are equal to or above the 99th percentile for age, height and sex plus 1.28 SD over the mean. These values are now added in Attachment 4.	
Section 10.2. Discontinuation of Study Treatment/Withdrawal from the Study	The following withdrawal criteria were added: • Requires treatment with ECT, TMS, ketamine or esketamine • Subjects whose postdose SBP or DBP measures are equal to or greater than the sex, age and height values in Attachment 4 (after a repeated measurement).
Rationale: Text related to early withdrawal and discontinuation during the Double-Blind and Post-Treatment Follow-Up phase was updated in Section 9.1.5. and deleted from Section 10.2. to avoid redundancy. Changes were made to reduce burden while still thoroughly assessing safety parameters for subjects who discontinue the study.	
Section 9.1.5. Early Withdrawal	The text was revised as follows: Subjects who discontinue Double-Blind Study treatment for reasons other than withdrawal of consent/assent, lost to follow-up or death will have the DB EW visit conducted at the time of discontinuation. In addition, if the DB EW visit occurs on Day 1 to Day 21, a remote contact visit (eg, by telephone) will be conducted 5 days (+/-2 days) after the last dose of study medication. If remote contact D+5 occurs within 2 days of the early withdrawal visit, use the +2 day window to conduct the remote contact D+5 visit. A remote contact visit will also be conducted on Day 25 to assess PWC-20, CDRS-R and MADRS, and for collection of concomitant therapies and AEs. If the DB EW visit occurs on or

Applicable Section(s)	Description of Change(s)
	after Day 22 (assuming dose administered), D25 RC visit is not required, however, RC D+5 (5 days after last dose) should be performed. Subjects who discontinue from the Post-Treatment Follow-Up phase for reasons other than withdrawal of consent/assent, lost to follow-up or death will have the Post-Treatment Early Withdrawal visit conducted at the time of discontinuation. In addition, if the PT EW visit occurs prior to completion of the Day 81 visit, a remote contact (eg, by telephone) will be performed on Day 81 for PWC-20, CDRS-R and MADRS, and for collection of concomitant therapies and AEs. If the PT EW visit occurs within ±5 days window of Day 81 (Visit 18), then early withdrawal visit will be adequate, and the Day 81 RC visit is not required. If subjects discontinue anytime between Day 25 postdose and Day 28 RC of the PT phase, the PT EW visit is not required; however, Day 28 RC should be performed.
Section 10.2. Discontinuation of Study Treatment/Withdrawal from the Study	The following text was deleted, and instructions added to refer to Section 9.1.5.: Subjects who discontinue study treatment prior to completion of the Double-Blind Treatment phase (Day 25 visit), will have an Early Withdrawal visit conducted at the time of treatment discontinuation. Subjects who discontinue double-blind study treatment for reasons other than withdrawal of consent, lost to follow-up or death will be contacted remotely 3 and 10 days after the last dose of intranasal study medication to assess adverse events, any withdrawal symptoms utilizing PWC 20, and rebound with assessment of CDRS-R and MADRS. Additionally, these subjects will return for the Day 25 and Day 81 visit assessments. If subjects refuse to return for in-person assessment on Day 25 and 81, remote contact (eg, by telephone) on Days 25 and 81 for CDRS-R and MADRS assessments and adverse event collection is acceptable. If the Early Withdrawal visit occurs within a window of ±1 days of the Day 25 visit of the Double-Blind Treatment phase, or within a window of ±5 days of the Day 81 visit of the follow-up phase, the Day 25 or Day 81 visits, respectively, are not required. Subjects who discontinue from the Post-Treatment Follow-Up phase prior to completion of the Day 81 visit will have the Post-Treatment Early Withdrawal visit conducted at the time of discontinuation. Subjects who discontinue for reasons other than withdrawal of consent, lost to follow-up or death will return for the Day 81 visit. For subjects who refuse to return for in-person assessment, remote contact (eg, by telephone) on Day 81 for CDRS-R and MADRS assessments and adverse event collection is acceptable. Subjects who discontinue from the Post-Treatment Follow-Up Phase after completion of the Day 81 visit will have the Post-Treatment Early Withdrawal visit conducted at the time of discontinuation.
Rationale: The CGI-SR-I was added to correct the inadvertent omission from the protocol as an objective and endpoint.	
Synopsis, Other Objectives, Endpoints; Overview of Study Design	CGI-SR-I was added to “Other Objectives” and “Endpoints”: • To evaluate the efficacy of single and repeated doses of intranasal esketamine compared with psychoactive placebo in reducing symptoms of suicidal ideation, as assessed by the Clinical Global Impression – Imminent Suicide Risk (CGI-SR-I) from the Suicide Ideation and Behavior Assessment Tool (SIBAT) at 4 hours and 24 hours post first dose and through the end of the Double-Blind Treatment phase (Day 25).

Applicable Section(s)	Description of Change(s)
	– CGI-SR-I from SIBAT o Changes from baseline, post single and repeated doses, at 4 hours and 24 hours post first dose, through the end of the Double-Blind Treatment phase (Day 25). CGI-SR-I was added as "other efficacy evaluation": • The primary efficacy evaluation is the CDRS-R; other efficacy evaluations are SIBAT/CGI-SS-R and CGI-SR-I, MADRS, CDI 2:SR(S).
Section 2.1.1. Objectives	CGI-SR-I was added to "Other Objectives" • To evaluate the efficacy of single and repeated doses of intranasal esketamine compared with psychoactive placebo in reducing symptoms of suicidal ideation, as assessed by the Clinical Global Impression – Imminent Suicide Risk (CGI-SR-I) from the Suicide Ideation and Behavior Assessment Tool (SIBAT) at 4 hours and 24 hours post first dose and through the end of the Double-Blind Treatment phase (Day 25).
Section 2.1.2. Endpoints	CGI-SR-I was added to "Other Efficacy Endpoints" – CGI-SR-I from SIBAT o Changes from baseline, post single and repeated doses, at 4 hours and 24 hours post first dose, through the end of the Double-Blind Treatment phase (Day 25).
Section 3.1. Overview of Study Design	CGI-SR-I was added as "other efficacy evaluation": • The primary efficacy evaluation is the CDRS-R; other efficacy evaluations are SIBAT/CGI-SS-R and CGI-SR-I, MADRS, CDI 2:SR(S).
Section 3.2.6. Efficacy Measures	Added description for "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 other objectives by 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
Synopsis, Other Efficacy Analyses; Section 11.3. Efficacy Analyses	CGI-SR-I was added to the text for "Other Efficacy Analyses": The ranks of changes from baseline over time for both CGI-SS-R and CGI-SR-I will be analyzed using an ANCOVA model using last observation carried forward data with factors for treatment and center and baseline CGI-SS-R and CGI-SR-I (unranked) as a covariate. Treatment differences 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 and CGI-SR-I.

Applicable Section(s)	Description of Change(s)
Rationale: Clarifications were made to indicate that biological data will be used to predict inter-individual variability in esketamine treatment response. Additionally, text was modified to make it clear that the Day 4 biomarker collection should occur at the same time as the PK collection during the 1.5 to 2.5 hour postdose window, thus reducing the number of separate venipunctures. Finally, text has been added to clarify the timing and duration of "fasting" prior to a blood sample collection, and to also make it clear that if fasting is not feasible, subjects should try to eat a low-fat diet for at least 8 hours prior to the sample collection. Added "RNA" to the title of Section 9.5. Biomarker and Pharmacogenomic (DNA and RNA) Evaluations.	
Synopsis, Endpoints; Section 2.1.2. Endpoints	Modified the text to include "biological predictors": • Biomarkers – Characteristics of esketamine mechanism of action or biological predictors of inter-individual variability
Time and Events Schedule, Double-Blind Treatment Phase, footnote "ii"	Added the following to the T&E table: On Day 4, biomarker sampling to be performed during the 1.5 to 2.5 hour PK window. Footnote "ii" was clarified as follows: ii. These samples will be collected along with the 1.5 to 2.5 hour PK collection.
Section 9.5. Biomarker and Pharmacogenomic (DNA and RNA) Evaluations	The text was modified as follows: If possible, blood samples should be collected under fasting conditions (minimum 8 hours prior to biomarker sample collection, water is permitted). When fasting is not feasible, subjects should follow a low fat diet for at least 8 hours prior to sample collection, if possible. Subjects should refrain from exercise/strenuous physical activity and the use of non-steroidal anti-inflammatory drugs (NSAIDs) for 24 hours prior to blood collection. Not following these recommendations will not constitute a protocol violation.
Rationale: There is a large body of evidence that depression and antidepressant treatment response are both related to changes in gene transcription. Thus, RNA collection was added to the study protocol to allow for explorations of these relationships. As a result, changes were made to the text to add collection of samples for RNA analyses, and to make clear that these samples will be collected predose. Additionally, text was added to make clear that the RNA will be used for analyses of gene transcription both in the present study, and in combination with RNA samples from other studies, to investigate the biological bases of inter-individual variability in depression phenotypes.	
Synopsis, Overview of Study Design and Biomarker and Pharmacogenomic (DNA and RNA) Evaluations	The text was modified to include RNA: Blood samples for DNA and RNA analyses will be collected from subjects who consent/assent separately to this component of the study (where local regulations permit). Subject participation in DNA and RNA research is optional.
Time and Events Schedule, Double-Blind Treatment Phase [Pharmacogenomic (DNA & RNA) – Optional]	Clarified in footnote "t" that blood sample collection for the pharmacogenomic blood sample collection at Day 25 will occur predose: t. Performed predose
Section 3.2.9. Biomarker and Pharmacogenomic (DNA and RNA) Evaluations, Section 3.2.9.2. Pharmacogenomic/ Epigenetic (DNA and RNA)	Added text for collection of samples for RNA analyses: The goal of the pharmacogenomic component is to collect DNA and RNA 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

Applicable Section(s)	Description of Change(s)
	and suicidality in patients with MDD assessed to be at imminent risk for suicide. 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.
Section 9.5. Biomarker and Pharmacogenomic (DNA and RNA) Evaluations, Pharmacogenomics, Epigenetics, and Gene Transcription Evaluations	Added text for collection of samples for RNA analyses and to clarify that RNA will be used for analyses of gene transcription: Subject participation in pharmacogenomics/epigenetic/gene transcription evaluations is optional. Whole blood samples for DNA and RNA analyses will be collected from all subjects who provide consent/assent for pharmacogenomic research at the time points indicated in the Time and Events Schedule. DNA and RNA samples will be analyzed for the assessment of genetic variation and transcription of 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 and RNA samples will be used for research related to esketamine or MDD. They may also be used to develop tests/assays related to esketamine and MDD. Pharmacogenomic research may consist of the analysis of one or more candidate genes or of the analysis of genetic markers throughout the genome (as appropriate) in relation to esketamine or MDD clinical endpoints. All genetic data obtained during this study may be included in ongoing cross-study analyses to investigate the relationship between depression severity and phenotypes and biomarkers.
Synopsis, Statistical Methods, Biomarker and Pharmacogenomic Analyses; Section 11.5. Biomarker and Pharmacogenomic Analyses	Added text for collection of samples for RNA analyses and to clarify that RNA will be used for analyses of gene transcription: Pharmacogenomic analyses (DNA and RNA) may include candidate gene analyses, genome-wide association analyses, and gene transcription analyses in relation to treatment response, non-response, and MDD. Additional exploratory analyses may be performed.
Rationale: Text was added to allow for collection of menstrual cycle information. Menstrual cycle phase can affect values for many biomarkers related to stress, metabolism, and inflammation. A line was added to the T&E table for clarity.	
Time and Events Schedule, Double-Blind Treatment Phase (Biomarkers)	In the Time and Events Schedule – Double Blind Treatment Phase, Menstrual Cycle Tracking was added as a line in the T&E table to be conducted when biomarker samples are taken.
Section 9.5. Biomarker and Pharmacogenomic (DNA and RNA) Evaluations	Text was added to indicate that menstrual cycle tracking was added to the Time and Events Schedule as a study procedure: Per the Time and Events Schedule, information on menstrual cycle (date of first day of last period, average length of cycle) will be recorded at each visit when blood samples for biomarker analysis are collected.

Applicable Section(s)	Description of Change(s)
Rationale: Under "Clinical Laboratory Tests", criteria were modified to allow standard of care local laboratory test results to be used for eligibility if performed up to 72 hours prior to signing of ICF (formerly 24 hours) to reduce the need for an additional blood draw if the timeframe exceeds 24 hours. The timing for collection of the screening central laboratory samples was clarified. Statement on the UDS test was updated to add qualifier on how UDS should be performed. Text was updated to clarify timing of assessments for Cogstate® computerized cognitive battery, pulse oximetry and MOAA/S.	
Section 9.6. Safety Evaluations, Clinical Laboratory Tests	Deleted "random" from urine sample for urinalysis: Blood samples for serum chemistry and hematology and a urine sample for urinalysis will be collected. Modified criteria for standard of care local laboratory test results: 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 72 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. 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. Added text to clarify that central laboratory samples must be collected at Day -1 (screening), following ICF process: At Day -1 (screening), following ICF process, central laboratory samples must also be collected. Under the Urinalysis bullet point, clarified that urinalysis is performed at the central laboratory using a dipstick and added "specific gravity" to list. Central laboratory wording added to sediment testing. • Urinalysis Dipstick performed at central laboratory -specific gravity Sediment (if central laboratory dipstick result is abnormal)
Section 9.6. Safety Evaluations, Clinical Laboratory Tests; Section 5. Treatment Allocation and Blinding	Added qualifier on how urine drug screen (UDS) should be performed: To maintain the integrity of the study blind, a urine drug screen (UDS) should not be performed during the DB period unless medically necessary. If deemed medically necessary, the medical monitor should be contacted and UDS should be performed predose on dosing days.
Section 9.6. Safety Evaluations, Cogstate computerized cognitive battery	Clarified timing of assessments: The Cogstate computerized cognitive battery is a validated set of assessments which will be performed to assess verbal learning and memory and evaluate cognitive function. There are 4 in-study assessment times for these: between Day 4 and Day 8 (prior to discharge; predose if performed on dosing day), Day 25 predose, DB EW, Day 81, Day 200, PT EW.
Section 9.6. Safety Evaluations, Vital Signs (Temperature, Pulse/Heart Rate, Respiratory Rate, Blood Pressure)	Clarified timing of assessments: Blood pressure, heart rate, and respiratory rate performed at predose (should be performed between t = -15 min and t = 0) and at t = 40 mins, 1 hr, and 1.5 hrs postdose; temperature at predose only.

Applicable Section(s)	Description of Change(s)
Section 9.6. Safety Evaluations, Pulse Oximetry	Clarified timing and documentation of assessment: On each dosing day, the device will be attached to the finger, toe, or ear, and SpO_2 should be monitored and documented once predose between t = -15 min and t =0 (first spray) and then every 15 minutes postdose for approximately 1.5 hours.
Section 9.6. Safety Evaluations, Modified Observer's Assessment of Alertness/Sedation (MOAA/S)	Clarified timing of assessment: On each intranasal dosing day, the MOAA/S should be performed once predose between t = -15 min and t = 0 (first spray), and every 15 min for approximately 1.5 hrs postdose (or longer, if necessary).
Section 9.6. Safety Evaluations, Brief Psychiatric Rating Scale, Positive Symptom Subscale (BPRS+)	Clarified timing of assessments: On each dosing day, BPRS+ to be performed predose and at 40 minutes and 1.5 hours postdose.
Section 16.2.1. Investigator Responsibilities, Safety during Study	Clarified timing of assessments: Based on previous studies, it is known that certain adverse drug reactions occur postdose, peak around 40 minutes, and then dissipate, usually within 4 hours. The study includes careful monitoring following study drug dosing. Vital signs are performed at predose (should be performed between t = -15 minutes and t = 0) and at 40 minutes, 1 hour, and 1.5 hours postdose. Oxygenation should be monitored predose (performed between t = -15 minutes and t = 0), and every 15 minutes thereafter through to approximately 1.5 hours postdose, or longer, if necessary. Additionally, other known side effects of esketamine (eg, dissociation, sedation, conceptual disorientation, hallucinogenic behavior, and abnormal thought content) are monitored closely during this time using specific assessment tools like CADSS, MOAA/S, and BPRS+. On each dosing day, CADSS and BPRS+ should be performed predose and at 40 minutes and 1.5 hours postdose; MOAA/S should be performed predose (between t = -15 minutes and t = 0) and every 15 minutes thereafter through to approximately 1.5 hours postdose, or longer, if necessary.
Rationale: Text was clarified with respect to the timing for repeat B3 and B10 administration.	
Section 9.7. Other Evaluations, Questions B3 and B10 from the MINI-KID	If screening is longer than 24 hours prior to randomization, the B3 and B10 MINI-KID assessment must be repeated to confirm eligibility.
Rationale: Footnotes were reordered for clarity. Extraneous text was removed from footnotes. Visits and visit windows for subjects who discontinue treatment have been updated. Standard of care psychological therapy line in the Post-Treatment Follow-Up T&E was added. UDS removed from Day 25 and footnote added to clarify how UDS testing should be performed. Weight measurement was added to Day 25 as it was previously omitted in error. Changes were made to the timing of collection of DNA and biomarkers to reduce subject burden. DNA collection was added to Day -1 to allow for the acquisition of epigenetic (methylation) markers prior to the first dose of esketamine. These epigenetic markers can then be compared to levels of gene methylation observed after treatment (Day 25). Menstrual cycle tracking added as a line under Biomarkers in the Double-Blind Treatment T&E table. Errors in the SIBAT T&E were corrected, some footnotes were deleted. Footnote “b” was added modify instructions for SIBAT assessments if hospital discharge occurs on a visit day.	
Time and Events Schedule, Double-Blind Treatment and Post-Treatment Follow-Up Phase, SIBAT Time and	Footnote “a” added:

Applicable Section(s)	Description of Change(s)
Events Schedule, Double-Blind Treatment and Post-Treatment Follow-Up Phase	a. Day -1 and Day 1 visits may occur on the same day. If done on same day, vital signs to determine eligibility must be performed both as part of the screening visit and as part of the Day 1 visit (predose). Modified footnotes “e”, “f” and “g” pertaining to discontinuation and early withdrawal from the Double-Blind Treatment phase: e. Subjects who discontinue from the DB phase for reasons other than lost to follow up, death, or withdrawal of consent/assent will have the DB EW visit conducted at the time of discontinuation. In addition, if the DB EW visit occurs on Day 1 to Day 21, subjects will have remote contact visit (eg, by telephone) on Day 25 to assess PWC-20, CDRS-R and MADRS, and for collection of concomitant therapies and AEs (Refer to Sections 9.1.5. and 10.2). f. If the DB EW visit occurs on or after Day 22 (assuming dose administered), D25 RC visit is not required, however, RC D+5 (5 days after last dose) should be performed. If subjects discontinue anytime between Day 25 postdose and Day 28 RC of the PT phase, the PT EW visit is not required; however, Day 28 RC should be performed. g. For subjects who discontinue DB treatment for reasons other than lost to follow up, death, or withdrawal of consent/assent, a remote contact visit will be conducted 5 days (+/-2 days) after the last dose of study medication. If RC D+5 occurs within 2 days of the EW visit, use the +2 day window to conduct the RC D+5 visit. Modified footnotes “mm”, “nn” and “oo” pertaining to discontinuation and early withdrawal from the Post-Treatment Follow-Up phase: mm. Subjects who discontinue from the PT phase for reasons other than lost to follow up, death, or withdrawal of consent/assent will have the PT EW visit conducted at the time of discontinuation. If the PT EW visit occurs prior to completion of the Day 81 visit, a remote contact will be performed on Day 81 for PWC-20, CDRS-R and MADRS, and for collection of concomitant therapies and AEs. (refer to Sections 9.1.5 and 10.2). nn. If the PT EW visit occurs within ±5 days window of Day 81 (Visit 18) of the PT phase, then EW visit will be adequate, and the Day 81 RC visit is not required. oo. Subjects who discontinue from the PT Follow-up Phase for reasons other than lost to follow up, death, or withdrawal of consent/assent after completion of the Day 81 visit will have the PT EW visit conducted at the time of discontinuation (refer to Section 10.2). Footnote “o” for urine pregnancy test was modified to remove “drug screen”: o. In addition to the scheduled time points, additional pregnancy tests can be performed during the study at the investigator’s discretion (refer to Section 5). UDS on Day 25 was removed in order to preserve the integrity of the study blind. Footnote “p” was added to clarify how UDS testing should be performed:

Applicable Section(s)	Description of Change(s)
	p. Due to the need to preserve the integrity of the study blind, a urine drug screen (UDS) should not be performed during the DB period unless medically necessary. If deemed medically necessary, the medical monitor should be contacted and UDS should be performed predose on dosing days. Weight measurement was added to Day 25. Modified footnotes "u", "x" and "z" to clarify timing of assessments: u. Blood pressure, heart rate, and respiratory rate performed at predose (should be performed between t = -15 min and t = 0) and at t = 40 mins, 1 hr, and 1.5 hrs postdose; temperature at predose only (tympanic recommended). x. On each dosing day, continuous arterial oxygen saturation monitoring by pulse oximetry (SpO_2) should be monitored and documented once predose between t = -15 min and t = 0 (first spray), and then every 15 mins postdose for approximately 1.5 hrs (see Section 9.6). z. On each dosing day, MOAA/S should be performed once predose between t = -15 min and t = 0 (first spray), and every 15 min for approximately 1.5 hrs postdose (longer, if necessary; refer to Section 9.6). In the Double-Blind Treatment Phase, Menstrual Cycle Tracking was added as a line in the T&E table to be conducted when biomarker samples are taken. Administrative and Standard of care psychological therapy rows were included in the Post-Treatment Follow-Up phase of the Time and Events Schedule. The following changes were made to the timing of sample collection: • Day 1 draws for biomarkers moved to Day -1 • DNA and RNA sampling added to Day -1 • RNA sampling added to Day 25/DB EW • On Day 4, biomarker sampling to be performed during the 1.5 to 2.5 hour PK window • On Day 25, clinical labs moved from postdose to predose; DNA, RNA and biomarkers collected at the same time. Updated the SIBAT Time and Events Schedule (Double- Blind Treatment Phase and Post-Treatment Follow-Up Phase) to be consistent with the main Time and Events Schedule (Double-Blind Treatment Phase and Post-Treatment Follow-Up Phase). Footnote "b" is new: b. 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.
Section 3.2.2. Treatment and Study Duration	Text was aligned with changes to the visit schedule per Section 9.1.4. Post-Treatment Follow-Up Phases: Visits will continue to occur twice a week for the first 2 weeks (Days 28, 32, 35, 39), after which visits will occur weekly (Days 46 and 53), then every 2 weeks (Days 67 and 81). The Day 28 and 35 visits are remote contact visits. After the Day 81 visit, subjects will enter the extended Post-Treatment Follow-Up phase (Days 81-200), during which they will have monthly visits to assess

Applicable Section(s)	Description of Change(s)
	safety. Investigators may add follow-up visits as dictated by the subject's clinical condition and the investigator's clinical judgment.
Section 9.1.4 Post-Treatment Follow-Up Phases	Text was aligned with the Time and Events schedule: The Day 28 and 35 visits are remote contact visits to assess the PWC-20, CDRS-R and MADRS, and collect concomitant therapies and AEs.
Rationale: PCP was added to the below sections to correct omissions. Mentions of esketamine were removed and sites will be directed to capture this information under ketamine.	
Synopsis, Objectives; Section 2.1.1. Objectives	Text modified as follows: • To evaluate the potential for ketamine or PCP abuse during the follow-up as measured by the Timeline Follow-Back (TLFB).
Synopsis, Endpoints; Section 2.1.2. Endpoints	Text modified as follows: • Safety endpoints will be evaluated throughout the study, as follows: – TLFB methodology to evaluate use of ketamine or PCP.
Section 9.6. Safety Evaluations, Timeline Follow-Back (TLFB)	Text modified as follows: The TLFB will be used to assess the potential for ketamine and PCP abuse during the follow-up phase. The Timeline Follow-Back (TLFB), a clinical and research tool used to obtain a variety of quantitative estimates of alcohol and drug use, will be used to evaluate the potential for ketamine or PCP abuse during the follow-up.
Rationale: Updated the informed consent/pediatric assent language to accurately reflect the pediatric study population requirements.	
Section 4.1. Inclusion Criteria; Section 9.1.2. Screening Phase; Section 10.3. Withdrawal from the Use of Research Samples; Section 16.1. Study-Specific Design Considerations; Section 16.2.1. Investigator Responsibilities; Section 16.2.3. Informed Consent/Pediatric Assent Form; Section 16.2.4. Privacy of Personal Data; Section 16.2.5. Long-Term Retention of Samples for Additional Future Research	Added "subject(s) and/or parent(s)/LAR(s)" and "pediatric assent/informed consent" wherever applicable. Section 16.2.3. Informed Consent/Pediatric Assent Form: Entire section was modified.
Rationale: Text was added to selectively permit subjects to be rescreened.	
Section 4. Subject Population	Text was modified as follows: Requests to rescreen an individual subject must be evaluated and approved by the sponsor representative or medical monitor on a case-by-case basis.

Applicable Section(s)	Description of Change(s)
Rationale: To clarify standard of care psychotherapy guidance, text was included to provide guidance on acceptable types of psychotherapies, and to state that the frequency of psychotherapy visits should be determined based on clinical need at the discretion of the treatment team.	
Section 6. Dosage and Administration; Section 9.1.3. Double-Blind Treatment Phase	Text was modified as follows: Treatment with a psychological intervention is also required, at least through the initial 8-week Post-Treatment Follow-Up phase (Day 81). The specific antidepressant and type of psychological intervention selected for a given subject will be based on the treating physician(s) clinical judgment, knowledge of the subject's prior treatment history, and practice guidelines. Acceptable types of psychological interventions include individual cognitive behavioral therapy (CBT), interpersonal therapy, family therapy, and psychodynamic psychotherapy. Other evidence -based psychotherapies may be allowed after consultation with the medical monitor. The frequency of psychotherapy visits should be determined based on clinical need, at the discretion of the treatment team.
Rationale: Text was modified to clarify the number of nights associated with the 5 days of recommended inpatient hospitalization, and to specify order of SIBAT administration.	

Section 9.1.3. Double-Blind Treatment Phase	Text was modified as follows:
	
	Subjects will remain in the inpatient psychiatry unit or other permitted setting for a recommended duration of 5 days (4 nights) from randomization, with shorter or longer hospitalizations permitted if clinically warranted per local standard of care.
	
	Specified the order of SIBAT as follows:
	
	• SIBAT
	  • Patient Portion
	  • Clinician Portion

Rationale: Text was revised to clarify that the TLFB includes a paper calendar.	
Section 17.4. Source Documentation	Test was revised as follows: Subject- and investigator-completed scales and assessments designated by the sponsor will be considered source data. The CDRS-R, MADRS, SIBAT, CDI 2:SR(S), MOAA/S, YMRS, PWC-20, BPRS+, MINI-KID, Cogstate computerized cognitive battery, TLFB **(**including paper calendar**)**, nasal symptom questionnaire, and CADSS will be considered source data.
Rationale: Redundant text was deleted.	
Section 3.2.7. Safety Evaluations	The following text was deleted: A list of prohibited therapies is provided in Attachment 1 for general guidance for the investigator; however, this list is not all-inclusive.

Applicable Section(s)	Description of Change(s)
Rationale: Text related to prohibitions and restrictions was clarified.	
Section 4.3. Prohibitions and Restrictions; Section 8. Prestudy and Concomitant Therapy	The text was modified as follows: Subjects may not receive electroconvulsive therapy (ECT), trans-cranial magnetic stimulation (TMS)**,** ketamine or other antidepressant therapies (aside from those allowed) during the study. A list of concomitant therapies that are prohibited, permitted, and permitted with restrictions is provided in Attachment 1 for general guidance for the investigator; however, this list is not all-inclusive.
Rationale: Table 2 and accompanying text were updated to clarify timing of sample collection and blood volumes collected from each subject during each study phase. Added DNA sampling at Day -1 and added RNA sampling to Day -1 and Day 25/DB EW.	
Section 9. Study Evaluations	The text was modified as follows: The Time and Events Schedule summarizes the frequency and timing of efficacy, PK, biomarker, pharmacogenomic (DNA and RNA), and safety measurements applicable to this study. The maximum total blood volume to be collected from each subject will be approximately 56.5 mL for subjects who are participating in pharmacogenomics/epigenetic evaluations (see Table 2); total blood volume will be less for subjects who are not participating in these evaluations, as presented in Table 2. Table 2 footnotes “b” and “d” were modified as follows: b. At screening, 2 samples will be collected for analysis – 1 sample each for the SoC local laboratory (to have results prior to Day 1 dose) and the central laboratory (see Section 9.6 for further details). Volume is approximate for local laboratories. d. Pharmacogenomic (DNA and RNA) blood sample(s) will be collected only from subjects who have consented to provide an optional sample for genetic research.
Rationale: Attachment 1 was modified to clarify the list of prohibited/permitted concomitant medications and the guidelines for concomitant medication use.	
Attachment 1: Prohibited/Permitted Concomitant Medications	Table of Prohibited/Permitted Concomitant Medications was edited to include new guidelines for washout timing, updated information on medications that are prohibited, permitted and permitted with restrictions and clarify the reasons in the comments column for some therapies that are permitted with restrictions. Information was reordered for clarity (therapies presented in alphabetical order by drug class) and additional medications were added.
Rationale: “Weight Chart” was replaced by a “Stature Chart” as the “Weight Chart” was erroneously included and stature is needed to determine individual blood pressure thresholds.	
Attachment 2: Growth Charts: Stature-for-Age Percentiles for Use in Blood Pressure Assessments	Added the following tables: Growth Charts: Stature-for-Age Percentiles for Use in Blood Pressure Assessments (Boys and Girls, 2 to 20 years)

Applicable Section(s)	Description of Change(s)
Rationale: Attachment (95th percentile blood pressure levels) was revised to be used with growth charts to determine appropriate criteria for exclusion.	
Attachment 3: 95th Percentile Blood Pressure Levels For Sex by Age and Height	Revised the following tables (for boys and girls): 95th Percentile Blood Pressure Levels for Sex by Age and Height
Rationale: New attachment (postdose blood pressure withdrawal criteria) was added to be used to determine individual postdose blood pressure thresholds.	
Attachment 4: Postdose Blood Pressure: Withdrawal Criteria Levels for Sex by Age and Height	Added the following tables (for boys and girls): Postdose Blood Pressure: Withdrawal Criteria Levels for Sex by Age and Height.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made

Amendment 2 (14 June 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 protocol was modified to 1) permit the initiation of standard of care antidepressant during the 1st 7 days of double-blind treatment, to reflect local standard of care in regions where it is not routine to initiate two medications simultaneously; 2) remove cognitive assessment at baseline and replace the RAVLT with the International Shopping List Test (ISLT); 3) expand description of safety evaluations; and 4) clarify within the Time & Events schedule the different recall periods for efficacy assessments used at certain study visits

Applicable Section(s)	Description of Change(s)
Rationale: Modification that subjects will receive standard of care antidepressant medication that may be initiated or optimized during the first 7 days of the double-blind phase if starting two medications simultaneously is not consistent with local clinical practice.	
Time & Events Schedule, Double-Blind Treatment Phase, footnote (kk)	Revision indicating that antidepressant treatment may be initiated or optimized within the first 7 days of the Double-Blind Treatment Phase if starting two medications simultaneously is not consistent with local clinical practice. T&E Schedule: Standard of Care Antidepressant Assignment: Predose: footnote (kk) added.
3.1. Overview of Study Design, Figure 1, legend, footnote (a)	The text was revised as follows (bold text added; strikeout text deleted): ~~Standard of care~~ Antidepressant ~~treatment~~ **medication** ~~will~~ **should** be initiated or optimized on Day 1. **However initiating standard of care antidepressant medication up to 7 days after the first dose of study medication (Day 1) is permitted if starting two medications simultaneously is not consistent with local clinical practice.**

Applicable Section(s)	Description of Change(s)
6. Dosage and Administration; 9.1.3. Double-Blind Treatment Phase	Antidepressant ~~therapy should be chosen and started on or before Study~~ **medication should be initiated or optimized on** Day 1**. However initiating standard of care antidepressant medication up to 7 days after the first dose of study medication (Day 1) is permitted if starting two medications simultaneously is not consistent with local clinical practice.**
16.1 Study-Specific Design	**Precautions to Ensure Subject Safety in the Study** The study will be conducted in the context of standard clinical care, including hospitalization the initiation or optimization of antidepressant and psychological 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 **should** ~~will~~ receive standard of care antidepressant medication ~~beginning on~~ **initiated or optimized on Day 1**. **However, initiating standard of care antidepressant medication up to 7 days after the first dose of study medication (Day 1) is permitted if starting two medications simultaneously is not consistent with local clinical practice.**
Rationale: Clarification that subjects must agree to take one of the prescribed antidepressant therapies at least during the double-blind treatment phase (Day 25).	
Synopsis, Subject Population; 4.1. Inclusion Criteria	Inclusion Criterion No. 7 was revised as follows (bold text added; strikeout text deleted): As part of **the newly initiated or optimized** standard of care treatment, subject must agree to take one of the prescribed non-investigational antidepressant medications (fluoxetine, escitalopram, sertraline) ~~for~~ at least ~~the duration of~~ **during** the double-blind treatment phase (Day 25).
Rationale: Modification to reflect that the Cogstate safety assessment will not be performed at screening as subjects in acute crisis may not be able to be accurately assessed.	
Time & Events Schedule, Double-Blind Treatment Phase	The following Safety Assessment will not be performed at screening: Cogstate test battery cognitive assessment
Rationale: Modification to reflect that instead of the Rey Auditory Verbal Learning Test (RAVLT) the ISLT will used to evaluate verbal learning and memory to accommodate all languages in countries where the study is being conducted.	
Synopsis, Objectives, Endpoints, Hypothesis; Synopsis, Safety Evaluations; Synopsis, Statistical Methods, Safety Analyses; Time & Events Schedule, Double Blind Treatment Phase, Post-Treatment Follow-up Phase, footnote (bb); 2.1.1. Objectives; 2.1.2. Endpoints; 3.1. Overview of Study Design; 3.2.7. Safety Evaluations; 9.6. Safety Evaluations; 11.6. Safety Analyses; 17.4. Source Documentation	The Rey Auditory Verbal Learning Test (RAVLT), designed to assess verbal learning and memory, will not be used to evaluate cognitive function as part of the safety and tolerability assessment for this study • Text referring to the Rey Auditory Verbal Learning Test (RAVLT) has been deleted and has been replaced with text referring to the ISLT where appropriate. The "Cogstate test battery cognitive assessment" has been changed to: • "Cogstate computerized cognition battery".

Applicable Section(s)	Description of Change(s)
9.6. Safety Evaluations	The following additional information is provided on safety evaluations: **Young Mania Rating Scale (YMRS)** YMRS will be administered to assess treatment-emergent occurrence and severity of manic episodes. The YMRS is an eleven-item multiple choice questionnaire which is used to measure the severity of manic episodes in children and young adults. It is based on the patient's subjective report of his or her clinical condition over the previous hours. Additional information is based upon clinical observations made during the clinical interview. The scale is completed by a clinician or other trained rater and takes 15-30 minutes to complete. The symptom items were selected based upon published descriptions of the core symptoms of mania; the YMRS is a reliable, valid and sensitive rating scale to measure the severity of mania.[122] **Physician Withdrawal Checklist (PWC-20)** The PWC-20 will be administered by the clinician to assess potential withdrawal symptoms following cessation of intranasal esketamine treatment. The PWC-20 is a 20-item simple and accurate method to assess potential development of discontinuation symptoms after stopping of study medication. The PWC-20 is a reliable and sensitive instrument for the assessment of anxiolytic discontinuation symptoms.[106] Discontinuation symptoms occur early and disappear rather swiftly, depending upon speed of taper, daily medication dose, and drug elimination half-life.[106] **Cogstate computerized cognitive battery** The Cogstate computerized cognitive battery, is a validated set of assessments which will be performed to assess verbal learning and memory and evaluate cognitive function. [12, 28, 64] There are 4 in-study assessment times for these: between Day 4 and Day 8 (prior to discharge; pre-dose if performed on dosing day), Day 25 pre-dose or early withdrawal from double-blind phase, Day 81, Day 200 or early withdrawal assessment for the post-treatment follow-up phase. The battery will provide assessment of multiple cognitive domains, including attention, visual and verbal learning and memory, and executive function. The tests use culture neutral stimuli, enabling use in multilingual/multicultural settings. The computerized battery includes: • Simple and choice reaction time tests; scored for speed of response: o Detection (DET; Psychomotor Function) o Identification (IDN; Attention) • Visual episodic memory; visual recall test o One Card Learning (OCL; Visual Learning) • Working memory (n back task); scored for speed of correct response o One Back (ONB; Working Memory) • Verbal learning and memory assessment o International Shopping List Task (ISLT) • Executive function; maze/sequencing test, scored for total number of errors: o The Groton Maze Learning Test (GML; Executive Function) All measures in the cognitive battery have been validated against traditional neuropsychological tests and are sensitive to the effects of various drugs on cognitive performance, including alcohol and benzodiazepines. The subject completed computerized cognitive test battery has been used for cognitive assessment in several child and adolescent research trials including attention deficit hyperactivity disorder,[7] and demonstrates good reliability and validity in child and adolescent populations.[6] The ISLT has also been used in adolescent

Applicable Section(s)	Description of Change(s)
	trials, demonstrating sensitivity, reliability and validity. The subject completed cognitive battery requires approximately 25 minutes; the clinician administered ISLT requires approximately 15 minutes in total.
9.6. Safety Evaluations	All assessments are completed by the subject except the verbal learning and memory assessment, the International Shopping List Task (ISLT), that will be administered by the clinician. The ISLT is a 12-word three-trial verbal list-learning test. The word lists used in the ISLT consist of foodstuffs common to the culture or language group. The verbal presentation of the word list and the recording of responses are completed by the rater and controlled by a laptop computer or tablet. For each 12-word list that is used, the software selects at random the order in which words are presented to subjects. After the third trial is completed, the subject will also complete a series of other tasks for 15-20 minutes, before being asked to recall the 12 words from the ISLT again – this is called a Delayed Recall trial. The subject will also be shown a list of words and asked to recognize previously presented words, a Word Recognition trial. **Timeline Follow-Back (TLFB)** TLFB will be used to assess the potential for ketamine, esketamine, and PCP abuse during the follow-up phase. The Timeline Follow Back (TLFB),[35] a clinical and research tool used to obtain a variety of quantitative estimates of alcohol and drug use, will be used to evaluate the potential for ketamine or esketamine or PCP abuse during the follow-up. The Timeline Follow-Back method has been used in studies to quantify ketamine use in adults, as well as to evaluate substance use in various adolescent populations.[62]
11.6. Safety Analyses	The text was revised as follows (bold text added; strikeout text deleted): **Cogstate Computerized Cognitive Battery ~~RAVLT and Cogstate test battery~~** Cognitive function data from the~~ RAVLT~~ Cogstate computerized cognitive battery~~ and Cogstate test battery cognitive screening assessment~~ will be summarized descriptively at each ~~designated~~ scheduled visit by treatment group. **TimeLine Follow-Back (TLFB)** The TLFB, a clinical and research tool used to obtain a variety of quantitative estimates of ketamine and PCP abuse, will be summarized descriptively at each scheduled visit by treatment group.
Rationale: Clarification that in addition to nasal examination, a nasal symptom questionnaire will be performed to monitor for any signs of adverse effects on the nasal mucosa, as part of the safety evaluations.	
Synopsis, Overview of Study Design; Synopsis, Safety Evaluations; 3.1. Overview of Study Design; 3.2.7. Safety Evaluations;	Safety Evaluations revised to include nasal symptom questionnaire

Applicable Section(s)	Description of Change(s)
Rationale: Clarification that the Children's Depression Inventory 2, Self-Report (Short Form) (CDI 2:SR[S]) is a 12-item patient rated self-assessment of depressive symptoms in youth. A 24-hour recall period will be used on Day 2; a 2-week recall period will be used at all other assessments.	
3.2.6. Efficacy Measures	The text was revised as follows (bold text added; strikeout text deleted) **Children's Depression Inventory 2, Self-Report (Short Form) (CDI 2:SR[S])** The CDI 2:SR(S) assessment is a ~~multi-rater~~ **patient rated** assessment of depressive symptoms in youth aged 7 to 17 years and an efficient screening measure that contains 12 items and takes 5 to 10 minutes to administer.
9.2.3. Children's Depression Inventory 2, Self-Report Study	Descriptive text regarding the multi-rater CDI 2 has been deleted since it is not applicable to this study. The CDI 2: SR(S) is based on the Children's Depression Inventory 2 (CDI 2) and Children's Depression Inventory 2 Self-Report (CDI 2:SR). ~~The CDI 2 is a comprehensive multirater assessment of depressive symptoms in youth aged 7 to 17 years. When used with other sources of verified information, the CDI 2 can aid in the early identification of depressive symptoms, the diagnosis of depression and related disorders, and the monitoring of treatment effectiveness. The CDI 2 quantifies depressive symptomatology using reports from children/adolescents (full length and short), teachers, and parents (or alternative caregivers).~~
9.2.3. Children's Depression Inventory 2, Self-Report Study	Correction to description of CDI 2: SR assessment: The CDI 2:SR is a **12**~~28~~ item **self-reported** assessment.
Time & Events Schedule	Footnote (u) CDI 2:SR(S) – Subject-completed assessment. A 24-hour recall period applies on Day ~~1~~**2**; a 2-week recall period applies at all other assessments.
Rationale: Clarification of the recall periods in this study used for assessment of the Efficacy Evaluations: CDRS-R and MADRS	
9.2.1. Children's Depression Rating Scale Revised (CDRS-R)	Efficacy Evaluations: CDRS-R and MADRS: clarification of the recall periods in this study The text was revised as follows (bold text added; strikeout text deleted) **9.2.1. Children's Depression Rating Scale, Revised (CDRS-R)** The typical recall period for the CDRS-R is 7 days. In this study, the CDRS-R 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. The~~ **4 recall periods: a 7-day recall on Day 1 (predose); a 4-hour recall at the 4-hour postdose assessment on Days 1 and 25; a 24-hour recall at the post-dose assessment on Day 2; and a "since last assessment" recall predose on Day 4 through Day 25 dosing days. "Since last assessment" recall will also be used in Post-Treatment Follow-up assessments on Days 28, 32, 35 and 39. A7-day recall will be used for Post-Treatment Follow-up assessments on Days 46-200. The sleep item score is not assessed at the 4-hour postdose time point on Day 1 and Day 25.** For the CDRS-R performed at 4 hours postdose on Days 1 and 25, the CDRS-R~~S~~ scores for the sleep item recorded predose on the same day will be carried forward to calculate the total score.
9.2.2. Montgomery-Asberg Depression Rating Scale	**9.2.2. Montgomery-Asberg Depression Rating Scale** The typical recall period for the MADRS is 7 days. In this study, the MADRS **will be administered using 4 recall periods: a 7-day recall on Day 1 (predose); a 4-hour recall at the 4 hour postdose assessment on Days 1 and 25; a 24-hour recall at the post-dose assessment on Day 2; and a "since last**

Applicable Section(s)	Description of Change(s)
	assessment" recall predose on Day 4 through Day 25 dosing days. "Since last assessment" recall will also be used in Post-Treatment Follow-up assessments on Days 28, 32, 35 and 39. A 7-day recall will be used for Post-Treatment Follow-up assessments on Days 46 -200. The sleep item score is not assessed at the 4-hour postdose time point on Day 1 and Day 25. ~~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,~~ ~~T~~the MADRS scores for the sleep item recorded predose on the same day will be carried forward to calculate the total score.
9.1.3. Double-Blind Treatment Phase	**MADRS and CDRS-R will be performed at both predose and 4-hour postdose assessments on Day 25 (visit 10) of the double-blind treatment phase.**
Rationale: Clarification of the recall periods for the MADRS and CDRS-R efficacy assessments during the Double-Blind Treatment Phase and the Post-Treatment Follow-up Phase	
Time & Events Schedule	The CDRS-R and MADRS assessments were expanded to indicate each of the four recall periods in order to clarify for the site. The following changes were made to the Time & Events Schedule: **Double-Blind Treatment Phase: Efficacy Assessments** Children's Depression Rating Scale Revised (CDRS-R)[o] and Montgomery-Asberg Depression Rating Scale (MADRS)[z]: assessments on Days 1 (predose and 4 hours), 2, 4, 8, 11, 15, 18, 22, 25, D/C and DB EW were modified. The following changes were made: – Children's Depression Rating Scale Revised (CDRS-R)[o] (recall: 7 days): assessment predose on Day 1; – Montgomery-Asberg Depression Rating Scale (MADRS)[z] (recall: 7 days): assessment predose on Day 1; – CDRS-R (recall: 4-hours postdose): Day 1, 4-hours (visit 2) and Day 25 (visit 10); – MADRS (recall: 4 hours postdose): Day 1, 4-hours (visit 2) and Day 25 (visit 10); – CDRS-R (recall: 24 hours postdose): Day 2; – MADRS (recall: 24 hours postdose): Day 2; – CDRS-R (recall: since last assessment predose): Day 4 through to Day 25, D/C and DB EW; – MADRS (recall: since last assessment predose): Day 4 through to Day 25, D/C and DB EW **Post-Treatment Follow-up Phase: Efficacy Assessments** Children's Depression Rating Scale Revised (CDRS-R)[o] and Montgomery-Asberg Depression Rating Scale (MADRS)[z]: assessments on Days 32, 39, 46, 53, 67, 81, every 4 weeks up to and including Day 200, and PT EW were modified The following changes were made: – Children's Depression Rating Scale Revised (CDRS-R): (recall: 7 days)[o]: Day 46, 53, 67, 81, every 4 weeks up to including Day 200, and PT EW – Montgomery-Asberg Depression Rating Scale (MADRS) (recall: 7 days)[z]: Day 46, 53, 67, 81, every 4 weeks up to including Day 200, and PT EW

Applicable Section(s)	Description of Change(s)
	– CDRS-R (recall: since last assessment): Days 28 RC, 32, 35 RC, 39 – MADRS (recall: since last assessment): Days 28 RC, 32, 35 RC, 39
Time & Events Schedule, Double-Blind and Post-Treatment Follow-up Phase, Footnotes	The following changes were made to the Time & Events Schedule Footnotes (text added in bold; strikethough text deleted): – Day 22 and Day 25 of the Double-Blind Treatment Phase: footnote (a) "visit can be performed ±3 days" changed to footnote (b) "visit can be performed ±1 day" – Footnote (a) **Intranasal treatment sessions should not be given on consecutive days.** – *The statement above in footnote (a) is made in Section 6. Dosage and Administration* – Footnote (d) Subjects who discontinue study treatment prior to completion of the double-blind treatment phase (Day 25 visit), will have an EW visit conducted at the time of treatment discontinuation. Subjects who discontinue double-blind study treatment for reasons other than withdrawal of consent, lost to follow-up or death ~~will be contacted remotely (eg, by telephone) 3 and 10 days after the last dose of intranasal study medication to assess adverse events, and any withdrawal symptoms utilizing PWC 20. Additionally, these subjects~~ will return for the Day 25 and Day 81 visit assessments. If subjects refuse to return for in-person assessment **on Day 25 and 81,** remote contact (eg, by telephone) on Days 25 and 81 for CDRS-R **and MADRS** assessment**s** and adverse event collection is acceptable. – Footnote (o) CDRS-R – Clinician-administered assessment. A predose total score of ≥58 is required for subject eligibility. There are 4 recall periods: a 7-day recall ~~period applies predose~~ on Day 1 **(predose); a** 4-hour **recall at the 4-hour postdose assessment on Day 1 and Day 25; ~~and~~ a** 24-hour **recall at the ~~4 hour~~** postdose **assessment on ~~and~~** Day 2; ~~assessments respectively. A~~ **and a** "since last assessment" recall ~~period applies~~ **predose on** Day 4 through Day 25 dosing days. **"Since last assessment" recall will also be used in Post-Treatment Follow-up ~~all other CDRS-R~~** assessments ~~performed~~ **on Days 28, 32, 35, and 39. A 7-day recall will be used for Post-Treatment Follow-up assessments on Days 46-200.** ~~at an interval <7 days. For all assessments performed at intervals ≥7 days, the 7 day recall version of the CDRS-R will be used (eg, Post-Treatment Follow-up visits 12 and 14-22). At the Day 1, 4 hour postdose time point and on Day 25, the sleep item score is not assessed~~. – Footnote (z) MADRS - Clinician-administered assessment. **There are 4 recall periods: a~~A~~** 7-day recall ~~period applies~~ on Day 1 **(predose); a 4-hour recall at the 4-hour postdose assessment on Day 1 and Day 25; a 24-hour recall at the post-dose assessment on Day 2; and** a "since last assessment" recall ~~period applies~~ **predose on Day 4 through Day 25 dosing days. "Since last assessment" recall will also be used in Post-Treatment Follow-up assessments on Days 28, 32, 35 and 39. A 7-day recall will be used for Post-Treatment Follow-up assessments on Days 46-200.**~~at all other assessments. At the Day 1, 4-hour time point and on Day 25, the sleep item score is not assessed.~~
Time & Events Schedule, Double-Blind Treatment Phase	The following footnote was added: Footnote (nn): MADRS and CDRS-R will be performed at both predose and 4-hour postdose assessments on Day 25 (visit 10) of the double-blind treatment phase

Applicable Section(s)	Description of Change(s)
SIBAT Time & Events Schedule	Day 22 and Day 25 of the Double-Blind Treatment Phase: footnote (a) "visit can be performed ±3 days" changed to footnote (b) "visit can be performed ±1 day"
Rationale: Time and Events Schedule was modified to include a Remote Contact (RC) visit during the Double-Blind Phase for CDRS-R, MADRS, PWC-20 and adverse event collection, in subjects who discontinue from double-blind treatment for reasons other than lost to follow-up, death, or withdrawal of consent.	
Time & Events Schedule, Double-Blind Treatment Phase;	The following changes were made to the Time and Events Schedule – Double-Blind Treatment Phase: Column added to the Double-Blind Treatment Phase for Remote Contact (DB RC) for the following assessments: – CDRS-R (recall: since last assessment) – MADRS (recall: since last assessment) – Physician Withdrawal Checklist (PWC-20) – Adverse event collection. The following footnote was added: Footnote (oo): For subjects who discontinue from double-blind treatment for reasons other than lost to follow up, death, or withdrawal of consent, Remote Contact (RC) will be implemented 3 and 10 days after the last dose of intranasal study medication to assess adverse events, withdrawal symptoms using PWC 20 and rebound using CDRS-R and MADRS assessments. If the EW visit is > 3 days from last dose, the 3 day RC will not be done.
Rationale: Study Evaluations, Table 2 and accompanying text updated to include blood volumes collected from each subject during the Post-Treatment Follow-up Phase, to correct for total blood volume collected during the Double-Blind Treatment Phase, and to delete statement that site participation in biomarker evaluations is optional.	
9.1.1. Study Evaluations, Overview	**Table 2: Approximate Volume of Blood to be Collected from Each Subject** The following changes were made: Correction of Approximate total blood volume for DB treatment phase with biomarker and pharmacogenomics/epigenetic samples: from 26.3 to 32.3 mL Inclusion of blood volumes for Post-Treatment Follow-up Phase – Central Serum Chemistry (Day 81, Day 200/EW): Total blood vol. 2.2 mL – Central Hematology (Day 81, Day 200/EW): Total blood vol. 2.4 mL – Approximate total blood volume for Post-Treatment Follow-up Phase: 4.6 mL Correction of Approximate total blood volume for study to include both Double-Blind and Post-Treatment Follow-up Phase: – Including biomarker and pharmacogenomic samples: from 44.9 to 49.5 mL – Without pharmacogenomic samples: 47.5 mL Editorial changes Changes to legend to include PT, post-treatment Changes to footnotes (bold text added, strikeout text deleted): – Footnote (c) **Biomarker samples are as scheduled in the Time and Events Schedule**~~Optional site participation (based on operational capabilities)~~.

Applicable Section(s)	Description of Change(s)
	– Footnote (d) **Pharmacogenomic b~~B~~**lood sample(s) will be collected only from subjects who have consented to provide an optional sample for genetic research.
9.5. Biomarker and Pharmacogenomic (DNA) Evaluations	**Biomarker Evaluations** The following text was deleted for consistency with Table 2, footnote (c) above: "Site participation in biomarker evaluations is optional based on operational capabilities; subjects at participating sites are required to participate."
Rationale: Correction of error. Revised text states that subject will have completed study if assessments up to and including Week 29 are completed.	
10.1 Completion	The following text was revised (bold text added; strikeout text deleted): A subject will be considered to have completed the study if he or she has completed assessments up to and including Week ~~25~~**29**.
Rationale: Clarification that the Post-Treatment Early Withdrawal visit will be conducted at the time of discontinuation for subjects who discontinue from the Post-Treatment Follow-up Phase	
10.2 Discontinuation of Study Treatment/Withdrawal from the study	Withdrawal from the Study During the Post-Treatment Follow-up Phase The following text was added (bold text): **Subjects who discontinue from the Post-Treatment Follow-up Phase after completion of the Day 81 visit will have the Post-Treatment Early Withdrawal visit conducted at the time of discontinuation.** In addition, the investigator must ensure the subject is appropriately transitioned and/or followed for any additional care required **when a subject discontinues participation in the study for any reason.**
Rationale: Clarification as to which safety and efficacy assessments will be performed for subjects who discontinue treatment prior to completion of the Double-Blind treatment phase.	
9.1.5. Early Withdrawal; 10.2 Discontinuation of Study Treatment/Withdrawal from the study	Discontinuation from study treatment prior to completion of the Double-Blind treatment phase. The text was revised as follows (bold text added): Subjects who discontinue study treatment prior to completion of the double-blind treatment phase (Day 25 visit), will have an EW visit conducted at the time of treatment discontinuation. Subjects who discontinue double-blind study treatment for reasons other than withdrawal of consent, lost to follow-up or death will be contacted remotely (eg, by telephone) 3 and 10 days after the last dose of intranasal study medication to assess adverse events, ~~and~~ any withdrawal symptoms utilizing PWC 20**, and rebound with assessment of CDRS-R and MADRS**. Additionally, these subjects will return for the Day 25 and Day 81 visit **assessments**. If ~~For~~ subjects ~~who~~ refuse to return for in-person assessment **on Day 25 and 81,** remote contact (eg, by telephone) on Days 25 and 81 for CDRS-R **and MADRS** assessments and adverse event collection is acceptable. **The investigator must ensure the subject is appropriately transitioned and/or followed for any additional care required when a subject discontinues participation in the study for any reason.**

Applicable Section(s)	Description of Change(s)
Rationale: Clarification as to which efficacy assessments will be performed for subjects who discontinue treatment prior to completion of the Post-Treatment Follow-up phase.	
9.1.5. Early Withdrawal; 10.2 Discontinuation of Study Treatment/Withdrawal from the study 9.1.5. Early Withdrawal	Discontinuation from study treatment prior to completion of the Post-Treatment Follow-up phase. The text was revised as follows (bold text added): For subjects who refuse to return for in-person assessment, remote contact (eg, by telephone) on Day 81 for CDRS-R **and MADRS** assessment**s** and adverse event collection is acceptable. For information obtained via remote contact, written documentation of the communication must be available for review in the source documents. During remote contact visits with the subject by site personnel, adverse event information will be obtained, and CDRS-R **and MADRS** assessment**s** will be performed by appropriately qualified staff. In addition, the investigator must ensure the subject is appropriately transitioned/followed for any additional care required.
Rationale: Clarification of timing of the Early Withdrawal visit and assessments in relation to the Day 25 and Day 81 visits.	
Time & Events Schedule, Double-Blind Treatment Phase, footnote (ll)	The following text was added: If the Early Withdrawal visit occurs within a window of ±1 day of Day 25 (visit 10) of the double-blind treatment phase, then the Early Withdrawal visit will be adequate and the Day 25 visit is not required. However, the subject must still complete the Day 81 clinic visit.
Time & Events Schedule, Post-Treatment Follow-up Phase, footnote (mm)	If the Early Withdrawal visit occurs within a window of ±5 days of Day 81 (visit 18) of the follow-up phase, then the Early Withdrawal visit will be adequate and the Day 81 visit is not required.
9.1.5. Early Withdrawal; 10.2. Discontinuation of Study Treatment/Withdrawal from the Study	If the Early Withdrawal visit occurs within a window of ±1 days of the Day 25 visit of the double-blind treatment phase, or within a window of ±5 days of the Day 81 visit of the follow-up phase, then the Day 25 or Day 81 visits, respectively, are not required.
Time & Events Schedule, footnote (d); SIBAT Time & Events Schedule, footnote (f) 9.1.5 Early Withdrawal; 10.2. Discontinuation of Study Treatment/Withdrawal from the Study	The text was revised as follows (bold text added): Additionally, these subjects will return for the Day 25 and Day 81 visit **assessments**.
9.1.5. Early Withdrawal	The following text was added: Subjects who discontinue from the Post-Treatment Follow-Up phase after completion of the Day 81 visit will have the Post-Treatment Early Withdrawal visit conducted at the time of discontinuation only.

Applicable Section(s)	Description of Change(s)
Rationale: Correction of investigational drug treatment dose in Table 1	
6.2 Intranasal Study Drug, Table 1	The following changes were made to the heading in Table 1 (bold text added; strikeout text deleted): Dose administration of Intranasal Esketamine 28, ~~54,~~ **56**, 84 mg or Placebo
Rationale: Changes to permit use of Isotretinoin, only in consultation with the medical monitor	
Attachment 1	Prohibited Concomitant medications with Intranasal Study Medication (esketamine or placebo) The following addition was made to the table: Isotretinoin may only be used in consultation with the medical monitor Restrictions: no episodic use, only continuous use.
Rationale: Clarification of text regarding Justification for use of Psychoactive Placebo, and aspects of the Investigators responsibilities for Safety, including monitoring potential adverse drug reactions.	
16.1. Study-Specific Design Considerations	The following text was deleted (bold text added; strikeout text deleted): **Justification for Using Psychoactive Placebo** Subjects and their consenting parent or legal guardian will be informed of the ~~equal~~ chance of receiving esketamine or psychoactive placebo.
16.2.1. Investigator Responsibilities	**Safety during study** ~~Blood volumes used for testing in pediatric populations are monitored closely and~~ A~~a~~ll phlebotomy volumes for this study have been minimized to adhere to the Committee for Human Medicinal Products (CHMP) and Paediatric Committee (PDCO) guideline recommendations. To increase subject comfort, an indwelling catheter has been recommended. Based on previous studies, it is known that certain adverse drug reactions occur postdose, peak around 40 minutes, and then dissipate, usually within 4 hours. The study includes careful monitoring following study drug dosing, ~~every 4 hours~~ **performed at predose and at 40 minutes, 1 hour, and 1.5 hours postdose,** with special attention to blood pressure, heart rate and oxygenation**, with the latter vital signs monitored 15 minutes predose, immediately after the first spray (t = 0), and every 15 minutes thereafter through to approximately 1.5 hours postdose, or longer, if necessary**. Additionally, other known after effects of esketamine (eg, dissociation, sedation, conceptual disorientation, hallucinogenic behavior, and abnormal thought content) are monitored closely ~~during this time~~ using specific assessment tools like CADSS, MOAA/S, and BPRS. **On each dosing day, CADSS and BPRS+ will be performed predose and at 40 minutes and 1.5 hours postdose, whereas MOAA/S will be performed every 15 minutes, from 15 minutes predose to 1.5 hours postdose, or longer, if necessary.**
Rationale: Text updated to include complete list of assessments to be considered source data	
17.4. Source Documentation	The text was revised as follows (bold text added; strikeout text deleted): Subject- and investigator-completed scales and assessments designated by the sponsor will be considered source data. The CDRS-R, MADRS, SIBAT, **CDI 2 SR(S),** MOAA/S, YMRS, PWC-20, ~~RAVLT,~~ BPRS+, MINI-KID, Cogstate computerized cognitive battery ~~Cogstate test battery~~, TLFB, nasal symptom questionnaire and CADSS will be considered source data

Applicable Section(s)	Description of Change(s)
Rationale: Clarification of subject and site staff entry of assessments and patient reported outcomes.	
9.1.3. Double-Blind Treatment Phase	The text was revised as follows (bold text added): 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 **if electronic entry is not functioning**.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made

Amendment 1 (28 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 revise the protocol to address feedback from Health Authorities, improve clarity, enhance safety, and align the protocol with currently ongoing studies in a related population.

Applicable Section(s)	Description of Change(s)
Rationale: Revisions were made to minimize risk to subjects.	
Treatment Time and Events Schedule; 3.2.7, Safety Evaluations; 9.1.5, Early Withdrawal; 10.2, Discontinuation of Study Treatment	Text was revised to indicate that monitoring visits will occur 3 and 10 days post treatment to assess adverse events and withdrawal symptoms.
4.1. Inclusion Criteria	Inclusion criterion #14 was revised to include that contraceptive methods should be discussed in detail with the subject by the investigator, and that subjects must be willing and able to participate in all study activities.
10.2. Discontinuation of Study Treatment	Worsening of underlying condition and a change from voluntary to involuntary hospitalization were added as reasons for discontinuing treatment.
Rationale: Exclusion criteria were revised to more precisely define the study population.	
Synopsis, Key Exclusion Criteria; 4.2, Exclusion Criteria	Exclusion Criterion #4 was revised to clarify that substance and alcohol use disorders must meet DSM-5 severity criteria of moderate to severe in order to be considered exclusionary; and that a lifetime history of ketamine, phencyclidine (PCP), lysergic acid diethylamide (LSD), or 3, 4-methylenedioxy-methamphetamine (MDMA) hallucinogen-related use disorder is exclusionary. Exclusion Criterion #6 was revised to include examples of clinically significant cardiac and endocrine conditions. Exclusion Criterion #7 was revised to indicate the following: – elevated blood pressure in children is based on a single measurement, rather than an average of 3 or more measurements; – on Day 1, prior to randomization, a supine or semi-supine SBP and/or DBP ≥ the 95th percentile for sex, age and height is exclusionary;

Applicable Section(s)	Description of Change(s)
	– an abnormal blood pressure measurement at screening may be repeated once after 5 minutes of relaxation for subject eligibility; – subjects with conditions in which blood pressure elevation could pose a serious risk are excluded.
Synopsis, Key Exclusion Criteria; 4.2, Exclusion Criteria	Exclusion Criterion #8 was revised to include methamphetamines, 3,4-methylenedioxy methamphetamine (MDMA) and heroin as drugs that result in exclusion from the study at screening, and that subjects who have a positive urine test result for cannabinoids may be eligible to participate in the study, provided they do not meet DSM-5 severity criteria for a moderate to severe substance abuse disorder.
3.2.1. Overview of Study Design	Text was revised to align with revisions related to exclusion criteria #4, 6, 7 and 8.
6.2.1. Guidance on Blood Pressure Monitoring	Guidance on blood pressure monitoring was revised to align with revisions related to Exclusion Criterion #7.
Rationale: Text was revised to correct and expand the description of procedures for pulse oximetry and Modified Observer's Assessment of Alertness/Sedation data.	
9.6. Safety Evaluations, Pulse Oximetry; Safety Evaluations, Modified Observer's Assessment of Alertness and Sedation (MOAA/S)	The text describing collection of data for pulse oximetry, and MOAA/S was revised as follows, respectively, and text was added to inform site personnel as to how to proceed in the event a subject's oxygen saturation level falls below 93% (bold text added and strike out text deleted): Pulse oximetry will be used to measure arterial oxygen saturation (SpO2). 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 SpO2 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.).~~ 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. **If oxygen saturation levels are <95% predose, dosing should be postponed, and the subject should be evaluated by an appropriate practitioner to determine suitability to continue in the study.** 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.)~~
Rationale: The text was updated to clarify that the duration of hospitalization may be shorter or longer than the recommended period, based on the clinical needs of a given subject and local practice; and that discharge before 5 days or after 10 days must be discussed with the sponsor.	
3.1. Overview of Study Design, Figure 1.	Figure 1 revised to indicate that visits on Days 28 and 35 will occur by remote contact. Footnote "c" was revised to indicate that continued hospitalization longer than 10 days must be discussed with the sponsor's medical monitor on a weekly basis.

Applicable Section(s)	Description of Change(s)
9.1.3. Double-blind Treatment Phase	Text was revised as follows (bold text added): 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 decision to discharge a subject from the hospital should be 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.**
Time and Events Schedule – Post-Treatment Follow-Up Phase; SIBAT Time and Events Schedule – Post-Treatment Follow-Up Phase;	Text in the footnotes was revised for consistency with the changes described above in Sections 3.1 and 9.1.3.
Rationale: The description of the urine drug test was revised to reflect the full range of drugs evaluated in the urine drug screen.	
9.6. Safety Evaluations, Clinical Laboratory Tests	The list of drugs screened in the urine drug test was replaced with the following list of drugs: amphetamine, barbiturates, benzodiazepines, cocaine, marijuana (THC), methadone, methamphetamine, methylenedioxymethamphetamine (MDMA), opiates, phencyclidine (PCP), and tricyclic antidepressants.
Rationale: Text was revised to improve clarity.	
Treatment Time and Events Schedule	Footnotes "o" and "u" were revised to better describe the recall periods used for CDRS-R and CDI 2:SR, respectively, at each time point they are administered.
Treatment and SIBAT Time and Events Schedules; 3.2.7. Safety Evaluations	All references to "remote contact" and "telephone contact" were revised to "remote contact (eg, by telephone)."
Synopsis, Overview of Study Design; Time and Events Schedule – Double-blind Treatment Phase; 3.1. Overview of Study Design; 9.1.2. Screening Phase; 9.1.3 Double-Blind Treatment Phase	As applicable for each section, the following changes were made: – The location "inpatient psychiatric unit" was revised to "inpatient psychiatric unit or other permitted setting". – The number of anticipated sites (45) was added. – A statement was added to clarify that the duration of hospitalization may vary per local standard of care.
Section 1.1.2.3. Efficacy	Text was revised to more clearly present efficacy results from Study ESKETINTRD2003.

Applicable Section(s)	Description of Change(s)
9.1.3. Double-blind Treatment Phase 9.1.4. Post-treatment Follow-up Phases 9.1.5. Early Withdrawal 10.2. Discontinuation of Study Treatment	The following text concerning procedures following the death of a subject was added to Section 9.1: If a subject dies, the date and cause of death will be collected and documented on the eCRF. Also, procedural instructions related to early withdrawal were moved within Section 9.1 to Section 9.1.5 and revised to reflect additional remote contact in the first 2 weeks post treatment for the assessment of adverse events and withdrawal symptoms.
9.6. Safety Evaluations, Targeted Nasal Examination and Nasal Symptom Questionnaire	Text describing the Nasal Examination and Nasal Symptom Questionnaire was revised as follows (bold text added and strikeout text deleted): Subsequent examinations 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 the presence and severity of symptoms** will be graded ~~as follows: none, mild, moderate, or severe~~. In addition, ~~subjects~~ **a clinician or designated study staff** will ~~be asked to~~ complete a nasal symptom questionnaire.
Rationale: Text was revised to accommodate differences in antidepressant prescribing practices.	
6. Dosage and Administration; 9.1.3. Double-blind Treatment Phase	Clarified that unless clinical judgment dictates otherwise, it is recommended that subjects who have not previously been treated with an antidepressant receive standard of care antidepressant treatment with fluoxetine.
Rationale: Text was revised to include evaluation of the post-treatment occurrence of PCP use.	
9.6. Safety Evaluations, Timeline Follow-back	PCP was added as a drug to be assessed by the Timeline Follow-back assessment for abuse potential.
Rationale: Text was revised to allow for collection and analysis of final laboratory values from subjects who withdraw from the study before the Day 81 visit.	
Treatment Time and Events Schedule – Post-treatment Follow-up Phase 9.6. Safety Evaluations, Timeline Follow-back	Schedule revised to indicate the collection of laboratory analytes at the post-treatment early withdrawal visit, including a footnote to indicate this collection only applies if the patient withdraws before the Day 81 visit.
Rationale: The recommended sequence in which patient-reported outcomes are performed was revised to include the Children's Depression Inventory 2: Self-Report (short version) (CDI 2-SR(S)).	
9.1.3. Double-blind Treatment Phase	The text describing the recommended sequence for performing patient-reported outcomes was revised as follows (bold text added): 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 and** CDRS-R • **CDI 2-SR(S)**

Applicable Section(s)	Description of Change(s)
Rationale: Text was added to support statistical methodology.	
Synopsis, Sample Size Determination; 11.2. Sample Size Determination	To support the assumed effect size of 0.65, the mean difference between treatment groups (-7.2) and pooled SD (11.02) observed in MADRS total score in Study ESKETINSUI2001 were added.
Synopsis, Primary Efficacy Analyses; Synopsis, Other Efficacy Analyses; 11.3. Efficacy Analyses	Text was revised to indicate that point estimates and 95% confidence intervals for treatment differences will be provided with the primary and other efficacy analyses; that the Hodges-Lehmann estimate will be used to estimate treatment differences; and that descriptive statistics will be provided, as appropriate.
Synopsis, Pharmacokinetics Analyses; 11.4. Pharmacokinetic Analyses	Text was revised to indicate that standard errors and 95% confidence intervals will be provided as part of the pharmacokinetic analysis.
Rationale: To avoid unnecessary restriction of study participation.	
Attachment 1. Prohibited Concomitant Medications	Text was revised to define the parameters around the use of corticosteroid and opioid medications.
Rationale: To correct minor errors.	
Synopsis	Literature references were deleted in the synopsis.
Synopsis, Safety Evaluations	Timeline Follow-Back (TLFB) was added to the list of safety evaluations.
1.1.2.2. Human Pharmacokinetics and Product Metabolism; 3.2.4. Esketamine Dose	Description of subjects in Study ESKETINTRD2003 was revised to state “adult subjects” instead of “subjects”.
4.1. Inclusion Criteria	The repeated text (“sexually active subjects”) was deleted in Inclusion Criterion #12 as shown below (strikeout text deleted): During the double-blind treatment phase (from Day 1 through the day of the last dose of study drug) and for a minimum of 1 spermatogenesis cycle, defined as approximately 90 days after receiving the last dose of study drug, sexual abstinence is strongly recommended; however, ~~sexually active subjects~~ heterosexually active male subjects must:… The last four inclusion criteria were renumbered as 13, 14, 15, and 16 (instead of 14, 15, 16, and 17).
9.1.2. Screening Phase	Text was revised as follows (strikeout text deleted): The clinician-administered assessments at screening can be performed in the order preferred by the clinical site.~~: MINI-KID, Questions B3 and B10 from MINI-KID (current status).~~ If the screening phase is longer than 24 hours, Question B3 and B10 from MINI-KID (current status) must be repeated to confirm eligibility.

Applicable Section(s)	Description of Change(s)
12. Adverse Event Reporting, Solicited Adverse Events	Missing word added to the following sentence (bold text added): Solicited adverse events are predefined local and systemic events for which the subject is specifically **questioned**.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

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

Esketamine is the S-enantiomer of ketamine, which has been widely used for the induction and maintenance of anesthesia since the 1970s. Because of its ability to block the N-methyl-D-aspartate (NMDA) glutamate receptor, ketamine has shown efficacy in the treatment of symptoms of major depressive disorder (MDD). This study is intended to evaluate the efficacy, safety and dose response of 3 doses of esketamine in subjects 12 to <18 years of age with MDD who are assessed to be at imminent risk for suicide.

Major depressive disorder is one of the most prevalent mental health conditions and the psychiatric diagnosis most commonly associated with suicide. Epidemiology studies estimate that the 12-month prevalence of MDD is 2% in children and 4% to 8% in adolescents; that MDD is the main predictor of suicidal ideation among children and adolescents; and that 40% to 80% of adolescents meet the diagnostic criteria for depression at the time of suicide attempt. Similar to adults, there is a substantial link between clinical depression and suicide in adolescents with up to 60% of adolescent suicide victims having a depressive disorder at the time of death. Therefore, MDD with imminent risk for suicide is a serious, potentially lethal condition that requires immediate intervention.

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 for depressed adolescents at imminent risk for suicide is hospitalization and treatment with antidepressant medication, combined with psychotherapy. However, hospitalization is temporary and not completely effective, and the risk for suicide remains high in the weeks after discharge. For example, one study found that 13.9% of hospitalized adolescents (12-15 years of age) reattempted suicide within 3 months of discharge.

According to several treatment guidelines, 3 antidepressants are recommended as pharmacological treatment options in children and adolescents with MDD: fluoxetine (Prozac®), escitalopram (Lexapro®), and sertraline (Zoloft®). However, because standard of care antidepressants may take up to 4 to 6 weeks to exert their full effect, there is a significant unmet need for a drug therapy with a rapid onset of effect to decrease depressive symptomatology, including suicidal ideation.

Ketamine and esketamine (the S-enantiomer of ketamine) are approved and widely used in children and adults for the induction and maintenance of anesthesia via intramuscular (IM) or intravenous (IV) administration. The desired analgesic-anesthetic effects of esketamine are attributed to the blockade of ionotropic N-methyl-D-aspartate (NMDA) glutamate receptors. Affinity for the NMDA receptor is approximately 3- to 4-fold greater for esketamine than for its enantiomer, arketamine (R ketamine, the R-enantiomer of ketamine).

Several pilot studies using IV ketamine in subjects with MDD or bipolar depression also suggested that ketamine may reduce suicidal ideation within hours of administration. In addition, 2 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).

The mechanism of action of esketamine is distinct from conventional antidepressant treatments, which target modulatory monoaminergic neurotransmitters (serotonin, norepinephrine, and/or dopamine), 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.

Administered intranasally, esketamine is rapidly and well-absorbed, and can offer patients better convenience. Janssen Research & Development is developing intranasal esketamine both for treatment-resistant depression (TRD) and for the rapid reduction of the symptoms of MDD, including suicidal ideation, in adult patients who are assessed to be at imminent risk for suicide. As part of the pediatric development program, this study is evaluating the efficacy, safety and dose response of esketamine in subjects 12 to <18 years of age with MDD who are assessed to be at imminent risk for suicide.

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

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

Objectives

Primary Objective

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

Other Objectives

The other objectives are the following:

- To evaluate the dose response of intranasal esketamine compared with psychoactive placebo in reducing the symptoms of MDD, including suicidal ideation, as assessed by the change from baseline in CDRS-R total score at 24 hours post first dose (Day 2) and Day 25.
- To evaluate the efficacy of single and repeated doses of intranasal esketamine compared with psychoactive placebo in reducing symptoms of suicidal ideation, as assessed by the Clinical Global Impression of Severity of Suicidality, revised version (CGI-SS-R) from the Suicide Ideation and Behavior Assessment Tool (SIBAT) 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 single and repeated doses of intranasal esketamine compared with psychoactive placebo in reducing symptoms of MDD as assessed by the following:
  - CDRS-R total score at 4 hours post first dose, through the end of the Double-Blind Treatment phase (Day 25), and during the 6-month Post-Treatment Follow-Up phase.
  - Montgomery-Asberg Depression Rating Scale (MADRS) total score at 4 hours and 24 hours post first dose, through the end of the Double-Blind Treatment phase (Day 25), and during the 6-month Post-Treatment Follow-Up phase.
  - Children's Depression Inventory 2: Self-Report (short version) (CDI 2:SR[S])^{TM} score at 24 hours post first dose and through the end of the Double-Blind Treatment phase (Day 25).
- To evaluate the efficacy of single and repeated doses of intranasal esketamine compared with psychoactive placebo in reducing symptoms of suicidal ideation, as assessed by the Clinical Global Impression – Imminent Suicide Risk (CGI-SR-I) from the Suicide Ideation and Behavior Assessment Tool (SIBAT) 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 single and repeated doses of intranasal esketamine compared with psychoactive placebo in reducing suicidal thoughts, as assessed by the following:
  - Change from baseline in SIBAT Module 3 (My Current Thinking) and Module 5 (My Risk) Question 3 (patient-reported frequency of suicidal thinking) through the end of the Double-Blind Treatment phase (Day 25) and during the 6-month Post-Treatment Follow-Up phase.
- To characterize the pharmacokinetics of intranasal esketamine and its metabolite noresketamine.
- To evaluate the safety and tolerability of intranasal esketamine through the end of the Double-Blind Treatment phase (Day 25) using the following assessments:
  - Effects on suicidal ideation and behavior using the SIBAT
  - Effects on dissociative symptoms using the Clinician-Administered Dissociative States Scale (CADSS)
  - Occurrence of psychosis-like side effects using a 4-item positive symptom subscale (consisting of: suspiciousness, hallucinations, unusual thought content, and conceptual disorganization) of the Brief Psychiatric Rating Scale, positive symptom subscale (BPRS+)
  - Occurrence of potential treatment-emergent symptoms of mania using the Young Mania Rating Scale (YMRS)
  - Effects on cognitive function as measured by the Cogstate® computerized cognitive battery
  - Effect on sedation using the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale
  - Local nasal tolerability, using targeted nasal examinations coupled with a nasal symptom questionnaire
- To evaluate the safety and tolerability of intranasal esketamine at specified times through the initial 25 day double-blind treatment period (Day 25), the 8-week post-treatment follow-up (Day 81) and 6-month post-treatment follow-up, with special attention given to the following assessments:
  - Effects on suicidal ideation and behavior using the SIBAT
  - Effects on cognitive function as measured by the Cogstate computerized cognitive battery
- To evaluate potential withdrawal symptoms during the post-treatment follow-up as measured by the Physician Withdrawal Checklist (PWC-20) on Days 25, 28, 32, 35 and 39.
- To evaluate the potential for ketamine or phencyclidine (PCP) abuse during the follow-up as measured by the Timeline Follow-Back (TLFB).
- To evaluate whether pretreatment concentrations of MDD-related biomarkers (eg, 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.
- To explore the change in MDD-related biomarkers in relation to clinical response or non-response to intranasal esketamine.

Endpoints

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

- Other efficacy endpoints will be evaluated throughout the study, as follows:
  - CDRS-R
    - Dose response at 24 hours post first dose and Day 25.
    - Changes from baseline, post single and repeated doses, at 4 hours post first dose, through the end of the Double-Blind Treatment phase (Day 25), and during the 6-month Post-Treatment Follow-Up phase.
  - MADRS
    - Changes from baseline, post single and repeated doses, at 4 hours and 24 hours post first dose, through the end of the Double-Blind Treatment phase (Day 25), and during the 6-month Post-Treatment Follow-Up phase.
  - CGI-SS-R from SIBAT
    - Changes from baseline, post single and repeated doses, at 4 hours and 24 hours post first dose, through the end of the Double-Blind Treatment phase (Day 25).
  - CGI-SR-I from SIBAT
    - Changes from baseline, post single and repeated doses, at 4 hours and 24 hours post first dose, through the end of the Double-Blind Treatment phase (Day 25).
  - SIBAT
    - Changes from baseline, post single and repeated doses, through the end of the Double-Blind Treatment phase (Day 25) and during the 6-month Post-Treatment Follow-Up phase in depressive symptoms and suicidal ideation (subject-completed modules 3, 4, and 5) and clinician impression of suicidality and judgment about management of suicidal thinking (clinician-completed modules 7 and 8).
  - CDI 2:SR (S)
    - Changes from baseline, post single and repeated doses, at 24 hours post first dose and through the end of the Double-Blind Treatment phase (Day 25).
- Safety endpoints will be evaluated throughout the study, as follows:
  - Monitoring of treatment-emergent adverse events (TEAEs)
  - Clinical laboratory tests, physical examination, nasal examination and nasal symptom questionnaire, 12-lead electrocardiogram (ECG), vital signs, pulse oximetry and body weight
  - SIBAT
  - BPRS+ score
  - CADSS
  - Cogstate computerized cognitive battery
  - YMRS score
  - Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score
  - Physician Withdrawal Checklist (PWC-20)
  - TLFB methodology to evaluate use of ketamine or PCP.

- 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. Plasma concentrations of other esketamine metabolites and midazolam may also be measured, if warranted.
- Biomarkers
  - Characteristics of esketamine mechanism of action or biological predictors of inter-individual variability.

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

Hypothesis

The primary hypothesis of this study is that, in addition to standard of care, intranasal esketamine is superior to psychoactive placebo in rapidly reducing the symptoms of MDD, including suicidal ideation, as assessed by the change from baseline in CDRS-R at 24 hours post first dose in subjects 12 to <18 years of age who are assessed to be at imminent risk for suicide.

OVERVIEW OF STUDY DESIGN

This Phase 2 study is a randomized, double-blind, double-dummy, psychoactive placebo-controlled, multicenter trial with 45 anticipated global sites. A target of 145 pediatric subjects, 12 to <18 years of age, will be enrolled in this study and randomized in a 1:1:1:2 ratio to one of 3 doses of intranasal esketamine (28, 56 or 84 mg) or a psychoactive placebo (oral midazolam 0.125 mg/kg), with approximately 29 subjects assigned to each dose of intranasal esketamine and approximately 58 subjects assigned to psychoactive placebo. All eligible subjects will have a diagnosis of MDD and will have presented to an emergency room (ER) or other permitted setting and been assessed to be at imminent risk for suicide. Given the vulnerability of the population, this study will be conducted in the context of standard of care treatment. This includes initial hospitalization in an inpatient psychiatric unit or other permitted setting for a recommended duration of 5 days counted from randomization, with shorter or longer hospitalizations permitted if clinically warranted per local standard of care; initiation or optimization of allowed antidepressant medication therapy, participation in a specific psychological intervention (individual cognitive behavioral therapy [CBT]), interpersonal therapy, family therapy or psychodynamic psychotherapy), and close outpatient follow-up.

There is only 1 approved antidepressant for the treatment of MDD in children and adolescents in both the United States (US) and European Union (EU): fluoxetine; however, if treatment with fluoxetine is unsuccessful or is not tolerated because of side effects, guidelines recommend treatment with escitalopram and sertraline. Escitalopram (the S-enantiomer of citalopram) is also approved for use in adolescents in the US. Therefore, this multi-national study will permit the use of fluoxetine, escitalopram or sertraline as the standard of care antidepressants.

The study will be conducted in 4 phases: a screening evaluation performed within 48 hours prior to Day 1 intranasal dose (if possible, screening should occur within 24 hours prior to the Day 1 intranasal dose); a 25-day Double-Blind Treatment phase (Days 1-25), during which study drug will be administered 2 times per week for 4 weeks on Days 1, 4, 8, 11, 15, 18, 22, and 25; an 8-week initial post-treatment follow-up phase (Days 25-81); and a subsequent phase to complete a full 6-month post-treatment follow-up (Days 81-200). During post-treatment follow-up phases, no study drug will be administered. The duration of the subject's participation will be approximately 29 weeks. The study is considered completed with the last study assessment for the last subject participating in the study.

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

- The primary efficacy evaluation is the CDRS-R; other efficacy evaluations are SIBAT/CGI-SS-R and CGI-SR-I, MADRS, CDI 2:SR(S).
- Safety evaluations include monitoring and collection of adverse events and concomitant therapies, physical examination, nasal examination and nasal symptom questionnaire, measurements of body weight and vital signs, 12-lead electrocardiogram (ECG), pulse oximetry, clinical laboratory tests, SIBAT, MOAA/S, CADSS, BPRS+, YMRS, PWC-20, TLFB, Cogstate computerized cognitive battery.
- 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.
- Blood samples for DNA and RNA analyses will be collected from subjects who consent/assent separately to this component of the study (where local regulations permit). Subject participation in DNA and RNA 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

- Male and female adolescents (12 to <18 years of age).
- Subject must meet DSM-5 diagnostic criteria for MDD, without psychotic features, based upon clinical assessment and confirmed by the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID).
- Subject must have current suicidal thinking with intent at the time of screening, confirmed by "Yes" responses to both MINI-KID Question B3 (*Think about hurting yourself with the possibility that you might die. Or did you think about killing yourself?)* AND Question B10 (*Expect to go through with a plan to kill yourself?)*.

  Note: the response to B3 must refer to the present, whereas the response to B10 may reflect the past 24 hours. If screening is longer than 24 hours, the assessment of questions B3 and B10 for the MINI-KID must be repeated to confirm eligibility.
- In the physician's opinion, acute psychiatric hospitalization is clinically warranted due to subject's imminent risk of suicide.
- Subject must have a CDRS-R total score of ≥ 58 predose on Day 1.
- As part of standard of care treatment, subject must agree 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).
- As part of the newly initiated or optimized standard of care treatment, subject must agree to take one of the prescribed non-investigational antidepressants medications (fluoxetine, escitalopram, sertraline) during the Double-Blind Treatment phase (Day 25).

- As part of standard of care treatment, subject must agree to participate in a specific psychological intervention (individual cognitive behavioral therapy [CBT], interpersonal therapy, family therapy or psychodynamic psychotherapy) at least through the initial 8-week follow-up period (Day 81).

Key Exclusion Criteria

- Subject has a current DSM-5 diagnosis of bipolar (or related disorders), intellectual disability, autism spectrum disorder, conduct disorder, anorexia nervosa, oppositional defiant 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 or prior DSM-5 diagnosis of a psychotic disorder or MDD with psychosis.
- 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 a history of seizure disorder.
- Subject has a history or current signs and/or symptoms of liver or renal insufficiency; has a current diagnosis of clinically significant cardiac (eg, congenital heart disease, cardiomyopathy, or tachyarrhythmias), vascular, pulmonary, gastrointestinal, endocrine (including severe dehydration/hypovolemia), neurologic, hematologic, rheumatologic, or metabolic disturbances; based on investigator judgment.
- On Day -1 (screening) or Day 1 of the double-blind phase prior to randomization, a supine or semi-supine SBP and/or DBP ≥ the 95th percentile for sex, age and height is exclusionary. Subjects who fall below the 5th or above the 95th percentile for their age, sex, and height should be evaluated using the parameters for the 5th or 95th percentile. Note that subjects whose SBP and/or DBP values are ≥ the 95th percentile for sex, age and height may be reevaluated with a repeated measure once after 5 minutes of rest to assess eligibility.

  Subjects with conditions in which blood pressure elevation could pose a serious risk (including severe cardiovascular disease, recent cerebral injury, increased intracranial pressure / intracranial mass lesion, intracranial bleeding or acute stroke, primary developmental or secondary acquired glaucoma or perforating eye injury) are excluded.

DOSAGE AND ADMINISTRATION

Intranasal Study Drug

For each intranasal esketamine or placebo dose, 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. Sprays to each nostril should be delivered in rapid succession at each of the 3 scheduled time points. A total of 3 devices will be used by all subjects to administer 3 doses of esketamine or placebo.

Oral Study Drug

Oral midazolam solution (2mg/ml) will be provided as a psychoactive placebo at a dose of 0.125mg/kg to all subjects randomized to intranasal placebo. A designated pharmacist (or other qualified healthcare

professional) will be unblinded in order to prepare the oral study drug. Subjects randomized to oral psychoactive placebo (midazolam) will receive a weight-based dose using a 2mg/mL solution; those randomized to intranasal esketamine will receive an oral placebo solution in an equivalent volume to that which they would receive if randomized to the psychoactive placebo.

EFFICACY EVALUATIONS

The primary efficacy evaluation will be the CDRS-R total score.

The other efficacy evaluations include SIBAT, MADRS, and CDI 2:SR(S).

PHARMACOKINETIC EVALUATIONS

Venous blood samples will be collected for measurement of plasma concentrations of esketamine, noresketamine, and other metabolites (if warranted).

BIOMARKER AND PHARMACOGENOMIC (DNA AND RNA) EVALUATIONS

Blood samples will be collected for exploratory analysis of biomarkers (protein and metabolites) 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.

Blood samples for DNA and RNA analyses will be collected from subjects who consent/assent separately to this component of the study (where local regulations permit). Subject participation in DNA and RNA research is optional.

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, nasal examination and nasal symptom questionnaire, MOAA/S, CADSS, BPRS+, YMRS, TLFB, Cogstate computerized cognitive battery, and PWC-20.

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.

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 receive at least 1 dose of double-blind study medication and have both a baseline and a postdose evaluation for the CDRS-R 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 sample size for this study was calculated assuming an effect size of 0.65 between any dose of esketamine and psychoactive placebo for the change from baseline at 24 hours postdose for the CDRS-R total score and a 2-sided significance level of 0.05. A total of 145 subjects will be randomized in this study. Using a 1:1:1:2 randomization ratio (esketamine 28 mg: esketamine 56 mg: esketamine 84 mg: psychoactive placebo), approximately 58 subjects will need to be randomized to psychoactive placebo and

29 subjects will need to be randomized to each esketamine treatment group to achieve 94% power for the comparison of the pooled doses of esketamine 56 mg and esketamine 84 mg versus psychoactive placebo and 92% power for at least one of the 2 esketamine higher doses (56-mg and 84-mg) versus psychoactive placebo. The effect size of 0.65 is based on results from study ESKETINSUI2001 (mean difference between treatment groups of -7.2 and a pooled SD of 11.02) for MADRS total score.

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 CDRS-R 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 CDRS-R total scores collected at Day 2 (24 hours post first dose).

Primary Efficacy Analysis

The primary analysis will be based on the full analysis set. The primary efficacy variable, change from baseline in CDRS-R total score at 24 hours post first dose, will be analyzed using an analysis of covariance (ANCOVA) model. The model will include factors for treatment and center, and baseline CDRS-R total score as a covariate A pooled sequential multiple testing procedure will be implemented to control for Type I error. The esketamine 56-mg and 84-mg treatment groups will be pooled and compared with psychoactive placebo at a 2-sided significance level of 0.05. If this comparison achieves statistical significance in favor of esketamine, the 56-mg dose and the 84-mg dose will each be simultaneously tested versus psychoactive placebo at the 2-sided significance level of 0.05 based on the closed testing procedure. The esketamine 28-mg dose will be tested only if both the individual doses of 56-mg and 84 mg are shown to be significant. Point estimates and 95% confidence intervals for treatment differences 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 CDRS-R 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. Missing data will be closely monitored throughout the trial.

Other Efficacy Analyses

A dose response analysis for the change from baseline in CDRS-R total score at 24 hours post first dose and at Day 25 will be conducted with various dose response models being explored. Details of the dose response analysis will be provided in the statistical analysis plan (SAP).

Changes from baseline over time in CDRS-R total score, MADRS total score, and CDI 2:SR[S]^{TM} score will be analyzed based on last observation carried forward (LOCF) data using an ANCOVA model with treatment and center as factors and baseline value as a covariate. Additionally, the change from baseline in CDRS-R total score at Day 25 will be analyzed using a mixed model for repeated measures (MMRM) analysis with baseline CDRS-R total score as a covariate, and treatment, center, day, and day-by-treatment interaction as fixed effects, and a random subject effect. Comparison of each esketamine dose versus placebo will be performed using the appropriate contrast. Point estimates and 95% confidence intervals for

treatment differences will be provided. Missing data will be closely monitored and additional sensitivity analyses will be specified in the SAP, if necessary.

The ranks of changes from baseline over time for both CGI-SS-R and CGI-SR-I will be analyzed using an ANCOVA model using LOCF data with factors for treatment and center and baseline CGI-SS-R and CGI-SR-I (unranked) as a covariate. Treatment differences 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 and CGI-SR-I.

SIBAT Module 3 (My Current Thinking) and Module 5 (My Risk) Question 3 (patient-reported frequency of suicidal thinking) 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

Data will be listed for all subjects with available plasma concentrations per treatment group. Subjects will be excluded from the pharmacokinetic (PK) analysis if their data do not allow for accurate assessment of the PK (eg, incomplete administration of the study drug; missing information of dosing and sampling times; concentration data not sufficient for PK parameter calculation). 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.

The plasma concentration-time data of esketamine (and noresketamine, if warranted) will be analyzed using population PK 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.

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. In addition to the final population PK parameter estimates, the corresponding standard errors and 95% confidence intervals will be provided.

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

Biomarker and Pharmacogenomic Analyses

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 be performed for additional biomarkers. Results may be presented in a separate Biomarkers report.

Pharmacogenomic analyses (DNA and RNA) may include candidate gene analyses or genome-wide association analyses, and gene transcription analyses in relation to treatment response, non-response, and MDD. Additional exploratory analyses may be performed.

Safety Analyses

The primary population for safety analysis will consist of all randomized subjects who receive at least one dose of double-blind study medication. 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). Treatment-emergent adverse events are adverse events with onset during the Double-Blind Treatment phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported adverse events with onset during the Double-Blind Treatment phase (ie, TEAEs 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. In addition, comparisons between treatment groups will be provided if appropriate. Adverse events during the follow-up phase will be summarized separately.

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

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. A listing of subjects with any markedly abnormal laboratory results will also be provided.

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 (the predose ECG will be used as baseline).

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).

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.)

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.

Changes in findings from the baseline nasal examination (including the upper respiratory tract/throat) will be listed by treatment group. Examinations will provide ratings of severity 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.

Scoring from the nasal symptom questionnaire will be summarized descriptively 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. Data on suicidal ideation and behavior from the SIBAT; psychosis-like side effects from the BPRS+; and potential treatment-emergent symptoms of mania from the YMRS will be summarized descriptively at each scheduled visit by treatment group. Cognitive function data from the Cogstate computerized cognitive battery, and withdrawal symptom data from the PWC-20 will be summarized descriptively at designated scheduled visits by treatment group.

TIME AND EVENTS SCHEDULE – DOUBLE-BLIND TREATMENT PHASE

Phase	Screening	Double-Blind Treatment																
Visit Number	1	2						3	4	5	6	7	8	9	10			
Week		1						1		2		3		4				
Day	-1[a,b]	1[a]						2	4[c]	8[c]	11[c]	15[c]	18[c]	22[c]	25[c]	Hospital Discharge[d]	DB EW[e,f]	DB RC[g]
		Pre dose	0 hr	40 min	1 hr	1.5 hr	4 hr[h]	24 hr[h]										
Study Procedures																		
Setting																		
Emergency Room (ER) or other permitted setting[i,j]	←	←	←	←	←	←	←	→										
Inpatient psychiatric unit or other permitted setting[k]								←	→									
Outpatient psychiatric unit[k,l]										←	←	←	←	←	←	→		
Screening/Administrative																		
Parental/Guardian consent and subject assent (study participation)	X																	
Parental/Guardian consent and subject assent (optional participation in genetic testing)	X																	
Inclusion/exclusion criteria	X	X																
Medical history and demographics	X																	
Standard of care antidepressant assignment	X	X[m]																
Standard of care psychological therapy								← To be initiated as soon as possible[n] →										
Urine pregnancy test for females of childbearing potential[o]	X														X		X	
Urine drug screen[p]	X																	
MINI International Psychiatric Interview for Children and Adolescents (MINI-KID)	X																	
Question B3 and B10 from MINI-KID (current status)[q]	X																	
Study Drug Administration																		
Randomization[r]		X																
Practice session for use of intranasal device		X																
Oral study control drug (midazolam or placebo)			X						X	X	X	X	X	X	X			
Study Drug Administration (intranasal esketamine or placebo)[s]			X						X	X	X	X	X	X	X			
Safety Assessments																		
Physical examination	X														X[t]		X	
Nasal examination	X														X[t]		X	
Vital signs[u]	X	X		X	X	X			X	X	X	X	X	X	X		X	
12-lead ECG	X[v]				X					X[w]					X[w]		X	
Pulse oximetry[x]		X							X	X	X	X	X	X	X			
Body weight / height	X														X[y]		X[y]	

Phase	Screening	Double-Blind Treatment																
Visit Number	1	2						3	4	5	6	7	8	9	10			
Week		1						1		2		3		4				
Day	-1[a,b]	1[a]						2	4[c]	8[c]	11[c]	15[c]	18[c]	22[c]	25[c]	Hospital Discharge[d]	DB EW[e,f]	DB RC[g]
		Pre dose	0 hr	40 min	1 hr	1.5 hr	4 hr[h]	24 hr[h]										
Modified Observer's Assessment of Alertness/Sedation (MOAA/S)[z]		X	*Every 15 minutes*						X	X	X	X	X	X	X			
Clinician-Administered Dissociative States Scale (CADSS)[aa]		X		X		X			X	X	X	X	X	X	X		X	
Brief Psychiatric Rating Scale, positive symptom subscale (BPRS+)[aa]		X		X		X			X	X	X	X	X	X	X		X	
Young Mania Rating Scale (YMRS)		X								X[t]					X[t]		X	
Physician Withdrawal Checklist (PWC-20)															X		X	X
Cogstate computerized cognitive battery									X[bb]						X[t]		X	
Nasal symptom questionnaire[cc]		X			X				X		X		X		X		X	
Efficacy Assessments																		
Suicide Ideation and Behavior Assessment Tool (SIBAT)[dd]		X					X	X	X	X	X	X	X	X	X	X	X	
Children's Depression Rating Scale-Revised (CDRS-R) (recall: 7 days)		X																
Montgomery-Asberg Depression Rating Scale (MADRS) (recall: 7 days)		X																
CDRS-R (recall: 4 hrs postdose)							X								X[ee]			
MADRS (recall: 4 hrs postdose							X								X[ee]			
CDRS-R (recall: 24 hrs postdose)								X										
MADRS (recall: 24 hrs postdose)								X										
CDRS-R (recall: since last assessment predose)									X	X	X	X	X	X	X[ee]	X	X	X
MADRS (recall: since last assessment predose)									X	X	X	X	X	X	X[ee]	X	X	X
Children's Depression Inventory 2, self-reporting, short form (CDI 2:SR [S])[ff]		X						X							X		X	
Clinical Laboratory Assessments																		
Hematology, Chemistry	X[gg]														X[t]		X	
Urinalysis	X[gg]														X[t]		X	
Pharmacokinetics																		
Blood sample collection[hh]				X		X	X		X									
Biomarkers																		
Blood sample collection (serum and plasma biomarkers)	X								X[ii]						X[t]		X	
Menstrual cycle tracking	X								X						X		X	
Pharmacogenomics (DNA & RNA) – Optional																		
Blood sample collection	X														X[t]		X	

Phase	Screening	Double-Blind Treatment																	
Visit Number	1	2						3	4	5	6	7	8	9	10				
Week		1						1		2		3		4					
Day	-1[a, b]	1[a]						2	4[c]	8[c]	11[c]	15[c]	18[c]	22[c]	25[c]	Hospital Discharge[d]	DB EW[e, f]	DB RC[g]	
		Pre dose	0 hr	40 min	1 hr	1.5 hr	4 hr[h]	24 hr[h]											
Ongoing Subject Review																			
Concomitant therapy	⟷																		
Adverse events	⟷																		

TIME AND EVENTS SCHEDULE – POST-TREATMENT FOLLOW-UP PHASE

Phase			Post-Treatment Follow-Up								
Visit Number	11	12	13	14	15	16	17	18	19, 20, 21	22	
Week	5		6		7	8	10	12	16, 20, 24	29	
Day	28 [c] RC	32 [c]	35 [c] RC	39 [c]	46 [ii]	53 [ii]	67 [kk]	81 [ll]	Every 4-weeks [ll]	200 [ll]	PT EW [f, mm, nn, oo]
Study Procedures											
Setting											
Outpatient psychiatric unit	←										→
Administrative											
Standard of care psychological therapy	←							→			
Safety Assessments											
Physical examination										X	X
Vital signs [u]										X	X
12-lead ECG										X	X
Body weight										X	X
Physician Withdrawal Checklist (PWC-20)	X	X	X	X							
Cogstate computerized cognitive battery								X		X	X
Timeline Follow-Back (TLFB)						X		X		X	X
Efficacy Assessments											
Suicide Ideation and Behavior Assessment Tool (SIBAT) [dd]		X		X	X	X	X	X	X	X	X
Children's Depression Rating Scale-Revised (CDRS-R) (recall: 7 days)					X	X	X	X	X	X	X
Montgomery-Asberg Depression Rating Scale (MADRS) (recall: 7 days)					X	X	X	X	X	X	X
CDRS-R (recall: since last assessment)	X	X	X	X							
MADRS (recall since last assessment)	X	X	X	X							
Clinical Laboratory Assessments											
Hematology, Chemistry								X			X [pp]
Urinalysis								X			X [pp]
Ongoing Subject Review											
Concomitant therapy	←										→
Adverse events	←										→

Abbreviations: BPRS+= 4-item positive symptom subscale of the Brief Psychiatric Rating Scale, CADSS=Clinician-Administered Dissociative States Scale, CDI 2:SR (S)=Children's Depression Inventory 2 self-reporting short form, CDRS-R=Children's Depression Rating Scale-Revised, DB=double-blind, DNA=deoxyribonucleic acid, ECG=electrocardiogram, ER=emergency room, EW=early withdrawal, ICF=informed consent form, MADRS=Montgomery-Asberg Depression Rating Scale, MINI-KID=Mini International Neuropsychiatric Interview for children and adolescents, MOAA/S= Modified Observer's Assessment of Alertness/Sedation, PWC-20=Physician Withdrawal Checklist, PT=post-treatment, RC=remote contact (eg, by telephone), RNA= ribonucleic acid, SIBAT=Suicide Ideation and Behavior Assessment Tool, SpO_2=oxygen saturation, TLFB=Timeline Follow-Back, YMRS=Young Mania Rating Scale.

Footnotes:

[a] Day -1 and Day 1 visits may occur on the same day. If done on same day, vital signs to determine eligibility must be performed both as part of the screening visit and as part of the Day 1 visit (predose).

[b] Subject should be screened within 48 hrs (if possible, 24 hrs) prior to study drug dosing on Day 1.

[c] Visit can be performed +/- 1 day. During the DB phase, study drug administration should not occur on consecutive days.

[d] Discharge visit is performed on the actual day of discharge from inpatient hospitalization. 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.

[e] Subjects who discontinue from the DB phase for reasons other than lost to follow up, death, or withdrawal of consent/assent will have the DB EW visit conducted at the time of discontinuation. In addition, if the DB EW visit occurs on Day 1 to Day 21, subjects will have remote contact visit (eg, by telephone) on Day 25 to assess PWC-20, CDRS-R and MADRS, and for collection of concomitant therapies and AEs (Refer to Sections 9.1.5 and 10.2).

[f] If the DB EW visit occurs on or after Day 22 (assuming dose administered), D25 RC visit is not required, however, RC D+5 (5 days after last dose) should be performed. If subjects discontinue anytime between Day 25 postdose and Day 28 RC of the PT phase, the PT EW visit is not required; however, Day 28 RC should be performed.

[g] For subjects who discontinue DB treatment for reasons other than lost to follow up, death, or withdrawal of consent/assent, a remote contact visit will be conducted 5 days (+/-2 days) after the last dose of study medication. If RC D+5 occurs within 2 days of the EW visit, use the +2 day window to conduct the RC D+5 visit.

[h] Day 1, 4-hr assessments should be performed within a 30 min window. Day 2, 24-hr assessments should be performed within a 2 hr window.

[i] Not applicable for subjects admitted directly into the inpatient psychiatric unit or other permitted setting (refer to Section 3.1).

[j] It is recommended that subjects dosed in the ER not be transferred to the inpatient psychiatric unit or other permitted setting until after the 4-hr postdose assessments are completed.

[k] Refer to Section 3.1.

[l] Subjects requiring psychiatric re-hospitalization may be eligible to continue in the study.

[m] Antidepressant medication should be initiated or optimized on Day 1. If starting 2 medications simultaneously is not consistent with local clinical practice, initiating SOC antidepressant medication up to 7 days after Day 1 is permitted (refer to Section 6).

[n] Outpatient psychotherapy should be initiated as soon as possible upon discharge from the hospital.

[o] In addition to the scheduled time points, additional pregnancy tests can be performed during the study at the investigator's discretion (refer to Section 5).

[p] Due to the need to preserve the integrity of the study blind, a urine drug screen (UDS) should not be performed during the DB period unless medically necessary. If deemed medically necessary, the medical monitor should be contacted and UDS should be performed predose on dosing days.

[q] Subjects will be asked to respond to Questions B3 and B10 of the MINI-KID regarding their current state. Response to B3 must refer to the present, response to B10 may reflect the past 24 hrs. If screening is longer than 24 hrs prior to first dose, the B3 and B10 MINI-KID assessment must be repeated to confirm eligibility.

[r] CDRS-R and BP should be performed prior to randomization in order to evaluate eligibility.

[s] Refer to Section 6.

[t] Performed predose.

[u] Blood pressure, heart rate, and respiratory rate performed at predose (should be performed between t = -15 min and t = 0) and at t = 40 mins, 1 hr, and 1.5 hrs postdose; temperature at predose only (tympanic recommended).

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

[w] Performed 1 hr postdose.

[x] On each dosing day, continuous arterial oxygen saturation monitoring by pulse oximetry (SpO_2) should be monitored and documented once predose between t = -15 min and t = 0 (first spray), and then every 15 mins postdose for approximately 1.5 hrs (see Section 9.6).

[y] Only weight will be recorded at the Day 25 and the DB EW visit.

[z] On each dosing day, MOAA/S should be performed once predose between t = -15 min and t = 0 (first spray), and every 15 min for approximately 1.5 hrs postdose (longer, if necessary; refer to Section 9.6).

[aa] On each dosing day, CADSS and BPRS+ to be performed predose and at 40 minutes and 1.5 hours postdose. If any CADSS items are scored zero at 40 mins, these items will not be repeated at 1.5 hrs postdose.

[bb] Cogstate computerized cognition battery will be performed between Day 4 and Day 8, prior to subject's discharge from the inpatient unit. On a dosing day, complete predose.

[cc] Nasal symptom questionnaire performed predose and at 1 hr postdose.

[dd] If a dose is administered, SIBAT is performed predose. Not all modules are completed at every visit; see SIBAT Time &Events Schedule.

[ee] MADRS and CDRS-R will be performed at both predose and 4-hr postdose on Day 25 (visit 10) of the DB phase.

[ff] CDI 2:SR[S] Completed predose at all timepoints. A 24-hr recall period applies on Day 2; a 2-week recall period applies at Day 1 and Day 25 or DB EW.

[gg] Samples will be collected for analysis by local laboratory (for eligibility) and central laboratory (refer to Section 9.6)

[hh] Window for PK collection as follows: 30-50 mins; 1.5 hr to 2.5 hrs; and 4 hrs to 12 hrs on Day 1 and Day 4.

[ii] These samples will be collected along with the 1.5 to 2.5 hour PK collection.

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

[kk] Visit can be performed +/- 5 days.

[ll] Visit can be performed +/- 7 days.

[mm] Subjects who discontinue from the PT phase for reasons other than lost to follow up, death, or withdrawal of consent/assent will have the PT EW visit conducted at the time of discontinuation. If subjects discontinue anytime between Day 25 postdose and Day 28 RC of the PT phase, the PT EW visit is not required; however, Day 28 RC should be performed. If the PT EW visit occurs prior to completion of the Day 81 visit, a remote contact will be performed on Day 81 for PWC-20, CDRS-R and MADRS, and for collection of concomitant therapies and AEs. (refer to Sections 9.1.5 and 10.2).

[nn] If the PT EW visit occurs within ±5 days window of Day 81 (visit 18) of the PT phase, then EW visit will be adequate, and the Day 81 RC visit is not required.

[oo] Subjects who discontinue from the PT Follow-up Phase for reasons other than lost to follow up, death, or withdrawal of consent/assent after completion of the Day 81 visit will have the PT EW visit conducted at the time of discontinuation (refer to Section 10.2).

[pp] Hematology, chemistry and urinalysis are done only if the subject has withdrawn from the study prior to the Day 81 visit.

SIBAT TIME AND EVENTS SCHEDULE – DOUBLE-BLIND TREATMENT PHASE

Phase	Screening	Double-blind Treatment															
Visit Number	1	2						3	4	5	6	7	8	9	10	–	–
Week		1								2		3		4			
Day	–	1						2	4[a]	8[a]	11[a]	15[a]	18[a]	22[a]	25[a]	Hospital Discharge[b]	DB EW
	-	Predose	0 hr	40min	1hr	1.5hr	4 hr	24 hr									
SIBAT																	
Subject-Completed Modules																	
Module 1 About me		X															
Module 2 My Risk/ Protective Factors		X								X		X			X	X	X
Module 3 My Current Thinking		X					X	X	X	X	X	X	X	X	X	X	X
Module 4 My Actions										X	X	X	X	X	X	X	X
Module 5 My Risk		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
Module 7. Clinical Global Impressions[c]		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

SIBAT TIME AND EVENTS SCHEDULE – POST-TREATMENT FOLLOW-UP PHASE

Phase	Post-Treatment Follow-Up										
Visit Number	11	12	13	14	15	16	17	18	19, 20, 21	22	
Week	5		6		7	8	10	12	16, 20, 24	29	
Day	28 RC	32	35 RC	39	46	53	67	81	Every 4-weeks	200	PT EW
SIBAT											
Subject-Completed Modules											
Module 1 About me											
Module 2 My Risk/ Protective Factors				X			X	X	X	X	X
Module 3 My Current Thinking		X		X	X	X	X	X	X	X	X
Module 4 My Actions		X		X	X	X	X	X	X	X	X
Module 5 My Risk		X		X	X	X	X	X	X	X	X
Clinician Completed Modules											
Module 6. Clinician Semi-Structured Interview				X			X	X	X	X	X
Module 7. Clinical Global Impressions[c]				X			X	X	X	X	X
Module 8. Clinical Judgment of optimal Suicide Management				X			X	X	X	X	X

Abbreviations: DB=double-blind, EW= early withdrawal, PT=post-treatment, SIBAT= Suicide Ideation and Behavior Assessment Tool

Note: For visit windows, please refer to main Time and Events Schedule

Footnotes:

[a] The SIBAT modules will be performed predose.

[b] 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.

[c] 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.

ABBREVIATIONS

AAP	American Academy of Pediatrics
AD	antidepressant
ADHD	Attention-deficit hyperactivity disorder
AE	adverse event
ANCOVA	analysis of covariance
BP	blood pressure
BPRS+	Brief Psychiatric Rating Scale, positive symptom subscale
CADSS	Clinician-Administered Dissociative States Scale
CBT	cognitive behavioral therapy
CDI 2:SR	Children's Depression Inventory 2 Self-Report
CDI 2:SR(S)	Children's Depression Inventory 2: Self-Report (short version)
CDRS-R	Children's Depression Rating Scale-Revised
CGI-SR-I	Clinical Global Impression – Imminent Suicide Risk
CGI-S	Clinical Global Impression Severity Scale
CGI-SS	Clinical Global Impression Severity of Suicidality
CGI-SS-R	Clinical Global Impression of Severity of Suicidality, revised version
eCRF	electronic case report form
DB	double-blind
DBP	diastolic blood pressure
D/C	hospital discharge
DCF	data clarification form
DSM-5	Diagnostic and Statistical Manual of Mental Disorders (5th edition)
ECG	electrocardiogram
eDC	electronic data capture
ER	emergency room
EU	European Union
EW	early withdrawal
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IM	intramuscular
IND	Investigational New Drug
InterSePT	International Suicide Prevention Trial
IRB	Institutional Review Board
IV	intravenous
IVRS	interactive voice response system
IWRS	interactive web response system
LAR	Legally acceptable representative
LC-MS/MS	liquid chromatography/mass spectrometry/mass spectrometry
MADRS	Montgomery-Asberg Depression Rating Scale
MADRS-SI	Montgomery-Asberg Depression Rating Scale – Suicidal Ideation
MedDRA	Medical Dictionary for Regulatory Activities
MDD	major depressive disorder
MINI	Mini International Neuropsychiatric Interview
MINI-KID	Mini International Neuropsychiatric Interview for Children and Adolescents
MOAA/S	Modified Observer's Assessment of Alertness/Sedation
NICE	National Institute for Health and Clinical Excellence
NSAID	non-steroidal anti-inflammatory drug
PD	pharmacodynamic(s)
PDCO	Paediatric Committee
PWC-20	Physician Withdrawal Checklist
PK	pharmacokinetic(s)

PCP	phencyclidine
PQC	Product Quality Complaint
PRO	patient-reported outcome(s) (paper or electronic as appropriate for this study)
RC	remote contact
RNA	ribonucleic acid
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SIBAT	Suicide Ideation and Behavior Assessment Tool
SoC	standard of care
SSRI	selective serotonin reuptake inhibitor
SUSAR	suspected unexpected serious adverse reaction
TMS	Trans-cranial magnetic stimulation
TLFB	Timeline Follow-Back
UDS	urine drug screen
US	United States
USP	United States Pharmacopeia
YMRS	Young Mania Rating Scale

1. INTRODUCTION

Esketamine is the S-enantiomer of ketamine, which has been widely used for the induction and maintenance of anesthesia since the 1970s. Because of its ability to block the N-methyl-D-aspartate (NMDA) glutamate receptor, ketamine has shown efficacy in the treatment of symptoms of major depressive disorder (MDD).[85] This study is intended to evaluate the efficacy, safety and dose response of 3 doses of esketamine in subjects 12 to <18 years of age with MDD who are assessed to be at imminent risk for suicide.

Major depressive disorder is one of the most prevalent mental health conditions and the psychiatric diagnosis most commonly associated with suicide.[54,91] Epidemiology studies estimate that the 12-month prevalence of MDD is 2% in children and 4% to 8% in adolescents,[2] that MDD is the main predictor of suicidal ideation among children and adolescents,[37,93] and that 40% to 80% of adolescents meet the diagnostic criteria for depression at the time of suicide attempt.[10,37] Similar to adults, there is a substantial link between clinical depression and suicide in adolescents with up to 60% of adolescent suicide victims having a depressive disorder at the time of death.[14,107] Therefore, MDD with imminent risk for suicide is a serious, potentially lethal condition that requires immediate intervention.

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 for depressed adolescents at imminent risk for suicide is hospitalization and treatment with antidepressant medication combined with psychotherapy.[91] However, hospitalization is temporary and not completely effective, and the risk for suicide remains high in the weeks after discharge. For example, one study found that 13.9% of hospitalized adolescents (12-15 years of age) reattempted suicide within 3 months of discharge.[102]

According to several treatment guidelines, 3 antidepressants are recommended as pharmacological treatment options in children and adolescents with MDD: fluoxetine (Prozac®), escitalopram (Lexapro®), and sertraline (Zoloft®).[20,21] However, because standard of care antidepressants may take up to 4 to 6 weeks to exert their full effect,[109,114] there is a significant unmet need for a drug therapy with a rapid onset of effect to decrease depressive symptomatology, including suicidal ideation.[30]

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 desired analgesic-anesthetic effects of esketamine are attributed to the blockade of ionotropic NMDA glutamate receptors.[112] Affinity for the NMDA receptor is approximately 3- to 4-fold greater for esketamine than for its enantiomer, arketamine (R-ketamine, the R-enantiomer of ketamine).[58,94]

Given the evidence that glutamate pathways are involved in the pathophysiology of depression, IV-administered ketamine has been investigated for antidepressant properties.[68,88] In animal models, blockage of NMDA receptors was shown to result in antidepressant-like effects[3]; and in humans, a single subanesthetic dose infusion of ketamine has been shown to have rapid, potent

antidepressant effects in patients with TRD.[4,84,85,100] Several pilot studies using IV ketamine in subjects with MDD or bipolar depression also suggested that ketamine may reduce suicidal ideation within hours of administration.[4,31,60,101,103,123] In addition, 2 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).[5,87]

The mechanism of action of esketamine is distinct from conventional antidepressant treatments, which target modulatory monoaminergic neurotransmitters (serotonin, norepinephrine, and/or dopamine), 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.

Administered intranasally, esketamine is rapidly and well-absorbed, and can offer patients better convenience. Janssen Research & Development is developing intranasal esketamine both for TRD and for the rapid reduction of the symptoms of MDD, including suicidal ideation, in adult patients who are assessed to be at imminent risk for suicide. As part of the pediatric development program, this study is evaluating the efficacy, safety and dose response of esketamine in subjects 12 to <18 years of age with MDD who are assessed to be at imminent risk for suicide.

For the most comprehensive nonclinical and clinical information regarding esketamine (JNJ-54135419), refer to the latest version of the Investigator's Brochure for esketamine, and associated addenda.[48,49,50]

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.[48,49,50] 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.[55] 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.[55]

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. No adverse effects were noted up to the highest dose tested (ie, 9 mg/day in rats, and 72 mg/day in dogs).[48,49,50]

The C_{max}-based exposure ratios for esketamine compared to the 84 mg human dose ranged from 1.3- and 0.7-fold. The AUC-based exposure ratios for esketamine compared to the 84 mg human dose ranged from 0.7- to 1.1-fold.[48,49,50]

Neurotoxicity: Racemic ketamine has been reported to induce neurotoxicity in animal fetuses, and in juvenile, adolescent, and adult animals, as evidenced by histopathological brain lesions and functional sequelae. The precise thresholds for dose and duration of ketamine exposure causing neurotoxicity in animals remain to be established. The relevance to humans of ketamine's neurotoxic action in animals is unknown.

In animal studies with intranasally-administered esketamine no evidence of neurotoxicity was found. In single-dose and 14-day repeat-dose neurotoxicity studies in rats, no histopathological brain lesions were noted up to 54 mg/day in the 14-day study, and 72 mg as a single intranasal dose. In the 14-day rat study the C_{max}- and AUC-based safety margins for esketamine compared to the 84 mg human dose were approximately 17- and 11-fold, respectively. At a single intranasal dose of 72 esketamine the C_{max}- and AUC-based safety margins compared to the 84 mg human dose were approximately 60- and 86-fold, respectively[48,49,50] In the 6-month rat and 9-month dog repeat-dose toxicity studies with intranasally-administered esketamine, where the animals were of adolescent age at initiation of treatment, and in the pre- and postnatal developmental toxicity study in rats, no morphological or functional evidence of neurotoxicity was observed either.[48,49,50]

Reproductive and Developmental Toxicity: In a fertility and early embryonic developmental study, no adverse effects of intranasal esketamine on the fertility and reproductive capacities of adult male and female rats were observed.[48,49,50] Rat and rabbit embryo-fetal developmental toxicity studies with intranasally-administered racemic ketamine did not reveal evidence of reproductive toxicity.[48,49,50] High dose levels of racemic ketamine, however, induced neuronal cell death in the brain when administered to early postnatal rat pups.[48,49,50] Also, when monkey fetuses were exposed in utero to high dose levels of racemic ketamine, neuronal cell death was found in the brain.[48,49,50] Ketamine anesthesia during the first week of life caused long-lasting cognitive deficits in monkeys.[48,49,50]

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.[48,49,50]

Abuse potential: The results of self-administration and withdrawal experiments in several animal models suggest that esketamine would have abuse potential in humans.[9,24,25,57,77,120,121]

1.1.2. Clinical Studies

1.1.2.1. Completed and Ongoing Clinical Studies with Intranasal Esketamine

A total of 10 Phase 1 studies with intranasal esketamine have been completed and reported, including 7 studies in healthy younger adult subjects, 2 studies in healthy elderly and younger adult subjects, and 1 study in subjects with a history of allergic rhinitis. In total, 320 subjects have been exposed to intranasal esketamine in the completed Phase 1 studies that have been reported.[48,49,50]

Two 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, subjects with renal impairment, and subjects with MDD.

One Phase 2 study has been completed in adult 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 TRD, with 107 subjects exposed to intranasal esketamine.[48,49,50] In addition, one Phase 2 study in subjects with TRD is ongoing in Japan.

In the clinical development program for intranasal esketamine, 6 Phase 3 clinical trials are ongoing in adult 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.[48,49,50]

1.1.2.2. Human Pharmacokinetics and Product Metabolism

Racemic Ketamine

The pharmacokinetics of IV ketamine has been examined in several studies with pediatric patients 1.5 to 14 years of age who were administered single doses of 1 to 6 mg/kg.[38,41,66] The PK estimates of key parameters, namely clearance and distribution volume, in children were similar relative to estimates in adult patients who received IV ketamine after standardization for body size. The absolute bioavailability of intranasally administered esketamine was estimated to be 50%, which is similar to the 42% and 45% bioavailability estimated in adults.[98,119]

It is evident from the published studies that racemic ketamine and esketamine are metabolized in children (1-9 years of age) to norketamine and noresketamine, respectively, based on the measured concentrations of each in plasma. A population PK analysis which included norketamine concentration-time data from 57 pediatric patients (1.5-14 years of age) and adults who received IV ketamine indicated that estimates were indistinguishable from each other when standardized to a 70 kg person.[42]

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 has a half-life in plasma of approximately 5 hours in humans.[40] The major human hepatic cytochromes that catalyze ketamine N-demethylation in vitro were CYP2B6 and CYP3A4,[43,99,118] and those that were responsible for the formation of norketamine metabolites included CYP2A6 and CYP2B6.[99] Pharmacokinetic (PK) results after IV administration of racemic ketamine and esketamine to human subjects suggest that inversion of esketamine to arketamine (the R-enantiomer of ketamine) does not occur.[36]

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.[115]

Intranasal Esketamine

The PK of intranasal esketamine have been characterized in healthy adult subjects (elderly and younger adults), subjects with a history of allergic rhinitis, subjects with treatment-resistant depression (TRD),[48,49,50] and subjects with MDD at imminent risk for suicide. In healthy adult subjects, intranasally-administered esketamine (28 mg 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).[48,49,50] When administered in healthy adult subjects via the intranasal route, esketamine was rapidly absorbed and had an absolute bioavailability of approximately 48% (ESKTINTRD1009).[48,49,50] In a Phase 2 study in adult 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.[48,49,50] Furthermore, the mean esketamine concentrations in plasma samples collected at corresponding time points on Days 1, 11, and 25 were similar suggesting that the PK was consistent after repeated intranasal administration.[48,49,50] 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.[67] Further, results from Panel A, part of 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 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.[48,49,50] 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 (mean differences [SE] between each esketamine group and the placebo group were -4.2 [2.09], p=0.021; -6.3 [2.07], p=0.001; and -9.0 [2.13], p<0.001 for esketamine 28, 56, and 84 mg, respectively). Additionally, there was a significant relationship between esketamine dose and change in MADRS total score (p<0.001).[48,49,50] 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.[48,49,50] 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 (least squares 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).[48,49,50] 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).[48 49,50]

Several pilot studies using IV ketamine in subjects with MDD or bipolar depression also suggested that ketamine may reduce suicidal ideation within hours of administration.[31,60,101,103,123] In addition, 2 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).[5,87]

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. Adult subjects with a diagnosis of MDD assessed to be at imminent risk for suicide from the US 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. Statistical significance for this proof-of-concept study was based on a two-sided significance level of 0.20. Esketamine 84 mg, compared to placebo, demonstrated evidence for a clinically meaningful and statistically significant reduction of depressive symptoms as assessed by changes from baseline in MADRS total score at 4 hours after the first dose (primary endpoint; least squares mean difference [SE] between esketamine 84 mg and placebo: -5.3 [2.10]; p=0.015), at approximately 24 hours after the first dose (least squares mean difference [SE]: -7.2 [2.85]; p=0.015). At the end of the double-blind phase esketamine 84 mg, compared to placebo, demonstrated evidence for a potential therapeutic effect (least squares mean difference [SE]: -4.5 [3.14]; p=0.159).[16] The changes from baseline in suicidal thoughts based on the MADRS-SI score also favored esketamine 84 mg at 4 hours after the first dose (p=0.002), at approximately 24 hours after the first dose (p=0.129), and at the end of the double-blind phase (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 support the hypothesis that esketamine, administered intranasally, is an efficacious treatment for the rapid reduction of the symptoms of MDD, including suicidality, 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.[39,56,105,110] 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.[55]

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.[48,49,50] 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).[48,49,50] 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).[48,49,50] 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 this event 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.[23] 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 postdose, with the majority returning within the normal range by 2 hours postdose.[23] 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 CADSS. Dissociative symptoms peaked at approximately 40 minutes after dosing and typically resolved by 2 hours after dosing.[23] The magnitude of postdose dissociative symptoms decreased over time with repeated consecutive doses for all esketamine doses.

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

In the Phase 2 study in adult subjects with MDD at imminent risk for suicide (ESKETINSUI2001, esketamine 84 mg versus placebo), 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. 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, dyspnea, aggression and agitation. In total, 3 of 35 subjects in the esketamine group had dose reductions from 84 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.[29,78,80,89] Overall, infrequent use did not appear to be associated with long-term cognitive impairment.[89] The most robust findings were that frequent ketamine users (more than 5 times a week) exhibited impairments in both short- and long-term memory.[80] 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.[81]

A controlled study of short-term esketamine use in patients with TRD demonstrated a decline in cognitive function shortly after a single 84-mg dose administration (40 minutes postdose) that returned to comparable baseline levels by 2 hours postdose.[82]

Ketamine-induced ulcerative cystitis is also an identified complication.[79] 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.[46,52,79,76,95] 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.[83] 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.[27,63,79]

1.2. Psychoactive Placebo Control

Midazolam

Oral midazolam solution, 0.125 mg/kg, will be used as a psychoactive placebo in a double-dummy study design. Given the transient dissociative and sedative side effects of esketamine, midazolam was selected as a psychoactive placebo in order to maintain blinding.[86] Midazolam is a short-acting benzodiazepine central nervous system depressant, with pharmacokinetic characteristics similar to those of ketamine; that is, fast onset of action and short elimination half-life. It also possesses psychoactive effects such as sedation and disorientation.[72,73] Oral midazolam is indicated for use in pediatric subjects for sedation, anxiolysis, muscle relaxation, and amnesia prior to a medical procedure, and before induction of anesthesia. Common reported effective doses range from 0.25 mg/kg to 1 mg/kg in children 6 months to <16 years of age.[71] While midazolam is anxiolytic, it has not been shown to be efficacious as a treatment for depression. Midazolam has been previously used as a psychoactive placebo in studies of ketamine.[86]

The midazolam dose of 0.125 mg/kg is based on a study of IV ketamine in adult subjects with TRD in which midazolam 0.045 mg/kg IV was used.[86] Assuming 36% bioavailability of the oral formulation in pediatric patients,[104] an oral dose of 0.125 mg/kg was calculated to be equivalent to the IV dose of 0.045 mg/kg. The midazolam dose selected for this study is approximately 25% of that recommended for pre-anesthetic use in pediatric populations.

Midazolam exhibits linear pharmacokinetics between oral doses of 0.25 to 1 mg/kg (up to a maximum dose of 40 mg) across the age groups ranging from 6 months to <16 years. The 36% absolute bioavailability of orally administered midazolam in pediatric patients is not affected by pediatric age or weight. Midazolam is rapidly absorbed after oral administration with t_{max} occurring between approximately 0.5 and 3 hours. The half-life of midazolam ranges between 2 and 6 hours. Midazolam is primarily metabolized to 1 hydroxymidazolam by CYP3A4 and is considered a sensitive probe of CYP3A4 activity. Fluoxetine, escitalopram or sertraline are not expected to influence the metabolic clearance of midazolam.

The sedative effects of midazolam are accentuated by any concomitantly administered medications that depress the central nervous system, particularly narcotics, secobarbital and droperidol. Caution is also advised when midazolam is administered with drugs that are known to inhibit the P450-3A4 enzyme system such as (not ranitidine), diltiazem, verapamil, ketoconazole, and itraconazole. These drug interactions may result in prolonged sedation due to a decrease in plasma clearance of midazolam.[70]

Adverse events associated with midazolam administration include sedation, vomiting, nausea, hypoxia, laryngospasm, respiratory depression, rhonchi, congestion, agitation, involuntary movements (including tonic-clonic movements and muscle tremor), bradycardia, bigeminy, and skin rash.[71] Benzodiazepines, including midazolam, are contraindicated in patients with acute narrow-angle glaucoma. Flumazenil is a specific reversal agent for midazolam.[70]

1.3. Overall Rationale for the Study

The current study is being conducted to evaluate the efficacy, safety and dose response of 3 fixed doses of intranasal esketamine (28, 56 and 84 mg) compared with a psychoactive placebo, each given in addition to comprehensive standard of care in subjects 12 to <18 years of age with MDD who are at imminent risk for suicide 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 assess the efficacy of a single (first) dose of 3 fixed doses of intranasal esketamine (28 mg, 56 mg, and 84 mg) compared with psychoactive placebo (oral midazolam) in rapidly reducing the symptoms of MDD, including suicidal ideation, in subjects 12 to <18 years of age who are assessed to be at imminent risk for suicide. Efficacy will be assessed by the change from baseline in Children's Depression Rating Scale, Revised (CDRS-R) total score at 24 hours post first dose (Day 2).

Other Objectives

The other objectives are the following:

- To evaluate the dose response of intranasal esketamine compared with psychoactive placebo in reducing the symptoms of MDD, including suicidal ideation, as assessed by the change from baseline in CDRS-R total score at 24 hours post first dose (Day 2) and at Day 25.
- To evaluate the efficacy of single and repeated doses of intranasal esketamine compared with psychoactive placebo in reducing symptoms of suicidal ideation, as assessed by the Clinical Global Impression of Severity of Suicidality, revised version (CGI-SS-R) from the Suicide Ideation and Behavior Assessment Tool (SIBAT) 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 single and repeated doses of intranasal esketamine compared with psychoactive placebo in reducing symptoms of MDD as assessed by the following:
  - CDRS-R total score at 4 hours post first dose, through the end of the Double-Blind Treatment phase (Day 25), and during the 6-month Post-Treatment Follow-Up phase.
  - MADRS total score at 4 hours and 24 hours post first dose, through the end of the Double-Blind Treatment phase (Day 25), and during the 6-month Post-Treatment Follow-Up phase.

  - Children's Depression Inventory 2: Self-Report (Short) version (CDI 2:SR[S])™ score at 24 hours post first dose and through the end of the Double-Blind Treatment phase (Day 25).

- To evaluate the efficacy of single and repeated doses of intranasal esketamine compared with psychoactive placebo in reducing symptoms of suicidal ideation, as assessed by the Clinical Global Impression – Imminent Suicide Risk (CGI-SR-I) from the SIBAT 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 single and repeated doses of intranasal esketamine compared with psychoactive placebo in reducing suicidal thoughts, as assessed by the following:
  - Change from baseline in SIBAT Module 3 (My Current Thinking) and Module 5 (My Risk) Question 3 (patient-reported frequency of suicidal thinking) through the end of the Double-Blind Treatment phase (Day 25) and during the 6-month Post-Treatment Follow-Up phase.
- To characterize the pharmacokinetics of intranasal esketamine and its metabolite noresketamine.
- To evaluate the safety and tolerability of intranasal esketamine through the end of the Double-Blind Treatment phase (Day 25) using the following assessments:
  - Effects on suicidal ideation and behavior using the SIBAT
  - Effects on dissociative symptoms using the Clinician-Administered Dissociative States Scale (CADSS)
  - Occurrence of psychosis-like side effects using a 4-item positive symptom subscale (consisting of: suspiciousness, hallucinations, unusual thought content, and conceptual disorganization) of the Brief Psychiatric Rating Scale, positive symptom subscale (BPRS+)
  - Occurrence of potential treatment-emergent symptoms of mania using the Young Mania Rating Scale (YMRS)
  - Effects on cognitive function as measured by the Cogstate computerized cognitive battery
  - Effect on sedation using the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale
  - Local nasal tolerability, using targeted nasal examinations coupled with a nasal symptom questionnaire
- To evaluate the safety and tolerability of intranasal esketamine at specified times through the initial 25 day double-blind treatment period (Day 25), the 8-week post-treatment follow-up (Day 81) and 6-month post-treatment follow-up, with special attention given to the following assessments:
  - Effects on suicidal ideation and behavior using the SIBAT
  - Effects on cognitive function as measured by the Cogstate computerized cognitive battery
- To evaluate potential withdrawal symptoms during the post-treatment follow-up as measured by the Physician Withdrawal Checklist (PWC-20) on Days 25, 28, 32, 35 and 39.
- To evaluate the potential for ketamine or PCP abuse during the follow-up as measured by the Timeline Follow-Back (TLFB).

- To evaluate whether pretreatment concentrations of MDD-related biomarkers (eg, 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.
- To explore the change in MDD-related biomarkers in relation to clinical response or non-response to intranasal esketamine.

2.1.2. Endpoints

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

- Other efficacy endpoints will be evaluated throughout the study, as follows:
  - CDRS-R
    - Dose response at 24 hours post first dose.
    - Changes from baseline, post single and repeated doses, at 4 hours post first dose, through the end of the Double-Blind Treatment phase (Day 25), and during the 6-month Post-Treatment Follow-Up phase.
  - MADRS
    - Changes from baseline, post single and repeated doses, at 4 hours and 24 hours post first dose, through the end of the Double-Blind Treatment phase (Day 25), and during the 6-month Post-Treatment Follow-Up phase.
  - CGI-SS-R from SIBAT
    - Changes from baseline, post single and repeated doses at 4 hours and 24 hours post first dose, through the end of the Double-Blind Treatment phase (Day 25).
  - CGI-SR-I from SIBAT
    - Changes from baseline, post single and repeated doses at 4 hours and 24 hours post first dose, through the end of the Double-Blind Treatment phase (Day 25).
  - SIBAT
    - Changes from baseline, post single and repeated doses, through the end of the Double-Blind Treatment phase (Day 25) and during the 6-month Post-Treatment Follow-Up phase in depressive symptoms and suicidal ideation (subject-completed modules 3, 4, and 5) and clinician impression of suicidality and judgment about management of suicidal thinking (clinician-completed modules 7 and 8).
  - CDI 2:SR (S)
    - Changes from baseline, post single and repeated doses, at 24 hours post first dose and through the end of the Double-Blind Treatment phase (Day 25).
- Safety endpoints will be evaluated throughout the study, as follows:
  - Monitoring of TEAEs

- Clinical laboratory tests, physical examination, nasal examination and nasal symptom questionnaire, 12-lead ECG, vital signs, pulse oximetry and body weight
- SIBAT
- BPRS+ score
- CADSS
- Cogstate computerized cognitive battery
- YMRS score
- Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score
- Physician Withdrawal Checklist (PWC-20)
- TLFB methodology to evaluate use of ketamine or PCP.

- 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. Plasma concentrations of other esketamine metabolites and midazolam may also be measured, if warranted.
- Biomarkers
  - Characteristics of esketamine mechanism of action or biological predictors of inter-individual variability.

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

2.2. Hypothesis

The primary hypothesis of this study is that, in addition to standard of care, intranasal esketamine is superior to psychoactive placebo in rapidly reducing the symptoms of MDD, including suicidal ideation, as assessed by the change from baseline in CDRS-R at 24 hours post first dose in subjects 12 to <18 years of age who are assessed to be at imminent risk for suicide.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This Phase 2 study is a randomized, double-blind, double-dummy, psychoactive placebo-controlled, multicenter trial with 45 anticipated global sites. A target of 145 male and female subjects, 12 to <18 years of age, will be enrolled in this study and randomized in a 1:1:1:2 ratio to one of 3 doses of intranasal esketamine (28, 56 or 84 mg) or a psychoactive placebo (oral midazolam 0.125 mg/kg), with approximately 29 subjects assigned to each dose of intranasal esketamine and approximately 58 subjects assigned to psychoactive placebo. All eligible subjects will have a diagnosis of MDD, and will have presented to an emergency room (ER) or other permitted setting and been assessed to be at imminent risk for suicide. Given the vulnerability of the population, this study will be conducted in the context of standard of care treatment. This includes initial hospitalization in an inpatient psychiatric unit or other permitted setting for a recommended duration of 5 days counted from randomization, with shorter or longer

hospitalizations permitted if clinically warranted per local standard of care; initiation or optimization of allowed antidepressant treatment; participation in a specific psychological intervention (individual cognitive behavioral therapy [CBT]), interpersonal therapy, family therapy or psychodynamic psychotherapy); and close outpatient follow-up.

There is only 1 approved antidepressant for the treatment of MDD in children and adolescents in both the United States (US) and European Union (EU): fluoxetine; however, if treatment with fluoxetine is unsuccessful or is not tolerated because of side effects, guidelines recommend treatment with citalopram and sertraline.[20,22,61,91] Escitalopram (the S-enantiomer of citalopram) is also approved for use in adolescents in the US. Therefore, this multi-national study will permit the use of fluoxetine, escitalopram or sertraline as the standard of care antidepressants.

The study will be conducted in 4 phases: a screening evaluation performed within 48 hours prior to Day 1 intranasal dose (if possible, screening should occur within 24 hours prior to the Day 1 intranasal dose); a 25-day Double-Blind Treatment phase (Days 1-25), during which study drug will be administered 2 times per week for 4 weeks on Days 1, 4, 8, 11, 15, 18, 22, and 25; an 8-week initial post-treatment phase (Days 25-81); and a subsequent phase to complete a full 6-month post-treatment follow-up (Days 81-200). During post-treatment follow-up phases, no study drug will be administered. The duration of the subject's participation will be approximately 29 weeks.

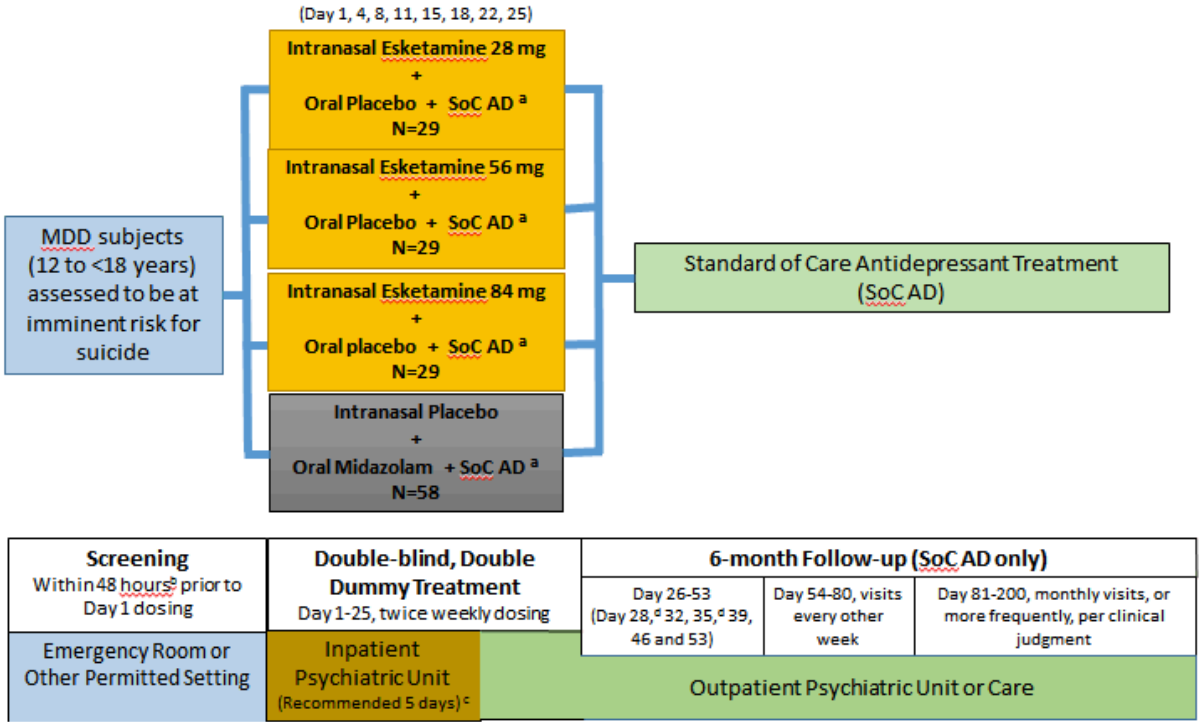
Efficacy, safety, pharmacokinetic, biomarker, and pharmacogenomic (DNA and RNA) evaluations will be performed as described in the Time and Events Schedule.

- The primary efficacy evaluation is the CDRS-R; other efficacy evaluations are SIBAT/CGI-SS-R and CGI-SR-I, MADRS, CDI 2:SR(S).
- Safety evaluations include monitoring and collection of adverse events and concomitant therapies, physical examination, nasal examination and nasal symptom questionnaire, measurements of body weight and vital signs, 12-lead electrocardiogram (ECG), pulse oximetry, clinical laboratory tests, SIBAT, MOAA/S, CADSS, BPRS+, YMRS, PWC-20, TLFB, and Cogstate computerized cognitive battery.
- 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.
- Blood samples for DNA and RNA analyses will be collected from subjects who consent/assent separately to this component of the study (where local regulations permit). Subject participation in DNA and RNA research is optional.

An Independent Data Monitoring Committee (IDMC) will be commissioned for this study (refer to Section 11.7, Data Monitoring Committee, for details).

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

Figure 1: Schematic Overview of the Study



Abbreviations: AD, antidepressant; SoC, standard of care.

[a] Antidepressant medication should be initiated or optimized on Day 1. However, initiating standard of care antidepressant medication up to 7 days after the first dose of study medication (Day 1), is permitted if starting two medications simultaneously is not consistent with local clinical practice.

[b] If possible, screening should be performed within 24 hours prior to Day 1 intranasal dose.

[c] Hospital discharge before 5 days (from randomization) must be discussed with 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.

[d] Remote contact.

3.2. Study Design Rationale

3.2.1. Study Population

This study will enroll subjects 12 to <18 years of age with MDD presenting with suicidal ideation who are assessed to be at imminent risk for suicide. MDD is the most prevalent mental health condition and the psychiatric diagnosis most commonly associated with suicide.[54,91] Depression is the main predictor of suicidal ideation.[37,93] In the US, the age standardized suicide rate increased 24.2% over the 12-year period from 2000 to 2012, rising from 9.8% to 12.1% per 100,000 individuals. Young people are among those most affected. Globally, suicide accounts for 8.5% of all deaths among young adults (15−29 years of age) and is ranked as the second leading cause of death.[92] In the US, suicide is the third leading cause of death for young people between the ages of 10 and 24, and results in approximately 4,600 deaths each year.[17] Data from the cross-national World Mental Health survey indicate that the risk of first onset of suicidal ideation increases sharply during adolescence and young adulthood.[92] Older adolescents (13 – 18 years) are at higher risk of MDD than those younger than 13 years (overall point prevalence estimates [±SE] 5.6±0.3%

versus 2.8±0.5%, respectively).[17,117] The age range of subjects 12 to < 18 was chosen due to the significant unmet need for effective treatment in this particularly vulnerable population.

The MINI-KID 7.0.2 will be utilized to identify adolescents with a primary diagnosis of MDD without psychotic features. Affirmative responses to questions B3 and B10 of the MINI-KID, along with clinical need for hospitalization, will confirm that subjects are experiencing active suicidal ideation with intent, and thus are considered to be at imminent risk for suicide. A requirement for a CDRS-R total score of ≥58 will ensure that subjects have level of depressive symptomatology that is moderate to severe.

Subjects with a current diagnosis of bipolar disorder**,** intellectual disability, autism spectrum disorder, conduct disorder, anorexia nervosa, oppositional defiant disorder, obsessive compulsive disorder, borderline personality disorder, or those who meet Diagnostic and Statistical Manual of Mental Disorders (5th edition) (DSM-5) severity criteria of moderate or severe substance or alcohol use disorders within the 6 months before screening will be excluded to ensure the subject's depression is not attributed to a disorder other than MDD, and 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[53] and post-hospitalization.[11,102,114] The dosing regimen in this study includes administration of esketamine twice a week 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 duration of follow-up in this study covers the period of greatest risk for recurrent suicidality post initial attempt and/or hospitalization.[11,15,102]

The follow-up after the 25-day double-blind treatment period is through Day 200 and will allow for the exploration of the continued effects of esketamine on depression and suicidal symptoms. No study medication will be administered during the follow-up phase. Visits will continue to occur twice a week for the first 2 weeks (Days 28, 32, 35, 39), after which visits will occur weekly (Days 46 and 53), then every 2 weeks (Days 67 and 81). The Day 28 and 35 visits are remote contact visits. After the Day 81 visit, subjects will enter the extended Post-Treatment Follow-Up phase (Days 81-200), during which they will have monthly visits to assess safety. Investigators may add follow-up visits as dictated by the subject's clinical condition and the investigator's clinical judgment. Additionally, throughout the follow-up period, suicide attempts, hospital re-admissions for suicidality, and ER visits will be followed and noted as part of safety outcomes.

3.2.3. Control, Randomization and Blinding

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.

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, a psychoactive placebo, midazolam, will be used. Midazolam has been used as a psychoactive placebo in previous studies of ketamine[88] because of its similar onset of action and side effect profile.

The effect of a placebo response is of particular concern in clinical trials of MDD.[97] Because a lower likelihood of randomization to placebo has been shown to be associated with placebo response,[97] a treatment allocation of 1:1:1:2 for 28 mg: 56 mg: 84 mg: psychoactive placebo is being used to minimize expectancy bias and to mitigate placebo response.

A double-dummy design will be used in order to preserve the blind since the active study drug (intranasal esketamine) and the psychoactive placebo (oral midazolam) are administered via different routes. Therefore, 2 matching placebo formulations, intranasal and oral, will be included in the treatment regimen. In order to maintain the blind, subjects randomized to intranasal esketamine will also receive an oral placebo, and subjects randomized to oral midazolam will also be administered an intranasal placebo.

3.2.4. Esketamine Dose

In a Phase 2 study, ESKETINTRD2003,[23] the efficacy of intranasal esketamine at 28 mg, 56 mg, and 84 mg doses was assessed in adult subjects with TRD. Data from the double-blind phase showed that intranasal esketamine had a rapid onset of effect, and repeated treatment sessions sustained the response throughout the study duration. A clear dose response was observed for the 28-, 56- and 84-mg doses, with the most robust and sustained efficacy observed at the 84 mg dose. The primary efficacy endpoint (change in MADRS total score from baseline to Day 8) demonstrated statistically significant improvement in all 3 esketamine dose groups.

In this study, the same intranasal esketamine doses of 28, 56, and 84 mg will be evaluated to establish optimal dose, taking into consideration benefits and tolerability, in young subjects with major depressive disorder with imminent suicidality (MDSI). A population PK analysis which included esketamine and its active metabolite, norketamine, concentration-time data from 57 pediatric subjects (1.5 to 14 years old) and adults who received IV ketamine indicated that estimates were indistinguishable from each other when standardized to a 70 kg person.[42] Therefore, standard allometric scaling was applied using the population pharmacokinetic model developed with adult data after intranasal administration of esketamine in order to simulate esketamine systemic exposure in pediatric subjects. Simulations (based on standard allometric scaling) of the exposure of 56 and 84 mg of esketamine after intranasal administration in the 12 to <18 years of age show a similar exposure as in adults.

3.2.5. Psychoactive Placebo

Midazolam

Oral midazolam solution, 0.125 mg/kg, will be used as a psychoactive placebo in a double-dummy study design. Given the transient dissociative and sedative side effects of esketamine, midazolam was selected as a psychoactive placebo in order to maintain blinding.[86] Midazolam is a short-acting benzodiazepine central nervous system depressant, with pharmacokinetic characteristics similar to those of ketamine; that is, fast onset of action and short elimination half-life. It also possesses psychoactive effects such as sedation and disorientation.[72,73]

The midazolam dose of 0.125 mg/kg is based on a study of IV ketamine in adult subjects with TRD in which midazolam 0.045 mg/kg IV was used.[86] Assuming 36% bioavailability of the oral formulation in pediatric patients,[104] an oral dose of 0.125 mg/kg was calculated to be equivalent to the IV dose of 0.045 mg/kg, approximately 25% of the pediatric dose recommended for pre anesthetic use (0.2-0.5 mg/kg).[72,73]

For further information regarding midazolam refer to the package insert[72] or Summary of Product Characteristics.[73]

3.2.6. Efficacy Measures

Children's Depression Rating Scale, Revised (CDRS-R)

The primary outcome measure in this study will be the CDRS-R, a validated 17-item, clinician-rated instrument developed to assess depressive symptomatology in children that measures the severity of a patient's depressive symptoms.[69] CDRS-R has been used in previous pivotal trials of selective serotonin reuptake inhibitors (SSRIs) in children and adolescents. It was selected as the primary outcome measure since it reflects the core symptoms of MDD, as defined by DSM-5, including a suicide-related item. The scale has demonstrated good reliability and validity in adolescents with depression.[69]

This study is aimed at evaluating the rapid reduction of symptoms of MDD, including suicidality, in subjects 12 to <18 years of age 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 CDRS-R 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 time point is relevant to current clinical practice as patients at imminent risk for suicide are typically hospitalized for at least 24 hours.

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 the antipsychotic medications clozapine and olanzapine to reduce suicidal behaviors in patients with schizophrenia

or schizoaffective disorder who are known to be at high risk for suicide. 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 of the InterSePT Scale for Suicidal Thinking (ISST).

A revised version of the CGI-SS (CGI-SS-R) with a 7-point scale will be used in this study. 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 is currently undergoing validation in adults and children as part of the SIBAT.

The CGI-SS-R, assessed at 4 hours and 24 hours post first dose and through the end of the Double-Blind Treatment phase, will be used to evaluate other objectives by assessing:

- Change in severity of suicidality at 4 and 24 hours post first dose 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 post first dose on Day 1, 24 hours post first dose on Day 2, and through the end of the Double-Blind Treatment phase
- 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 (Section 9.2.2).

The CGI-SR-I will be used to evaluate other objectives by 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

Montgomery-Asberg Depression Rating Scale (MADRS)

The MADRS has been used as an efficacy outcome parameter in several adolescent treatment trials.[32,113] A 10-item clinician-administered scale that was designed to be used in subjects with MDD to measure the overall severity of depressive symptoms in adults.[74,75] 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[5,31,60,87,100,101] as well as in the sponsor's Phase 2 adult studies of esketamine in MDD with imminent risk for suicide (ESKETINSUI2001) and in TRD (ESKETINTRD2003 and the Phase 3 studies of esketamine in TRD).

Although not validated in children, the MADRS has been included in previous pediatric trials of antidepressants.[19,33,51] The MADRS will be used to evaluate the change from baseline in MADRS total score at 4 hours post first dose and 24 hours post first dose, through the end of the Double-Blind Treatment phase (Day 25), and through the 6-month Post-Treatment Follow-Up phase. The MADRS is included as an additional efficacy measure because in previous trials of esketamine

and ketamine in depression, it has been shown to be sensitive to rapid change in symptoms of depression and suicidal thoughts.

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, developed by a team of experts in suicide and psychometrics will be used. The SIBAT is presently undergoing validation in adults and children.

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 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 ISST,[65] 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), as well as a Clinical Global Impression of Imminent Suicide Risk (CGI-SR-I), which will be used to evaluate other objectives (further details are provided above). In addition, Module 3 (My Current Thinking) and Module 5 (My Risk) Question 3 (patient-reported frequency of suicidal thinking) from the SIBAT will be used to evaluate the other objective of assessing patient-reported suicidality through the end of the Double-Blind Treatment phase and during the 6-month Post-Treatment Follow-Up phase.

Children's Depression Inventory 2, Self-Report (Short Form) (CDI 2:SR[S])

The CDI 2:SR(S) assessment is a patient rated assessment of depressive symptoms in youth aged 7 to 17 years and an efficient screening measure that contains 12 items and takes 5 to 10 minutes to administer. The CDI 2:SR(S) has excellent psychometric properties and yields a total score that is generally very comparable to the one produced by the full-length version, CDI 2, a validated screening instrument for depression in children.[59]

3.2.7. Safety Evaluations

Physical examination, nasal examination, nasal symptom questionnaire, 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 girls of childbearing potential), urine drug screen, and evaluation of TEAEs and concomitant therapies will be performed during the study per the Time and Events Schedules to monitor subject safety.

The TEAEs of special interest will be examined separately grouped in the following Medical Dictionary for Regulatory Activities (MedDRA) based categories: drug abuse, dependence and withdrawal (standardized MedDRA queries [MedDRA SMQ]), 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 6.3.

In order to help investigators identify signs and events suggestive of withdrawal, the sponsor has included remote (eg, by telephone) contact 3 and 10 days after the last dose of study drug to assess adverse events.

As described further in Section 2.1.1, the following assessments will be used at the time points defined in the Time & Events Schedule to evaluate safety and tolerability, assess the severity and duration of any sedation, and detect any treatment-emergent worsening of psychiatric symptoms or cognition: MOAA/S, CADSS, BPRS+, YMRS, and Cogstate computerized cognitive battery. The PWC-20 and TLFB will be used to assess for signs and/or symptoms of withdrawal and abuse, respectively. A nasal examination and nasal symptom questionnaire will monitor for any signs of adverse effects on the nasal mucosa.

Although the SIBAT will be an efficacy evaluation, it will also be used as a safety evaluation to detect any worsening of suicidal ideation and behavior throughout the study.

On all outpatient 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 post dose 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.

3.2.8. Pharmacokinetic Assessments

The concentration-time data to be obtained in the present study will allow for estimation of individual PK parameters of esketamine (and noresketamine, if warranted) in adolescent subjects using a population modeling approach. The time and days of plasma sampling were chosen to gather maximal information about the PK properties of esketamine while minimizing subject burden regarding blood sampling.

3.2.9. Biomarker and Pharmacogenomic (DNA and RNA) Evaluations

3.2.9.1. Biomarker

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, and serum) will be collected to evaluate the mechanism of action of esketamine or help to explain inter-individual 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.

3.2.9.2. Pharmacogenomic/Epigenetic (DNA and RNA)

It is recognized that genetic variation can be an important contributory factor to inter-individual differences in drug distribution and response and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain inter-individual variability in clinical outcomes and may help to identify population subgroups that respond differently to a drug. The goal of the pharmacogenomic component is to collect DNA and RNA to allow the identification of genetic 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 in patients with MDD assessed to be at imminent risk for suicide.

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.

4. SUBJECT POPULATION

Screening for eligible subjects will 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). Note: Subjects with acute alcohol intoxication or other ingestion should not be screened but can be screened once sober. Requests to rescreen an individual

subject must be evaluated and approved by the sponsor representative or medical monitor on a case-by-case basis.

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 permitted.

For a discussion of the statistical considerations of subject selection, refer to Section 11.2, Sample Size Determination.

4.1. Inclusion Criteria

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

1. Male and female adolescents (12 to <18 years of age)

2. Subject must meet DSM-5 diagnostic criteria for MDD, without psychotic features, based upon clinical assessment and confirmed by the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID).[108]

3. Subject must have current suicidal thinking with intent at the time of screening, confirmed by "Yes" responses to both MINI-KID Question B3 (*Think about hurting yourself with the possibility that you might die. Or did you think about killing yourself?)* AND Question B10 (*Expect to go through with a plan to kill yourself?)*.

   Note: the response to B3 must refer to the present, whereas the response to B10 may reflect the past 24 hours. If screening is longer than 24 hours, the assessment of questions B3 and B10 for the MINI-KID must be repeated 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 must have a CDRS-R total score of ≥58 predose on Day 1.

6. As part of standard of care treatment, subject must agree 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).

7. Criterion modified per Amendment 2:

   7.1 As part of the newly initiated or optimized standard of care treatment, subject must agree to take one of the prescribed non-investigational antidepressants medications (fluoxetine, escitalopram, sertraline) at least during the Double-Blind Treatment phase (Day 25).

8. As part of standard of care treatment, subject must agree to participate in a specific psychological intervention (individual cognitive behavioral therapy [CBT], interpersonal therapy, family therapy or psychodynamic psychotherapy) at least through the initial 8-week post-treatment follow-up period (Day 81).

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

10. 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.

11. 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.

12. Criterion modified per Amendment 1

12.1. During the Double-Blind Treatment phase and for at least 6 weeks after the last dose of study drug, contraception is required. Sexual abstinence is strongly recommended; however heterosexually active female subjects must practice a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly).

Examples of highly effective contraceptives include: implantable progestogen-only hormone contraception associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); vasectomized partner; 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. For each subject, 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.

During the Double-Blind Treatment phase (from Day 1 through the day of the last dose of study drug) and for a minimum of 1 spermatogenesis cycle, defined as approximately 90 days after receiving the last dose of study drug, sexual abstinence is strongly recommended; however, heterosexually active male subjects must:

- practice 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).
- use a condom if his partner is pregnant.
- agree not to donate sperm.

Contraceptive use by males or females should be consistent with local regulations regarding the use of contraceptive methods for subject participating in clinical studies and should be discussed in detail with the subject by the study investigator.

13. A female subject of childbearing potential must have a negative urine pregnancy test at screening, baseline, and end of double-blind phase.

14. Subject must be willing and able to participate in all study activities and to adhere to the prohibitions and restrictions specified in this protocol (Section 4.3).

15. Criterion modified per Amendment 3

15.1 Subject's parent(s) or legally acceptable representative(s) [(LAR(s)] 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 allow the subject to participate in the study. Assent is also required of subjects as described in Section 16.2.3, Informed Consent/Pediatric Assent.

16. Criterion modified per Amendment 3

16.1 Subject's parent(s) or legally acceptable representative(s) [(LAR(s)] must sign a separate informed consent form if he or she agrees to have the subject provide an optional DNA/RNA sample for research (where local regulations permit). Assent is also required from the subject as described in Section 16.2.3 Informed Consent/Pediatric Assent. Refusal to give consent/assent for the optional DNA/RNA 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), intellectual disability, autism spectrum disorder, conduct disorder, anorexia nervosa, oppositional defiant 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 or prior DSM-5 diagnosis of a psychotic disorder or MDD with psychosis.

4. Criterion modified per Amendment 1

   4.1. 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.

5. Subject has a history of seizure disorder.

6. Criterion modified per Amendment 1

   6.1. Subject has a history or current signs and/or symptoms of liver or renal insufficiency; has a current diagnosis of clinically significant cardiac (eg, congenital heart disease, cardiomyopathy, or tachyarrhythmias), vascular, pulmonary, gastrointestinal, endocrine (including uncontrolled hyperthyroidism), neurologic, hematologic, rheumatologic, or metabolic (including severe dehydration/hypovolemia) disease based on investigator judgment.

7. Criterion modified per Amendment 1

   7.1. Subject has uncontrolled hypertension (SBP and/or DBP that is greater than or equal to the 95th percentile for sex, age, and height) despite diet, exercise or a stable dose of an allowed anti-hypertensive treatment at screening; or any past history of hypertensive crisis. See Attachment 2 for pediatric blood pressure tables with percentile ranking by age, sex, and height for determination of hypertensive status.

   Criterion modified per Amendment 3

   7.2. On Day -1 (screening) or Day 1 of the double-blind phase prior to randomization, a supine or semi-supine SBP and/or DBP ≥ the 95th percentile for sex, age and height is exclusionary (see Attachment 3). Subjects who fall below the 5th or above the 95th percentile for their age, sex, and height should be evaluated using the parameters for the 5th or 95th percentile. Note that subjects whose SBP and/or DBP values are ≥ the 95th percentile for sex, age and height may be reevaluated with a repeated measure once after 5 minutes of rest to assess eligibility.

   Subjects with conditions in which blood pressure elevation could pose a serious risk (including severe cardiovascular disease, recent cerebral injury, increased intracranial pressure / intracranial mass lesion, intracranial bleeding or acute stroke, primary developmental or secondary acquired glaucoma or perforating eye injury) are excluded.

8. Criterion modified per Amendment 1

   8.1. Subject has a positive urine test result(s) for phencyclidine (PCP), cocaine, methamphetamines, or amphetamines/3,4-methylenedioxy-methamphetamine (MDMA) at screening. Subjects known to be using heroin should be excluded from the study.

   Note: Subjects who have a positive test due to the appropriate use of prescribed opiates, methadone, benzodiazepines, barbiturates, or attention-deficit hyperactivity disorder (ADHD) medications may be eligible for study

participation per clinician judgment. In addition, subjects who have a positive test of 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 who have a positive test due to cannabinoids may be eligible provided they do not meet DSM-5 criteria for a moderate to severe substance abuse disorder.

Subjects who have a positive test due to opiates, including 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.

9. Subject has a history of malignancy within 5 years before screening, with the exception of a malignancy that, in the opinion of the investigator and in concurrence with the sponsor's medical monitor, is considered to have minimal risk of recurrence.

10. Subject has anatomical or medical conditions that may impede delivery or absorption of intranasal study medication.

11. Subject has an abnormal or deviated nasal septum with any 1 or more of the following symptoms: blockage of 1 or both nostrils, nasal congestion (especially 1-sided), frequent nosebleeds, and frequent sinus infections (and at times has facial pain, headaches, and postnasal drip with the sinus infection).

12. Subject has known allergies, hypersensitivity, intolerance or contraindications to midazolam, esketamine or ketamine, or their excipients.

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

14. Subject has received an investigational drug (including esketamine, ketamine, or investigational vaccines) or used an invasive investigational medical device within 60 days before the first dose of study drug or is currently enrolled in an investigational study.

15. Subject is a female who is pregnant, breastfeeding, or planning to become pregnant while enrolled in this study or within 3 months after the last dose of study drug.

16. 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.

17. Subject, parent or legal guardian 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. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. 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. Subjects should be accompanied by a responsible adult 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 details regarding prohibited and restricted therapy during the study.

4. Subjects may not receive electroconvulsive therapy (ECT), trans-cranial magnetic stimulation (TMS), ketamine or other antidepressant therapies (aside from those allowed) during the study.

5. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria.

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 4 treatment groups, in a 1:1:1:2 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. The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment

assignment. 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

Because the routes of administration differ between the active study drug and the psychoactive placebo, to maintain the study blind, 2 matching placebo formulations (intranasal and oral) will be used. A designated pharmacist (or other qualified healthcare professional), who has no involvement otherwise with either the study conduct or data collection, will be unblinded in order to prepare the oral study drug. Further details can be found in the investigational product preparation instructions, as part of the pharmacy manual. When possible, it is requested that different raters perform safety and efficacy ratings.

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 (ie, 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.

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. However, an analysis is planned after the last subject completes the Day 25 visit. Randomization codes will be disclosed to the sponsor in order to plan for Phase 3 studies. Subjects, site personnel, external medical monitors and external vendors will remain blinded to individual subject treatment assignments until the end of the study when the last subject completes the Day 200 visit.

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.

To maintain the blinding of oral study medication, the midazolam and placebo solutions will be indistinguishable. Additionally, the final dose of midazolam or equivalent oral placebo volume will be prepared by a designated pharmacist (or other qualified healthcare professional).

To maintain the integrity of the study blind, a urine drug screen (UDS) should not be performed during the DB period unless medically necessary. If deemed medically necessary, the medical monitor should be contacted and UDS should be performed predose on dosing days.

6. DOSAGE AND ADMINISTRATION

All subjects will be treated in the context of comprehensive standard clinical care, including the initiation or optimization of antidepressant treatment with one of 3 antidepressants allowed per protocol during double-blind treatment: fluoxetine, escitalopram, and sertraline. Treatment with a psychological intervention is also required, at least through the initial 8-week Post-Treatment Follow-Up phase (Day 81). The specific antidepressant and type of psychological intervention selected for a given subject will be based on the treating physician(s) clinical judgment, knowledge of the subject's prior treatment history, and practice guidelines. Acceptable types of psychological interventions include individual cognitive behavioral therapy (CBT), interpersonal therapy, family therapy, and psychodynamic psychotherapy. Other evidence-based psychotherapies may be allowed after consultation with the medical monitor. The frequency of psychotherapy visits should be determined based on clinical need, at the discretion of the treatment team. Unless clinical judgment dictates otherwise, it is recommended that subjects who have not previously been treated with an antidepressant receive standard of care antidepressant treatment with fluoxetine, as this is the only antidepressant approved in both the US and EU. Antidepressant medication should be initiated or optimized on Day 1. However, initiating standard of care antidepressant medication up to 7 days after the first dose of study medication (Day 1), is permitted if starting two medications simultaneously is not consistent with local clinical practice.

All study medication will be self-administered under the direct supervision of the investigator or designee. Instructions for use of the intranasal spray device will be provided as a separate document. On Day 1 of the Double-Blind Treatment phase, subjects will be randomized in a 1:1:1:2 ratio to treatment with one of 3 doses of intranasal esketamine (28, 56, or 84 mg) or oral psychoactive placebo (midazolam 0.125 mg/kg), administered 2 times per week for 4 weeks. Study medication dosing sessions should not take place on consecutive days. Randomization will be stratified by study center.

A double-dummy design will be used, with each subject receiving 1 dose of oral study drug followed closely by intranasal study drug (3 devices) as described below (Table 1) for each dosing event. Thus, subjects randomized to intranasal esketamine will also receive an oral placebo, and subjects randomized to oral midazolam will also be administered an intranasal placebo (3 devices).

See Section 9.1.3 for further details on dosing procedures during the Double-Blind Treatment phase.

6.1. Oral Study Drug

Oral midazolam solution (2 mg/ml) will be provided as a psychoactive placebo at a dose of 0.125 mg/kg to all subjects randomized to intranasal placebo. A designated pharmacist (or other qualified healthcare professional) will be unblinded in order to prepare the oral study drug. Subjects randomized to oral psychoactive placebo (midazolam) will receive a weight-based dose using a 2 mg/mL solution; those randomized to intranasal esketamine will receive an oral placebo solution in an equivalent volume to that which they would receive if randomized to the psychoactive placebo.

6.2. 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 study medication dosing days, a site staff member with basic life support training that is up to date per local regulations must be present with the subject during the dosing of study medication and the postdose observation period. In addition, a hand-held bag valve mask (Ambu bag) for manual ventilation support must be available.

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. For each intranasal esketamine or placebo dose, 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. Sprays to each nostril should be delivered in rapid succession at each of the 3 scheduled time points. Table 1 describes how esketamine or placebo will be administered in the Double-Blind Treatment phase. A total of 3 devices will be used by all subjects to administer 3 doses of esketamine or placebo.

A physical description of the study drugs is provided in Section 14.

Table 1: Dose administration of Intranasal Esketamine 28, 56, 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
Esketamine 56 mg	1 spray of esketamine to each nostril	1 spray of esketamine to each nostril	1 spray of placebo to each nostril
Esketamine 28 mg	1 spray of esketamine to each nostril	1 spray of placebo 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).

6.3. Guidance on Blood Pressure Monitoring on Study Medication Dosing Days

Elevated blood pressure in children is defined as SBP and/or DBP ≥ the 95th percentile for sex, age and height. Attachment 2 (Growth Charts: Stature-for-Age Percentiles for Use in Blood Pressure Assessments) and Attachment 3 (95th Percentile Blood Pressure Levels For Sex by Age and Height) will be used to determine the 95th percentile for both the systolic (SBP) and diastolic blood pressures (DBP) by sex, age and height percentile (refer to Attachment 3 for instructions).

If the predose SBP and/or DBP is elevated on any dosing day, blood pressure measurement should be repeated after the subject rests for at least 5 minutes in a supine or semi-supine position to confirm the measurement. If SBP and/or DBP remain ≥ the 95th percentile for sex, age and height (Attachment 3), 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 should be scheduled for a consultation by cardiologist, other specialist, or primary care physician prior to further dosing. Any elevation in blood pressure after dosing is expected to be transient. If an elevation is observed, continue monitoring until blood pressure returns to normal.

On any dosing day, if either the postdose SBP or DBP levels are equal to or greater than the sex, age and height values in Attachment 4 (Postdose Blood Pressure: Withdrawal Criteria Levels for Sex by Age and Height), the blood pressure should be repeated after the subject rests for at least 5 minutes (ie, sitting or supine). If the values are still equal to or greater than the sex, age and height values in Attachment 4, the subject should be withdrawn from the study and appropriate follow-up clinical care should be initiated.

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.

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 pre-existing therapy should not be made for the explicit purpose of entering a subject into the study.

A list of concomitant therapies that are prohibited, permitted, and permitted with restrictions is provided in Attachment 1 for general guidance for the investigator; 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 may not receive electroconvulsive therapy (ECT), TMS, ketamine or other antidepressant therapies (aside from those allowed) during the study. 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 (DNA and RNA), and safety measurements applicable to this study.

If multiple assessments are scheduled for the same time point, 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 serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

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

The maximum total blood volume to be collected from each subject will be approximately 56.5 mL for subjects who are participating in pharmacogenomics/epigenetic evaluations (see Table 2); total blood volume will be less for subjects who are not participating in these evaluations, as presented in Table 2.

Table 2: Approximate Volume of Blood to be Collected from Each Subject

Type of Sample ***Approximate total blood volume by phase***	Volume (mL) per sample	Number Samples/ Subject	Total Volume of Blood (mL) [a]
PRIOR TO DOUBLE-BLIND TREATMENT PHASE			
Serum chemistry (local SoC; central [Day -1]) [b]	1.1	2	2.2
Hematology (local SoC; central [Day -1]) [b]	1.2	2	2.4
Approximate total for serum chemistry + hematology			**4.6**
Biomarker evaluation [Day -1] [c]	4.0 (serum) 4.0 (plasma)	1 1	4.0 4.0
Pharmacogenomics/epigenetic evaluation [Day -1] [d]	2.0 (DNA) 2.5 (RNA)	1 1	2.0 2.5
Approximate total for all evaluations			**17.1**
DOUBLE-BLIND TREATMENT PHASE			
Serum chemistry (Day 25/EW)	1.1	1	1.1
Hematology (Day 25/EW)	1.2	1	1.2
Pharmacokinetic evaluation (Day 1 and Day 4)	2.0	6	12.0
Approximate total for serum chemistry + hematology+ PK evaluation			**14.3**
Biomarker evaluation (Days 4, Day 25/EW) [c]	4.0 (serum) 4.0 (plasma)	2 2	8.0 8.0
Approximate total for serum chemistry + hematology+ PK + biomarker evaluations			**30.3**
Pharmacogenomics/epigenetic evaluation (Day 25/EW) [d]	2.0 (DNA) 2.5 (RNA)	1 1	2.0 2.5
Approximate total for all evaluations			**34.8**
POST-TREATMENT FOLLOW-UP PHASE			
Serum Chemistry (Day 81, EW)	1.1	2	2.2
Hematology (Day 81, EW)	1.2	2	2.4
Approximate total for all evaluations			**4.6**
ALL STUDY PHASES			
Approximate total without pharmacogenomic samples			**47.5**
Approximate total for all evaluations			**56.5**

Abbreviation: DB: double-blind, PT: post-treatment, SoC: standard of care, EW: early withdrawal, PK: pharmacokinetic

[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 SoC local laboratory (to have results prior to Day 1 dose) and the central laboratory (see Section 9.6 for further details). Volume is approximate for local laboratories.

[c] Biomarker samples are as scheduled in the Time and Events Schedule.

[d] Pharmacogenomic (DNA and RNA) 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. Also note that there will be a small amount of blood discarded if a cannula is used.

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

Subjects will be instructed that study drug will not be made available to them after they have completed/discontinued study drug.

If a subject dies, the date and cause of death will be collected and documented on the eCRF.

9.1.2. Screening Phase

Prior to conducting any study procedure, the investigator (or designated study personnel) will review and explain the written pediatric assent to each potential subject, and the ICF to the subject's parent(s) or their legally acceptable representative(s)/[LAR(s)]. Potential subjects are aged 12 to <18 years with MDD presenting to an ER, psychiatric unit or other permitted setting and assessed to be at imminent risk for suicide (See Section 16.2.3).

After the ICF is signed by the subject's LAR, and the subject's assent is obtained, potential subjects will be screened under close supervision within 48 hours of intranasal dosing on Day 1 to determine eligibility for study participation. 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 or other permitted setting 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-KID. In addition, the subject must have a CDRS-R total score of ≥58 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. However, if the screening phase is longer than 24 hours, Question B3 and B10 from MINI-KID (current status) must be repeated 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 145 subjects will be randomly assigned in a 1:1:1:2 ratio to 1 of 3 doses of intranasal esketamine (28, 56 or 84 mg) or a psychoactive placebo (oral midazolam 0.125 mg/kg), with approximately 29 subjects assigned to each dose of intranasal esketamine and approximately 58 subjects assigned to psychoactive placebo. Study drug will be administered two times per week for 4 weeks (Days 1, 4, 8, 11, 15, 18, 22, and 25). Study medication dosing should not take place on consecutive days.

All subjects will be treated in the context of comprehensive standard clinical care, including hospitalization and the initiation or optimization of antidepressant treatment with one of 3 antidepressants allowed per protocol during double-blind treatment: fluoxetine, escitalopram, and sertraline. Treatment with a psychological intervention is also required, at least through the initial 8-week post-treatment phase (Day 81). The specific antidepressant and type of psychological intervention selected for a given subject will be based on the treating physician(s) clinical judgment, knowledge of the subject's prior treatment history, and practice guidelines. Acceptable types of psychological interventions include individual CBT, interpersonal therapy, family therapy, and psychodynamic psychotherapy. Other evidence-based psychotherapies may be allowed after consultation with the medical monitor. The frequency of psychotherapy visits should be determined based on clinical need, at the discretion of the treatment team. Unless clinical judgment dictates otherwise, it is recommended that subjects who have not previously been treated with an antidepressant receive standard of care antidepressant treatment with fluoxetine, as this is the only antidepressant approved in both the US and EU. Antidepressant medication should be initiated or optimized on Day 1. However, initiating standard of care antidepressant medication up to 7 days after the first dose of study medication (Day 1), is permitted if starting two medications simultaneously is not consistent with local clinical practice.

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 (initiated <2 weeks prior) may continue taking the antidepressant at the current dose through the end of the double-blind phase (Day 25), if deemed clinically appropriate by the treating physician. During the Double-Blind Treatment phase, the investigator should consult with the sponsor's medical monitor in advance if additional changes on antidepressant treatment are clinically indicated. Any changes to the standard of care antidepressant treatment, that is different from what was planned at the time of randomization, should be clearly documented including the reason for the change.

The first dose of study medication will be administered in the ER, inpatient psychiatric unit or other permitted setting that has appropriate staffing to manage acutely suicidal subjects and perform postdose study-related procedures. 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 or other permitted setting until after the postdose assessments (approximately 4 hours in length) are completed. Subjects who have been admitted directly into the inpatient psychiatric unit or other permitted setting 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 or other permitted setting.

Subjects will remain in the inpatient psychiatry unit or other permitted setting for a recommended duration of 5 days (4 nights) from randomization, with shorter or longer hospitalizations permitted if clinically warranted per local standard of care. The decision to discharge a subject from the hospital should be 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 or other permitted setting, subsequent visits for the Double-Blind Treatment phase will be conducted twice-weekly at an outpatient psychiatric facility through Day 25.

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

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).

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.

After the first dose on Day 1, whole blood samples (up to 6 samples, 2 mL each, from each subject) will be collected from a peripheral vein using an indwelling intravenous catheter at the time points specified in the TIME AND EVENTS SCHEDULE – Double-Blind Treatment Phase. The concentrations of esketamine and noresketamine in plasma will be measured using a validated bioanalytical method under the supervision of the sponsor's bioanalytical laboratory.

Efficacy, safety, pharmacokinetic, biomarker, and pharmacogenomics (DNA and RNA) evaluations will be performed as described in the TIME AND EVENTS SCHEDULE – Double-Blind Treatment Phase. 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
  - Patient Portion
  - Clinician Portion

- MADRS and CDRS-R
- CDI 2-SR(S)

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 if electronic entry is not functioning (refer to Section 15, Study-Specific Materials).

MADRS and CDRS-R will be performed at both predose and 4-hour postdose assessments on Day 25 (visit 10) of the Double-Blind Treatment phase.

9.1.4. Post-Treatment Follow-up Phases

Upon completion of the double-blind phase, subjects will enter a Post-Treatment Follow-Up phase. Visits will continue to occur twice a week for the first 2 weeks (Days 28, 32, 35, 39), after which visits will occur weekly (Days 46 and 53), then every 2 weeks (Days 67 and 81). The Day 28 and 35 visits are remote contact visits to assess the PWC-20, CDRS-R and MADRS, and collect concomitant therapies and AEs. After the Day 81 visit, subjects will enter the extended Post-Treatment Follow-Up phase (Days 81-200), during which they will have monthly visits to assess safety. Investigators may add follow-up visits as dictated by the subject's clinical condition and the investigator's clinical judgment. Evaluations will be performed as described in the TIME AND EVENTS SCHEDULE – Post-Treatment Follow-Up Phase.

9.1.5. Early Withdrawal

Subjects who discontinue Double-Blind Study treatment for reasons other than withdrawal of consent/assent, lost to follow-up or death will have the DB EW visit conducted at the time of discontinuation. In addition, if the DB EW visit occurs on Day 1 to Day 21, a remote contact visit (eg, by telephone) will be conducted 5 days (+/-2 days) after the last dose of study medication. If remote contact D+5 occurs within 2 days of the early withdrawal visit, +2 day window should be used to conduct the remote contact D+5 visit. A remote contact visit will also be conducted on Day 25 to assess PWC-20, CDRS-R and MADRS, and for collection of concomitant therapies and AEs. If the DB EW visit occurs on or after Day 22 (assuming dose administered), D25 RC visit is not required, however, RC D+5 (5 days after last dose) should be performed.

Subjects who discontinue from the Post-Treatment Follow-Up phase for reasons other than withdrawal of consent/assent, lost to follow-up or death will have the Post-Treatment Early Withdrawal visit conducted at the time of discontinuation. In addition, if the PT EW visit occurs prior to completion of the Day 81 visit, a remote contact (eg, by telephone) will be performed on Day 81 for PWC-20, CDRS-R and MADRS, and for collection of concomitant therapies and AEs. If the PT EW visit occurs within ±5 days window of Day 81 (Visit 18), then early withdrawal visit will be adequate, and the Day 81 RC visit is not required. If subjects discontinue anytime between Day 25 postdose and Day 28 RC of the PT phase, the PT EW visit is not required; however, Day 28 RC should be performed.

The investigator must ensure the subject is appropriately transitioned and/or followed for any additional care required when a subject discontinues participation in the study for any reason.

For information obtained via remote contact, written documentation of the communication must be available for review in the source documents. During remote contact visits with the subject by site personnel, concomitant therapies and adverse event information will be obtained, and CDRS-R and MADRS assessments will be performed by appropriately qualified staff.

9.2. Efficacy Evaluations

9.2.1. Children's Depression Rating Scale, Revised (CDRS-R)

The primary outcome measure in this study will be the CDRS-R, a validated 17-item, clinician-rated instrument developed to assess depressive symptomatology in children that measures the severity of a patient's depressive symptoms. The scale has demonstrated good reliability and validity in adolescents with depression.[69]

The typical recall period for the CDRS-R is 7 days. In this study, the CDRS-R will be administered using 4 recall periods: a 7-day recall on Day 1 (predose); a 4-hour recall at the 4-hour postdose assessment on Days 1 and 25; a 24-hour recall at the postdose assessment on Day 2; and a "since last assessment" recall predose on Day 4 through Day 25 dosing days. "Since last assessment" recall will also be used in Post-Treatment Follow-up assessments on Days 28, 32, 35 and 39. A 7-day recall will be used for Post-Treatment Follow-up assessments on Days 46-200. The sleep item score is not assessed at the 4-hour postdose time point on Day 1 and Day 25. For the CDRS-R performed at 4 hours postdose on Days 1 and 25, the CDRS-R scores for the sleep item recorded predose on the same day will be carried forward to calculate the total score.

9.2.2. Suicide Ideation and Behavior Assessment Tool (SIBAT)

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 a 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 reduction of suicidal ideation 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. Also included in this module is the CGI-SR-I,

which 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. Montgomery-Asberg Depression Rating Scale

The MADRS will be performed using the Structured Interview Guide for the Montgomery-Asberg Depression Rating Scale.[116]

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.[74,75] 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 be administered using 4 recall periods: a 7-day recall on Day 1 (predose); a 4-hour recall at the 4-hour postdose assessment on Days 1 and 25; a 24-hour recall at the postdose assessment on Day 2; and a "since last assessment" recall predose on Day 4 through Day 25 dosing days. "Since last assessment" recall will also be used in Post-Treatment Follow-up assessments on Days 28, 32, 35, and 39. A 7-day recall will be used for Post-Treatment Follow-up assessments on Days 46-200. The sleep item score is not 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 to calculate the total score.

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.

9.2.4. Children's Depression Inventory 2: Self-Report (Short)

The CDI 2:SR(S) assessment is based on the Children's Depression Inventory 2 (CDI 2) and Children's Depression Inventory 2 Self-Report (CDI 2:SR).

The CDI 2:SR is a 12-item self-reported assessment that yields a total score, 2 scale scores (emotional problems and functional problems), and 4 subscale scores (negative mood, negative self-esteem, ineffectiveness, interpersonal problems).

The CDI 2 SR(S), which will be used in this study, is a shortened version of the CDI 2:SR and is an efficient screening measure that contains 12 items and takes about half the time of the full-length version to administer (5–10 minutes). The CDI 2:SR(S) has excellent psychometric

properties and yields a total score that is generally very comparable to the one produced by the full-length version.[1]

9.3. Pharmacokinetics

Whole blood samples will be used to evaluate the PK of esketamine (and noresketamine, if warranted). 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 of pharmacokinetic blood sampling must be recorded.

Samples collected for analyses of esketamine plasma concentration may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period or for the evaluation of additional relevant biomarkers. Genetic analyses will not be performed on these plasma samples. Subject confidentiality will be maintained. Additional information about the collection, handling, and shipment of biological samples can be found in the Laboratory Manual.

9.3.2. Analytical Procedures

Pharmacokinetics

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 esketamine metabolites or midazolam 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.

Based on the individual plasma concentration-time data, using the actual dose taken and the actual sampling times, PK parameters and exposure information of esketamine will be derived using population PK modelling. Baseline covariates (eg, body weight, age, sex, CrCL, race) may be

included in the model, if relevant. The results of population PK analyses may be reported separately.

9.4. Pharmacokinetic/Pharmacodynamic Evaluations

The relationship between CDRS-R total score (and possibly other efficacy endpoints such as MADRS and 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 and RNA) Evaluations

Biomarker Evaluations

Blood samples will be collected as indicated in the Time and Events Schedule for exploratory analysis of biomarkers (protein and metabolites) 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.

If possible, blood samples should be collected under fasting conditions (minimum 8 hours prior to biomarker sample collection, water is permitted). When fasting is not feasible, subjects should follow a low fat diet for at least 8 hours prior to sample collection, if possible. Subjects should refrain from exercise/strenuous physical activity and the use of non-steroidal anti-inflammatory drugs (NSAIDs) for 24 hours prior to blood collection. Not following these recommendations will not constitute a protocol violation.

Biomarkers may be added or deleted based on scientific information or technical innovations under the condition that the total volume of blood collected will not be increased.

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

Per the Time and Events Schedule, information on menstrual cycle (date of first day of last period, average length of cycle) will be recorded at each visit when blood samples for biomarker analysis are collected.

Pharmacogenomics, Epigenetics, and Gene Transcription Evaluations

Subject participation in pharmacogenomics/epigenetic/gene transcription evaluations is optional. Whole blood samples for DNA and RNA analyses will be collected from all subjects who provide consent/assent for pharmacogenomic research at the time points indicated in the Time and Events Schedule.

DNA and RNA samples will be analyzed for the assessment of genetic variation and transcription of 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 and RNA samples will be used for research related to esketamine or MDD. They may also be used to develop tests/assays related to esketamine and MDD. Pharmacogenomic research may

consist of the analysis of one or more candidate genes or of the analysis of genetic markers throughout the genome (as appropriate) in relation to esketamine or MDD clinical endpoints.

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

9.6. Safety Evaluations

Details regarding the IDMC are provided in Section 11.7.

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

AEs will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's LAR) 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 Section 3.2.7 and Section 11.6 for further details).

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology and a 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 72 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. 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.

At Day -1 (screening), following ICF process, central laboratory samples must also be collected.

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 performed at central laboratory
  -specific gravity
  -pH
  -glucose
  -protein
  -blood
  -ketones
  -bilirubin
  -urobilinogen
  -nitrite
  -leukocyte esterase

  Sediment (if central laboratory 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 at the study site:

- Urine Pregnancy Testing (for female subjects of childbearing potential only)

- Urine drug test will screen for amphetamine, barbiturates, benzodiazepines, cocaine, marijuana (THC), methadone, methamphetamine, methylenedioxymethamphetamine (MDMA), opiates, phencyclidine, and tricyclic antidepressants. To maintain the integrity of the study blind, a urine drug screen (UDS) should not be performed during the DB period unless medically necessary. If deemed medically necessary, the medical monitor should be contacted and UDS should be performed predose on dosing days.

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. 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.

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 required to review the ECG locally to determine subject eligibility.

Physical Examination, Body Weight and Height

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

Young Mania Rating Scale (YMRS)

YMRS will be administered to assess treatment-emergent occurrence and severity of manic episodes. The YMRS is an eleven-item multiple choice questionnaire which is used to measure the severity of manic episodes in children and young adults. It is based on the patient's subjective report of his or her clinical condition over the previous hours. Additional information is based upon clinical observations made during the clinical interview. The scale is completed by a clinician or other trained rater and takes 15–30 minutes to complete. The symptom items were selected based upon published descriptions of the core symptoms of mania; the YMRS is a reliable, valid and sensitive rating scale to measure the severity of mania.[122]

Physician Withdrawal Checklist (PWC-20)

The PWC-20 will be administered by the clinician to assess potential withdrawal symptoms following cessation of intranasal esketamine treatment. The PWC-20 is a 20-item simple and accurate method to assess potential development of discontinuation symptoms after stopping of

study medication. The PWC-20 is a reliable and sensitive instrument for the assessment of anxiolytic discontinuation symptoms.[106] Discontinuation symptoms occur early and disappear rather swiftly, depending upon speed of taper, daily medication dose, and drug elimination half-life.[106]

Cogstate computerized cognitive battery

The Cogstate computerized cognitive battery is a validated set of assessments which will be performed to assess verbal learning and memory and evaluate cognitive function.[12,28,64] There are 4 in-study assessment times for these: between Day 4 and Day 8 (prior to discharge; predose if performed on dosing day), Day 25 predose, DB EW, Day 81, Day 200, PT EW.

The battery will provide assessment of multiple cognitive domains, including attention, visual learning and memory, and executive function. The tests use culture neutral stimuli, enabling use in multilingual/multicultural settings. The computerized battery includes:

- Simple and choice reaction time tests; scored for speed of response:
    - Detection (DET; Psychomotor Function)
    - Identification (IDN; Attention)
- Visual episodic memory; visual recall test:
    - One Card Learning (OCL; Visual Learning)
- Working memory (n back task); scored for seed of correct response:
    - One Back (ONB; Working Memory)
- Verbal learning and memory assessment
    - International Shopping List Task (ISLT)
- Executive function; maze/sequencing test, scored for total number of errors:
    - The Groton Maze Learning Test (GML; Executive Function)

All measures in the cognitive battery have been validated against traditional neuropsychological tests and are sensitive to the effects of various drugs on cognitive performance, including alcohol and benzodiazepines. The subject completed Cogstate computerized cognitive battery has been used for cognitive assessment in several child and adolescent research trials including attention deficit hyperactivity disorder,[7] and demonstrates good reliability and validity in child and adolescent populations.[6] The ISLT has also been used in adolescent trials, demonstrating sensitivity, reliability and validity. The subject completed cognitive battery requires approximately 25 minutes; the clinician administered ISLT requires approximately 15 minutes in total.

All assessments are completed by the subject except the verbal learning and memory assessment, the ISLT, that will be administered by the clinician. The ISLT is a 12-word three-trial verbal list-learning test. The word lists used in the ISLT consist of foodstuffs common to the culture or language group. The verbal presentation of the word list and the recording of responses are done by the rater and controlled by a laptop computer or tablet. For each 12-word list that is used, the software selects at random the order in which words are presented to subjects. After the third trail is completed, the subject will also complete a series of other tasks for 15-20 minutes, before being asked to recall the 12 words from the ISLT again – this is called a Delayed Recall trial. The subject will also be shown a list of words and asked to recognize previously presented words, a Word Recognition trial.

Timeline Follow-Back (TLFB)

The TLFB will be used to assess the potential for ketamine and PCP abuse during the follow-up phase. The Timeline Follow-Back (TLFB),[35] a clinical and research tool used to obtain a variety of quantitative estimates of alcohol and drug use, will be used to evaluate the potential for ketamine or PCP abuse during the follow-up. The Timeline Follow-Back method has been used in studies to quantify ketamine use in adults, as well as to evaluate substance use in various adolescent populations.[62]

Dosing Day Assessments

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). Blood pressure, heart rate, and respiratory rate performed at predose (should be performed between t = -15 min and t = 0) and at t = 40 mins, 1 hr, and 1.5 hrs postdose; temperature at predose only.

For further details regarding blood pressure monitoring, please see Guidance on Blood Pressure Monitoring on Study Medication Dosing Days (Section 6.3).

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

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 should be monitored and documented once predose between t = -15 minutes and t = 0 (first spray) and then every 15 minutes postdose for approximately 1.5 hours. 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. If oxygen saturation

levels are <95% predose, dosing should be postponed, and the subject should be evaluated by an appropriate practitioner to determine suitability to continue in the study.

Targeted Nasal Examination and Nasal Symptom Questionnaire

Targeted nasal examinations (including the upper respiratory tract/throat) will be conducted by a qualified healthcare practitioner. 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 examinations 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 the presence and severity of symptoms will be graded. Any treatment-emergent change or worsening from baseline examination will be recorded as an adverse event.

In addition, a clinician or designated study staff will complete a nasal symptom questionnaire.

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.[96] 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 dosing day, the MOAA/S should be performed once predose between t = -15 minutes and t = 0 (first spray), and every 15 minutes for approximately 1.5 hours postdose (or longer, if necessary).

If the score is ≤3 at any time during the 90-minute postdose interval, the MOAA/S should 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[13] and will be administered to assess treatment-emergent dissociative symptoms. On each dosing day, the CADSS should be performed 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.

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.

Brief Psychiatric Rating Scale, Positive Symptom Subscale (BPRS+)

The BPRS+ is an instrument that uses a 4-item positive symptom subscale (consisting of: suspiciousness, hallucinations, unusual thought content, and conceptual disorganization) to assess psychosis-like side effects. On each dosing day, BPRS+ to be performed predose and at 40 minutes and 1.5 hours postdose.

9.7. Other Evaluations

MINI International Neuropsychiatric Interview for Children and Adolescents (MINI-KID)

The MINI-KID 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. The MINI-KID follows the structure and format of the adult version of the interview (MINI) but was revised and validated for use in children aged 6 to 17 years. It is administered to the child or adolescent together with their parents(s), or can be administered without a parent present for adolescents.[108] It has an administration time of approximately 15 to 30 minutes and provides an accurate structured psychiatric interview for multicenter clinical trials. The MINI-KID 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-KID

Current suicidal ideation with intent will be evaluated at screening using Question B3 (*Think about hurting yourself with the possibility that you might die. Or did you think about killing yourself?)* AND B10 (*Expect to go through with a plan to kill yourself?)* from the MINI-KID. Subjects will be asked to answer these questions (Yes or No) 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 screening is longer than 24 hours prior to randomization, the B3 and B10 MINI-KID assessment must be repeated to confirm eligibility.

9.8. 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 Treatment 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 Week 29 (Day 200).

10.2. Discontinuation of Study Treatment/Withdrawal from the Study

Discontinuation of Study Treatment During the Double-blind Phase

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

- Lost to follow-up
- Withdrawal of consent/assent
- Death
- Subjects whose postdose SBP or DBP measures are equal to or greater than the sex, age and height values in Attachment 4 (after a repeated measurement).
- 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.

Refer to Section 9.1.5 for details on early withdrawal information.

The investigator must ensure the subject is appropriately transitioned and/or followed for any additional care required when a subject discontinues participation in the study for any reason.

Withdrawal from the Study During the Post-Treatment 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/assent
- Death
- 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.
- Requires treatment with ECT, TMS, ketamine or esketamine

Refer to Section 9.1.5 for details on early withdrawal information.

The investigator must ensure the subject is appropriately transitioned and/or followed for any additional care required when a subject discontinues participation in the study for any reason.

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(s):

- The collected sample will be retained and used in accordance with the subject and parent(s)/LAR(s) original separate pediatric assent/informed consent form for optional research sample(s).
- The subject or parent(s)/LAR(s) may withdraw pediatric assent/informed consent for optional research sample(s), in which case the sample(s) 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 pediatric assent/informed consent for the optional research sample(s) 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 or parent(s)/LAR(s) may withdraw pediatric assent/ informed consent for optional research sample(s) while remaining in the study. In such a case, the optional research sample(s) will be destroyed. The sample destruction process will proceed as described above.

Withdrawal from the Use of Samples in Future Research

The subject or parent(s)/LAR(s) may withdraw pediatric assent/ informed 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.

An analysis of efficacy and safety will be performed after the last subject completes the 25-day Double-blind Treatment Period (Day 25). This analysis will enable selection of a dose for the planned Phase 3 trial, facilitating Phase 3 trial design and preparation. Database locks will also be performed after the last subject completes the Day 81 Visit and Day 200 Visit, respectively.

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 receive at least 1 dose of double-blind study medication and have both a baseline and a postdose evaluation for the CDRS-R 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 sample size for this study was calculated assuming an effect size of 0.65 between any dose of esketamine and psychoactive placebo for the change from baseline at 24 hours postdose for the CDRS-R total score and a 2-sided significance level of 0.05. A total of 145 subjects will be randomized in this study. Using a 1:1:1:2 randomization ratio (esketamine 28 mg: esketamine 56 mg: esketamine 84 mg: psychoactive placebo), approximately 58 subjects will need to be randomized to psychoactive placebo and 29 subjects will need to be randomized to each esketamine treatment group to achieve 94% power for the comparison of the pooled doses of esketamine 56 mg and esketamine 84 mg versus psychoactive placebo and 92% power for at least one of the 2 esketamine higher doses (56-mg and 84-mg) versus psychoactive placebo. The effect size of 0.65 is based on results from study ESKETINSUI2001 (mean difference between treatment groups of -7.2 and a pooled SD of 11.02) for MADRS total score.[16]

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 CDRS-R 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 CDRS-R total scores collected at Day 2 (24 hours post first dose).

Primary Efficacy Analysis

The primary analysis will be based on the full analysis set. The primary efficacy variable, change from baseline in CDRS-R total score at 24 hours post first dose, will be analyzed using an analysis of covariance (ANCOVA) model. The model will include factors for treatment and center, and baseline CDRS-R total score as a covariate. A pooled sequential multiple testing procedure will be implemented to control for Type I error. The esketamine 56 mg and 84 mg treatment groups will be pooled and compared with psychoactive placebo at the 2-sided significance level of 0.05. If this comparison achieves statistical significance in favor of esketamine, the 56-mg dose and 84-mg dose will be simultaneously tested versus psychoactive placebo at the 2-sided significance level of 0.05 based on the closed testing procedure. The 28-mg dose will be tested only if both the 56-mg and 84-mg doses are shown to be significant. Point estimates and 95% confidence intervals for treatment differences 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 CDRS-R 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. Missing data will be closely monitored throughout the trial.

Other Efficacy Analyses

A dose response analysis for the change from baseline in CDRS-R total score at 24 hours post first dose and at Day 25 will be conducted with various dose response models being explored. Details of the dose response analysis will be provided in the SAP.

Changes from baseline over time in CDRS-R total score, MADRS total score, and CDI 2:SR(S) score will be analyzed based on last observation carried forward (LOCF) data using an ANCOVA model with treatment and center as factors and baseline value as a covariate. Additionally, the change from baseline in CDRS-R total score at Day 25 will be analyzed using a mixed model for repeated measures (MMRM) analysis with baseline CDRS-R total score as a covariate, and treatment, center, day, and day-by-treatment interaction as fixed effects, and a random subject effect. Comparison of each esketamine dose versus placebo will be performed using the appropriate contrast. Point estimates and 95% confidence intervals for treatment differences will be provided. Missing data will be closely monitored and additional sensitivity analyses will be specified in the SAP, if necessary.

The ranks of changes from baseline over time for both CGI-SS-R and CGI-SR-I will be analyzed using an ANCOVA model using last observation carried forward data with factors for treatment and center and baseline CGI-SS-R and CGI-SR-I (unranked) as a covariate. Treatment differences 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 and CGI-SR-I.

SIBAT Module 3 (My Current Thinking) and Module 5 (My Risk) Question 3 (patient-reported frequency of suicidal thinking) 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 of the other analyses will be provided in the SAP.

11.4. Pharmacokinetic Analyses

Data will be listed for all subjects with available plasma concentrations per treatment group. Subjects will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (eg, incomplete administration of the study drug; missing information of dosing and sampling times; concentration data not sufficient for PK parameter calculation). 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.

The plasma concentration-time data of esketamine (and noresketamine, if warranted) will be analyzed using population PK 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.

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. In addition to the final population PK parameter estimates, the corresponding standard errors and 95% confidence intervals will be provided.

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

11.5. Biomarker and Pharmacogenomic Analyses

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 be performed for additional biomarkers. Results may be presented in a separate Biomarkers report.

Pharmacogenomic analyses (DNA and RNA) may include candidate gene analyses, genome-wide association analyses, and gene transcription analyses in relation to treatment response, non-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.

11.6. Safety Analyses

The primary population for safety analysis will consist of all randomized subjects who receive at least one dose of double-blind study medication. 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). Treatment-emergent adverse events are adverse events with onset during the Double-Blind Treatment phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported adverse events with onset during the Double-Blind Treatment phase (ie, TEAEs 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. In addition, comparisons between treatment groups will be provided if appropriate. Adverse events during the follow-up phase will be summarized separately.

The TEAEs of special interest will be examined separately (refer to Section 3.2.7 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. 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).[8,44,47,109]

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 and Nasal Symptom Questionnaire

Changes in findings from the baseline nasal examination (including the upper respiratory tract/throat) will be listed by treatment group. Examinations will provide ratings of severity 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.

Scoring from the nasal symptom questionnaire will be summarized descriptively 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.

SIBAT, BPRS+, and YMRS

Suicidal ideation and behavior data from the SIBAT, psychosis-like side effect data from the BPRS+, and potential treatment-emergent symptoms of mania data from the YMRS will be summarized descriptively at each scheduled visit by treatment group.

Cogstate Computerized Cognitive Battery

Cognitive function data from the Cogstate computerized cognitive battery will be summarized descriptively at each scheduled visit by treatment group.

PWC-20

Withdrawal symptoms data from the PWC-20 will be summarized descriptively at designated scheduled visit by treatment group.[106]

Time Line Follow-Back (TLFB)

The TLFB, a clinical and research tool used to obtain a variety of quantitative estimates of ketamine and PCP abuse, will be summarized descriptively at each scheduled visit by treatment group.

11.7. Independent Data Monitoring Committee

In addition to investigator judgment concerning standard of care and subject safety, an external IDMC, comprised of individuals with appropriate pediatric expertise including pediatric psychiatric expertise, 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 periodically to review interim safety data. After the review, 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.

Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events or SAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence. For some studies, subjects are not always able to provide valid verbal responses to open-ended questions. In these circumstances, certain adverse events are solicited by efficacy and safety assessments (see Section 3.2.6 and Section 3.2.7).

Solicited Adverse Events

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

Unsolicited Adverse Events

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

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.[48,49,50] For midazolam, with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the package insert or summary of product characteristics.[72,73]

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.

One of the principal aims of this trial is to define safety of intranasal esketamine use in the adolescent population. Anticipated events will not be applied to this adolescent trial. There are no common causes of hospitalization or serious events collectively in this age group. There is not enough information in this age group to define anticipated events due to major depression or major depression with suicidal intention at this time.

All events that meet the definition of a serious adverse event will be reported as SAEs, regardless of whether they are protocol-specific assessments.

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 SAEs 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 SAEs 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 SAEs 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 hospitalization that extends beyond the protocol-recommended 5 days (not due to adverse event; e.g. 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 be promptly withdrawn from the study and 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)

Study drug will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a list of excipients for esketamine,[48] and to the midazolam product label[72,73] for a list of excipients for midazolam.

Intranasal Esketamine and Placebo Solution

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 intranasal 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.

Oral Midazolam and Placebo

The oral midazolam supplied for this study is available as a clear, colorless solution of midazolam-ratiopharm® 2 mg/ml. Other ingredients include raspberry flavoring, sodium benzoate, sodium cyclamate, hydrochloric acid (0.8%) and distilled water. It is provided in a glass bottle with dropper and child-proof plastic cap, measuring cap, and application syringe.

The oral placebo solution will be provided as a clear, colorless oral solution of purified water with a preservative (sodium benzoate) at a concentration of 2.36 mg/mL with a buffer (citric acid) at 3.00 mg/mL. Sucralose (sweetener) is added at a concentration of 1.00 mg/mL and artificial raspberry flavor is added at a concentration of 1.00 mg/mL. The oral placebo solution is provided in 30-mL amber glass bottles with a child-resistant cap.

14.2. Packaging

All study drug will be administered under the supervision of site staff.

Intranasal Esketamine and Placebo Solution

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.

Oral Midazolam and Placebo

The oral midazolam (2mg/ml) and oral placebo solutions will be provided in 30-mL amber glass bottles with a child-resistant cap and packaged in cartons. Storage conditions are as indicated on the label.

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. 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. 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
- SmPC or Package Insert for midazolam
- 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
- Visit procedures checklist
- 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.[54,91] Epidemiology studies estimate that the 12-month prevalence of MDD is 2% in children and 4% to 8% in adolescents,[2] that MDD is the main predictor of suicidal ideation among children and adolescents,[37,93] and that 40% to 80% of adolescents meet the diagnostic criteria for depression at the time of suicide attempt.[10,37] 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 and psychological therapy. However, these therapies are unable to rapidly reduce depressive symptoms and suicidal ideation. Thus, subjects remain at risk for suicide, with up to 13.9% of subjects reattempting suicide within the 3 months following hospitalization.[102] 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.[31,60,101,103,123] 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. Thus, esketamine treatment for 25 days added to standard care for these at-risk adolescents has the potential to reduce MDD symptoms, including suicidal ideation, while standard therapies are becoming effective.

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 MDD, including suicidal ideation, in young 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 and parent(s)/LAR(s) in this trial will be providing voluntary pediatric assent/informed consent to participate in the study of a potentially efficacious treatment, given in the context of standard of care treatment (ie, hospitalization, antidepressant treatment and psychological therapy). Thus, ethical concerns regarding subjects' decision to participate are minimal.

Subjects and parent(s)/LAR(s) may participate in the study only if they have adequate capacity to give assent and after fully understanding the potential risks and giving a pediatric assent/informed consent. Determination of capacity to provide assent 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. Further each subject's parent(s)/LAR(s), as required by local regulations, must give written consent.

Justification for Using Psychoactive Placebo

Assessment of the potential efficacy of a new compound for the treatment of MDD 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 psychoactive 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, psychological therapy and close outpatient follow up) is ethically appropriate.

The rationale for use of a psychoactive placebo to protect the blind of study medication is discussed in Section 3.2.3. As its pharmacokinetic characteristics and transient psychoactive effects are similar to ketamine, midazolam has been used as a psychoactive control in studies of ketamine.[85] It will be used in doses approximately 25% of those recommended for use in pediatric populations.[72,73]

Subjects and their consenting parent or legal guardian will be informed of the chance of receiving esketamine or psychoactive placebo, the rationale for use of a psychoactive placebo, and of the potential side effects of midazolam as well as esketamine.

Precautions to Ensure Subject Safety in the Study

The study will be conducted in the context of standard clinical care, including hospitalization the initiation or optimization of antidepressant and psychological treatment, and close outpatient follow up. Subjects will remain hospitalized for a recommended period of 5 days and may stay longer if clinically warranted. Subjects should receive standard of care antidepressant medication

initiated or optimized on Day 1. However, initiating standard of care antidepressant medication up to 7 days after the first dose of study medication (Day 1) may be permitted if starting two medications simultaneously is not consistent with local clinical practice.

Subjects will be followed closely throughout the study: twice a week during the 25-day treatment period, followed by weekly visits through week 8, visits every 2 weeks through week 12 then monthly through Week 29. The frequency of visits may be increased as per the judgment of the caregiver and needs of the subject. This is consistent with numerous recommendations from professional and health authorities. Specific assessments to measure depressive symptoms and suicidal ideation are collected at these visits, enabling early identification of any changes in the subject's condition and possible intervention.

If subjects 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.

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 and their parent(s) or LAR(s) 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 respective assent and 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 and parent(s)/LAR(s) who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their pediatric assent/informed consent voluntarily will be enrolled.

When referring to the signing of the ICF, the terms legal guardian and legally acceptable representative refer to the legally appointed guardian of the child with authority to authorize participation in research. For each subject, his or her parent(s) (preferably both parents, if available) or LAR(s), as required by local regulations, must give written consent (permission) according to local requirements after the nature of the study has been fully explained and before the performance of any study-related assessments. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically subjects 7 years of age and older, depending on the institutional policies. For the purposes of this study, all references to subjects who have provided consent (and assent as applicable) refers to the subjects and his or her parent(s) or the subject's legal guardian(s) or LAR(s) who have provided consent according to this process. Minors who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if their parents still want them to participate.

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 based upon European Medicines Agency and Food and Drug Administration (FDA) requirements and strategies for pediatric drug development.[124] Weight and age charts for 12-year-olds in the 5th percentile, show a weight of

approximately 30 kg for both girls and boys.[26,45,34,111] Assuming a conservative phlebotomy protocol that is 1% of total blood volume drawn within 24 hours and a total of 3% total blood volume drawn over 30 days, total blood volume for the study population was calculated based on an assumption of 80 mL/kg, as follows:

- Maximum total blood volume per 24 hours = 30 kg x 80 mL/kg x 0.01 = 24 mL
- Maximum total blood volume per 30 days = 30 kg x 80 mL/kg x 0.03 = 72 mL

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

The blood volumes estimated for this study (Section 9.1.1, Table 2) are lower than maximum recommended blood volumes.

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.

The risks and inconveniences related to Study ESKETINSUI2002 participation will be minimal. Any risk or inconvenience will be mitigated through strict adherence to study procedures by the investigator, and compliance with study procedures by the subject/guardians. To that end, the investigator is responsible for ensuring precise study conduct as specified by the protocol, which will be achieved through training on the study protocol, review of important supporting documents pertaining to risks (see Section 15, Study-Specific Materials), and compliance with all aspects of study conduct.

The following are the foreseeable risks to be monitored by the investigator throughout the study, and the associated mitigations, as defined in respective protocol sections:

Voluntary consent/assent

For this study, both parental consent and subject assent is required. Subjects may participate only if their parent(s)/LAR(s) have adequate capacity to give consent and fully understand the potential risks. 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. Determination of capacity will be made by the study investigator. See Section 4.1, Inclusion Criteria.

Clinical management

To ensure appropriate clinical management of this potentially lethal condition in subjects assessed to be at imminent risk for suicide, the study will be conducted in the context intensive standard clinical care, including hospitalization, the initiation or optimization of antidepressant treatment and psychological therapy. Additionally, close outpatient follow up will occur, consistent with practice guideline recommendations from the National Institute for Health and Clinical Excellence (NICE) and the American Academy of Pediatrics (AAP).[90] 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 or shorter if clinically warranted. Very frequent clinical visit and assessments monitoring symptoms of the subject's MDD, including suicidal ideation, occur throughout the study, thus optimizing early identification of changes in depressive status. See Section 9.1, Study Procedures.

Post-treatment follow-up period

After the 4-week double-blind phase, no study medication will be administered. During the initial 8-week follow-up phase, subjects will have visits conducted weekly through Day 53, then every other week until Day 81, then monthly safety appointments for the remainder of the 6 months (Day 81-200). The duration of follow-up in this study covers the period of greatest risk for recurrent suicidality post initial attempt and/or hospitalization.[11,102] The follow-up through Day 200 will allow for appropriate outpatient monitoring and the exploration of the continued effects of esketamine on depression and suicidal symptoms.

Study discontinuation and follow-up

Subjects may discontinue the study at any time for a variety of reasons, including withdrawal of consent. If subjects 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. 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. See Section 10.

Safety during study

All phlebotomy volumes for this study have been minimized to adhere to the Committee for Human Medicinal Products (CHMP) and Paediatric Committee (PDCO) guideline recommendations.[26] To increase subject comfort, an indwelling catheter has been recommended.

Study requirements for frequent and close follow-up, coupled with use of recommended pharmacologic and psychological therapies in addition to study drug, assures that adolescents participating in the study receive care consistent with recognized guidelines for care of subjects with MDD and suicidal ideation.

Based on previous studies, it is known that certain adverse drug reactions occur postdose, peak around 40 minutes, and then dissipate, usually within 4 hours. The study includes careful monitoring following study drug dosing. Vital signs are performed at predose (should be

performed between t = -15 minutes and t = 0) and at 40 minutes, 1 hour, and 1.5 hours postdose. Oxygenation should be monitored predose (performed between t = -15 minutes and t = 0), and every 15 minutes thereafter through to approximately 1.5 hours postdose, or longer, if necessary. Additionally, other known side effects of esketamine (eg, dissociation, sedation, conceptual disorientation, hallucinogenic behavior, and abnormal thought content) are monitored closely during this time using specific assessment tools like CADSS, MOAA/S, and BPRS+. On each dosing day, CADSS and BPRS+ should be performed predose and at 40 minutes and 1.5 hours postdose; MOAA/S should be performed predose (between t = -15 minutes and t = 0) and every 15 minutes thereafter through to approximately 1.5 hours postdose, or longer, if necessary.

Other measures

Additional safeguards have also been included to facilitate subject safety; eg, specific guidance provided regarding management of elevated blood pressure, pre- and postdose (Section 6.3), and intensive post-administration monitoring on outpatient days (Section 10). In addition, an external IDMC will be established to monitor unblinded safety data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study. The committee will meet regularly to review safety data and determine if it is appropriate for the study to continue (Section 11.7).

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 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/Pediatric Assent Form

Subject’s parent(s) or LAR(s) must give written consent, granting permission for his/her child to participate in the study according to local requirements after the nature of the study has been fully explained. Written assent must be obtained from the subject.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects and their parent(s)/LAR(s), the methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. This discussion should be documented. Subjects and parent(s)/LAR(s) 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. Subjects and parent(s)/LAR(s) will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, the subject and parent/LAR will be told that the investigator will maintain a subject ID 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 pediatric assent/ICF the subject and parent/LAR are authorizing such access, including permission to obtain information about his or her survival status, and agree to allow their study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, and subsequent disease-related treatment, or to obtain information about his or her survival status. The subject and parent/LAR will be given sufficient time to read the ICF and the opportunity to ask questions. Parent/LAR ICF(s) and the pediatric assent form(s) must be signed before performance of any study-related activity. The ICF(s) and assent form(s) that are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the parent/LAR and subject can read and understand. The informed consent/assent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy. After having obtained the consent and assent, a copy both must be given to the subject and parent/LAR.

Children (minors) who reach the age of majority during the study will be reconsented using a provided adult written ICF per applicable local regulations and the IRB/IEC requirements.

Subjects and parent(s)/LAR(s) 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 and his or her parent(s)/LAR(s) 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(s)/assent(s) will be given to the subject and parent(s)/LAR(s).

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/pediatric assent obtained from the subject and his or her parent(s)/LAR(s) 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(s) or their parent(s)/LARs 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 and suicidality, to understand differential drug responders, and to develop tests/assays related to esketamine and depression and suicidality. 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 or their parent(s)/LAR(s) may withdraw their consent for their/their child's samples to be stored for research (refer to Section 10.3, Withdrawal from the Use of Research Samples).

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 sub-investigator 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 number 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/pediatric assent; 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).

Subject- and investigator-completed scales and assessments designated by the sponsor will be considered source data. The CDRS-R, MADRS, SIBAT, CDI 2:SR(S), MOAA/S, YMRS, PWC-20, BPRS+, MINI-KID, Cogstate computerized cognitive battery, TLFB (including paper calendar), nasal symptom questionnaire, and CADSS will be considered source data.

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 CRF 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) will be completed by the same individual who made the initial baseline determinations whenever possible.

The investigator must verify that all data entries in the eCRF 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 an 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 the 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. Allgaier A, Frühe, B, Pietsch K, Saravo B, Baethmann M, Schulte-Körne, G. Is the Children's Depression Inventory Short version a valid screening tool in pediatric care? A comparison to its full-length version. Journal of Psychosomatic Research. 2012;75(5),369-374.
2. American Academy of Child and Adolescent Psychiatry. Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. J Am Acad Child Adolesc Psychiatry. 2007;46:1503-1526.
3. Ates-Alagoz Z, Adejare A. NMDA receptor antagonists for treatment of depression. Pharmaceuticals. 2013;6(4):480-499.
4. Ballard ED, Ionescu DF, Vande Vort JL, et al. Improvement in suicidal ideation after ketamine infusion: relationship to reductions in depression and anxiety. J Psych Res. 2014;58:161-166.
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. Bangirana P, Sikorskii A, Giordani B, Nakasuija N, Boivin MJ. Validation of the CogState battery for rapid neurocognitive assessment in Ugandan school age children. Child Adolesc Psychiatry Ment Health. 2015: 9(38).
7. Barnett R, Maruff P, Vance A. An investigation of visuospatial memory impairment in children with attention deficit hyperactivity disorder (ADHD), combined type. Psychol Med. 2005; 35(10): 1433-1443.
8. Bazett HC. An analysis of the time-relationship of electrocardiograms. Heart. 1920;7:353-380.
9. Beardsley PM, Balster RL. Behavioral dependence upon phencyclidine and ketamine in the rat. J Pharmacol Exp Ther. 1987;242:203-211.
10. Beautrais AL, Joyce PR, Mulder RT. Psychiatric illness in a New Zealand sample of young people making serious suicide attempts. N Z Med J. 1998;111(1060):44–48.
11. 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.
12. Bredlau AL, Harel BT, McDermott MP, Dworkin RH, Korones DN, Dolan JG, Adams HR. Neurocognitive Changes after Sustained Ketamine Administration in Children with Chronic Pain. J Palliat Care Med. 2015: 2; pii 215.
13. Bremmer 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.
14. Brent DA, Baugher M, Bridge J, Chen T, Chiappetta L. Age- and sex-related risk factors for adolescent suicide. J Am Acad Child Adolesc Psychiatry. 1999;38(12):1497-1505.
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. Centers for Disease Control: Suicide Prevention Available from: http://www.cdc.gov/violenceprevention/suicide/youth_suicide html. Accessed 12 January 2016.
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. Cheung A, Emslie G, Mayes TL. Review of the efficacy and safety of antidepressants in youth depression. J Child Psychol and Psychiatry. 2005;46(7):735-754.
20. Cheung A, Zuckerbrot RA, Jensen PS, et al. Guidelines for Adolescent Depression in Primary Care (GLAD-PC): II. Treatment and Ongoing Management. PEDIATRICS Volume 120, Number 5, November 2007. e1313-1326.

21. Cincinnati Children's Hospital Medical Center. Best Evidence Statement (BESt): Treatment of Children and Adolescents With Major Depressive Disorder (MDD) During the Acute Phase. Cincinnati, OH: Cincinnati Children's Hospital Medical Center; 2010.

22. Clark MS, Jansen KL, Cloy JA. Treatment of childhood and adolescent depression. Amer Fam Physician. 2012; 86(5):442-448.

23. 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).

24. 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.

25. 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.

26. Committee for Medicinal Products for Human Use (CHMP) and Paediatric Committee (PDCO). Guideline on the investigation of medicinal products in the term and preterm neonate; London, 25 June 2009. Doc Ref EMEA/536810/2008.

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

28. Crutcher E, Ali M, Harrison J, Sovag J, Gomez-Mancilla B, Schaaf CP. Assessment of Cognitive Outcome Measures in Teenagers with 15q13.3 Microdeletion Syndrome. J Autism Dev Disord. 2016: 46(4); 1455-1463.

29. 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.

30. 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.

31. 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;71(12):1605-1611.

32. Emslie GJ, Heiligenstein JH, Wagner KD, et al. Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. J Am Acad Child Adolesc Psychiatry. 2002;41(10):1205–1215.

33. Emslie GJ, Heiligenstein JH, Wagner KD, et al. Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. J Am Acad Child Adolesc Psychiatry. 2002;41(10):1205-1215.

34. European Medicines Agency. Ethical considerations for clinical trials on medicinal products with the paediatric population. Available from: http://ec.europa.eu/health/files/eudralex/vol-10/ethical_considerations_en.pdf. Accessed 11 August 2015.

35. Fals-Stewart W, O'Farrell TJ, Freitas TT, McFarlin SK, Rutigliano P. The timeline followback reports of psychoactive substance use by drug-abusing patients: psychometric properties. J Consul Clin Psychol. 2000: 68(1); 134-144.

36. 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.

37. Gould MS, King R, Greenwald S, et al. Psychopathology associated with suicidal ideation and attempts among children and adolescents. J Am Acad Child Adolesc Psychiatry. 1998;37(9):915–923.

38. Grant IS, Nimmo WS, McNicol LR, Clements JA. Ketamine disposition in children and adults. Br J Anaesth. 1983;55(11):1107-1111.

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

40. 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.

41. Herd D, Anderson BJ. Ketamine disposition in children presenting for procedural sedation and analgesia in a children's emergency department. Paediatr Anaesth. 2007;17(7):622-629.

42. Herd DW, Anderson BJ, Holford NH. Modeling the norketamine metabolite in children and the implications for analgesia. Paediatr Anaesth. 2007;17(9):831-840.

43. 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.

44. 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.

45. Howie SRC, Blood sample volumes in child health research: review of safe limits. Bull World Health Organ 2011;89:46-53.

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

47. International Council for 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.

48. Investigator's Brochure, JNJ-54135419-AAC (esketamine hydrochloride). Edition 4, Janssen Research & Development, LLC (12 February 2015).

49. Investigator's Brochure, JNJ-54135419-AAC (esketamine hydrochloride). Edition 4, Addendum 1. Janssen Research & Development, LLC (21 June 2016).

50. Investigator's Brochure, JNJ-54135419-AAC (esketamine hydrochloride). Edition 4, Addendum 2. Janssen Research & Development, LLC (14 September 2016).

51. Jain S, Carmody TJ, Trivedi M, et al. A psychometric evaluation of the CDRS and MADRS in assessing depressive symptoms in children. J Am Acad Child Adolesc Psychiatry. 2007;46(9):1204-1212.

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

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

54. 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; 293(20):2487-2495.

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

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

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

58. Kohrs R, Durieux ME. Ketamine: teaching an old drug new tricks. Anesth Analg. 1998;87:1186-1193.

59. Kovacs M. Children's Depression Inventory 2 (CDI 2) (2nd edition). J Psychoeducational Assessment. 2012;30(3)304-308.

60. 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.

61. Lewandowski RE, Acri,MC, Hoagwood KE, et al. Evidence for the management of adolescent depression. Pediatrics. 2013;132(4):e996-e100.

62. Lewis-Esquerre JM, Colby SM, Tevyaw TO, Eaton CA, Kahler CW, Monti PM. Validation of the timeline follow-back in the assessment of adolescent smoking. Drug Alcohol Depend. 2005: 79(1); 33-43.

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

64. Lim YY, Prang K H, Cysique L, Pietrzak R H, Snyder PJ, Maruff P. A method for cross-cultural adaptation of a verbal memory assessment. Behavior Research Methods. 2009: 41(4); 1190-1200.

65. Lindenmayer JP, Czobor P, Alphs L, et al. InterSePT Study Group. The InterSePT Scale for Suicidal Thinking reliability and validity. Schizophr Res. 2003;63(2):161-170.

66. Malinovsky JM, Servin F, Cozian A, Lepage JY, Pinaud M. Ketamine and norketamine plasma concentrations after i.v., nasal and rectal administration in children. Br J Anaesth. 1996;77(2):203-207.

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

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

69. Mayes TL, Bernstein IH, Haley CL, Kennard BD, Emslie GJ. Psychometric properties of the Children's Depression Rating Scale-Revised in adolescents. J Child Adolesc Psychopharmacol. 2010;20(6):513-516.

70. Midazolam Injection USP. [United States Prescribing Information]. Sagent Pharmaceuticals; September, 2012.

71. Midazolam Syrup. Available at http://www.drugs.com/pro/midazolam-syrup.html.

72. Midazolam-ratiopharm® 2mg/ml Oral Solution: Full Prescribing Information. Ratiopharm GmbH; November, 2015.

73. Midazolam-ratiopharm® 2mg/ml Oral Solution: Summary of Product Characteristics. Ratiopharm GmbH; November 2015.

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

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

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

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

78. 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.

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

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

81. 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.

82. Morrison R, Fedgchin M, Singh J, et al. Effect of intranasal esketamine on cognitive functioning in healthy participants: A randomized, double-blind, placebo-controlled study. Poster presented at: Society of Biological Psychiatry, May, 2016, Atlanta GA.

83. 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.

84. Murrough J, Perez, A, Pillemer S, et al. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. Biol Psychiatry. 2013;74(4):250-256.

85. Murrough JW, Iosifescu MD, Chang L, et al. Antidepressant Efficacy of Ketamine in Treatment-Resistant Major Depression: A Two-Site Randomized Controlled Trial. Am J Psychiatry. 2013;170(10):1134-1142.

86. Murrough JW, Perez AM, Pillemer S, et al. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. Biol Psychiatry. 2013;74(4):250-256.

87. Murrough JW, Soleimani L, deWilde KE, et al. Ketamine for rapid reduction of suicide ideation: a randomized controlled trial. Psychol Med. 2015;45(16);3571-3580.

88. Murrough, JW, Burdick KE, Levitch CF, et al. Neurocognitive effects of ketamine and association with antidepressant response in individuals with treatment-resistant depression: A randomized controlled trial. Neuropsychopharmacology. 2015;40:1084–1090.

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

90. National Institute for Health and Clinical Excellence (NICE) Depression in children and young people: identification and management. Clinical Guideline 28. National Collaborating Centre for Mental Health, London: March 2015. Available from: https://www.nice.org.uk/guidance/cg28. Accessed 5 December 2016.

91. 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.

92. Nock MK, Borges G, Bromet EJ, et al. Cross-national prevalence and risk factors for suicidal ideation, plans, and attempts in the WHO World Mental Health Surveys. Br J Psychiatry. 2008;192(2):98-105.

93. Nock MK, Green JG, Hwang I, et al. Prevalence, correlates, and treatment of lifetime suicidal behavior among adolescents: results from the National Comorbidity Survey Replication Adolescent Supplement. JAMA Psychiatry. 2013;70(3):300-310.

94. Oye I, Paulsen O, Maurset A. Effects of ketamine on sensory perception: evidence for a role of N-methyl-D-aspartate receptors. J Pharmacol Exp Ther. 1992;260:1209-1213.

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

96. 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.

97. Papakostas G, Fava M. Does the probability of receiving placebo influence clinical trial outcome? A meta-regression of double-blind, randomized clinical trials in MDD. Eur Neuropsychopharmacol. 2008;19(1):34-40.

98. Pharmacokinetic Report KET-PK-007. A randomized, open label, single center, single dose, cross-over study to determine the absolute bioavailability and the nasopharyngeal absorption of PMI-150 (intranasal ketamine) in healthy adult volunteers. Javelin Pharmaceuticals, Inc (31 October 2008).

99. 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.

100. 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;31(4):335-343.

101. 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.

102. Prinstein M, Nock M, Simon V, Aikins JW, Cheah CSL, Spirito A. Longitudinal trajectories and predictors of adolescent suicidal ideation and attempts following inpatient hospitalization. J Consult Clin Psychol. 2008;76(1):92-103.

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

104. Reed MD, Rodarte A, Blumer JL, et al. The single-dose pharmacokinetics of midazolam and its primary metabolite in pediatric patients after oral and intravenous administration. J Clin Pharmacol. 2001;41(12):1359-1369.

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

106. Rickels K, Garcia-Espana F, Mandos LA, Case GW. Physician Withdrawal Checklist (PWC-20). Journal of Clinical Psychopharmacology. 2008; 28(4):447-451.

107. Shafii M, Steltz-Lenarsky J, Derrick AM, et al. Comorbidity of mental disorders in the post-mortem diagnosis of completed suicide in children and adolescents. J Affect Disord. 1988;15(3):227–233.

108. Sheehan DV, Sheehan KH, Shytle RD, et al. Reliability and validity of the mini international neuropsychiatric interview for children and adolescents (MINI-KID). J Clin Psychiatry. 2010;71(3):313-326.

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

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

111. Veal GJ. Blood volumes in pediatric clinical trials: a review of current regulations and guidance for research studies. Clin Invest (Lond) 2014;4(11):1005-1011.

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

113. Vitiello B, Brent D, Greenhill LL, et al. Depressive symptoms and clinical status during the treatment of adolescent suicide attempters study (TASA). J Am Acad Child Adolesc Psychiatry 2009;48(10):997-1004.

114. 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.

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

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

117. World Health Organization (WHO 2014). Preventing suicide: A global imperative. Available from: http://www.who.int/mental_health/suicide-prevention/world_report_2014/en/. Accessed 20 December 2015.

118. 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.

119. Yanagihara Y, Ohtani M, Kariya S, et al. Plasma concentration profiles of ketamine and norketamine after administration of various ketamine preparations to healthy Japanese volunteers. Biopharm Drug Disp. 2003;24(1):37-43.

120. 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.

121. 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.

122. Young RC, Biggs JT, Ziegler VE, Meyer, DA. A rating scale for mania: reliability, validity and sensitivity. British Journal of Psychiatry (1978), 133, 429-435.

123. 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.

124. Zisowski J, Krause A, Diingemanse J. Druge development for pediatric populations: Regulatory aspects. Available from: http://www.ncbi nlm.nih.gov/pmc/articles/PMC3967144/. Accessed 20 December 2016.

Attachment 1: Prohibited/Permitted Concomitant Medications

This list of medications is **not all-inclusive**; it is intended for general guidance. Please contact the medical monitor for any questions regarding medications.

The pharmacotherapies listed below are permitted (Y), permitted with restrictions (Y*) with additional guidance or restrictions in the "Comments" column, 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 table below, the prohibited therapies listed in this table are prohibited from screening until at least 1 day (24 hours) after the last dose of study medication.

Drug Class	Episodic Use (as needed)	Continuous Use	Comments
ADHD medications			
Atomoxetine	N	N	
Amphetamines	N	Y	On dosing days, should be held until at least 2 hours postdose. If, for a given subject, it is not clinically appropriate to delay dosing of these medications for at least 2 hours after study medication is given, the investigator should contact the medical monitor to discuss an alternate plan regarding the timing of dosing of these medications, relative to study drug.
Methylphenidate	N	Y	
Clonidine	Y	Y	Dose as usual
Guanfacine	Y	Y	Dose as usual
Aldehydes and Derivatives			
Chloral hydrate	N	N	
Anorexiants			
Phentermine	N	N	
Phendimetrazine	N	N	
Anticonvulsants	Y*	N	Use of anticonvulsants as adjunctive treatment for major depressive disorder (MDD) is prohibited. – Note: Anticonvulsants used for indications other than seizures (eg valproate for migraine) may be permitted upon discussion with medical monitor
Antidepressants (*other than the three (3) specific antidepressants permitted as SoC per protocol)*	N	N	Taper and/ or Washout from prohibited antidepressant(s) will be per clinician's judgment on or before screening visit day. Antidepressants that are not permitted during the double-blind period may be started on Day 25 following the last assessment (eg, 4-hour postdose assessment). **Note the exception of the use of Monoamine Oxidase Inhibitors (MAOIs see below).** Antidepressant medications used for indications other than depression (eg trazodone for sleep) may be permitted upon discussion with the medical monitor. Trazodone should not be used within 8 hours prior to the start of study drug administration.

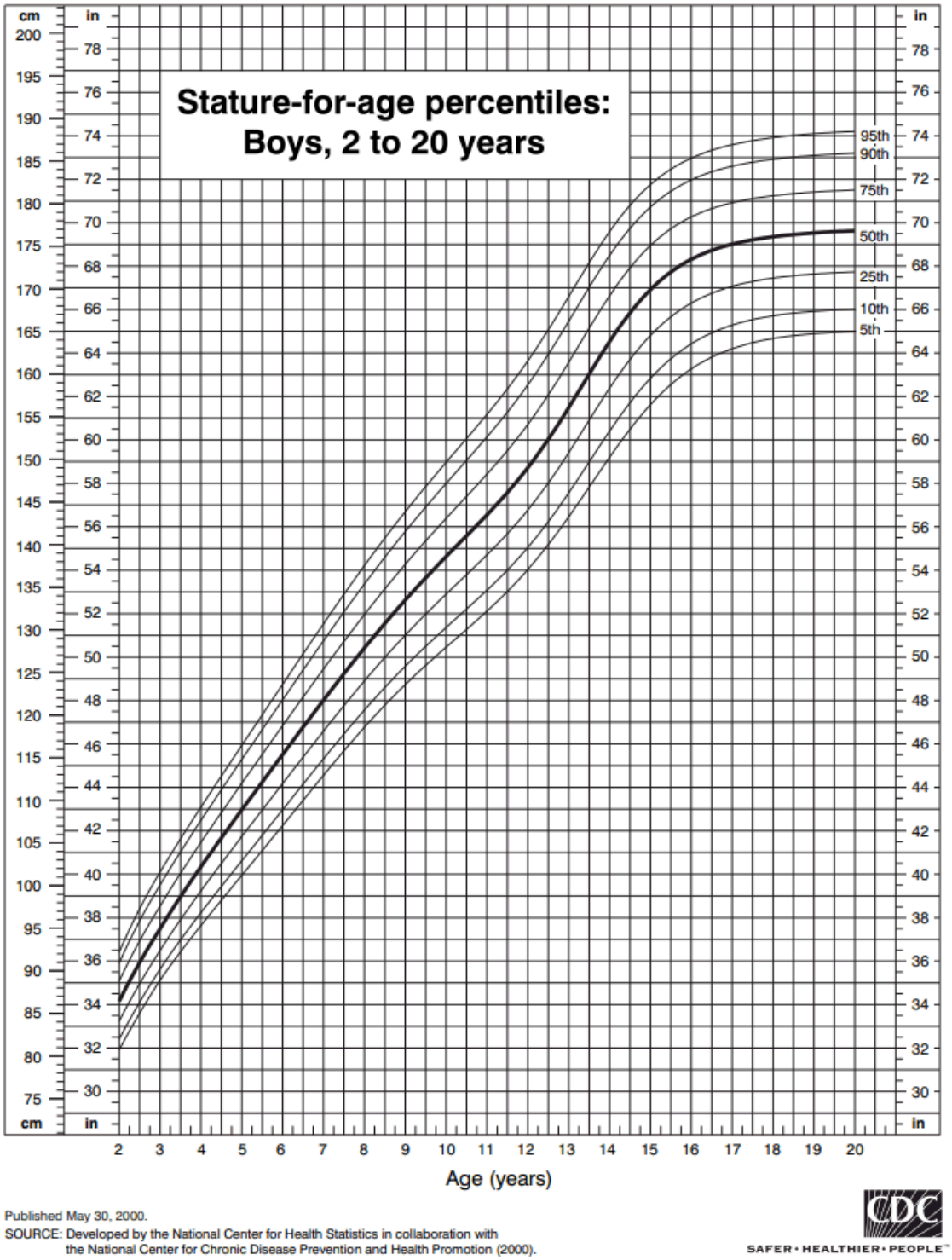
Drug Class	Episodic Use (as needed)	Continuous Use	Comments
Antidepressants			
Monoamine Oxidase Inhibitors	N	N	Prohibited from within 2 weeks prior to study drug administration on Day 1, and throughout the study.
Antihistamines			
First Generation	Y*	Y*	Should not be used within 8 hours prior to study drug administration.
Second Generation Non-sedating	Y	Y	
Antihypertensive Agents			
Ketanserin	N	N	
Antipsychotics	Y	N	Low dose antipsychotic medications used for indications other than psychosis, bipolar disorder or antidepressant augmentation (eg, quetiapine for sleep) may be permitted upon discussion with the Medical Monitor; however, they may not be used prior to the completion of Day 2 assessments If clinically necessary, antipsychotics may be started on Day 25 following the last assessment (eg, 4-hour postdose assessment).
Antivertigo Products			
Scopolamine	N	N	
Antivirals			
Amantadine	N	N	
Anxiolytics and Sleep Aids			
Benzodiazepines (at dosages equal to or less than the equivalent of 6 mg/day lorazepam)	Y*	Y*	Anxiolytics and Sleep Aids should not be used within 8 hours prior to study drug administration and/or cognitive testing. On Day 2, should not be used within 8 hours of assessments.
Hydroxyzine	Y*	Y*	
Diphenhydramine	Y*	Y*	
Zolpidem, Zaleplon, Eszopiclone, and Ramelteon)	Y*	Y*	
Melatonin	Y	Y	
Cyamemazine (maximum of 75 mg/day, in doses no larger than 50 mg at a time)	Y*	Y*	
Cardiac Preparations			
Metyrosine	N	N	
Centrally Acting Alpha Agonists			
Clonidine	Y	Y	
Methyldopa	N	N	

Drug Class	Episodic Use (as needed)	Continuous Use	Comments
Corticosteroids	Y*	Y*	Intermittent and continuous use of inhaled, intranasal, topical, and ophthalmic corticosteroids are permitted. Continuous use of oral corticosteroids may be acceptable for maintenance of stable chronic disease states (eg, rheumatologic and respiratory conditions) but must be discussed with the medical monitor. Likewise, intermittent use of IM steroid must be discussed with the medical monitor. Intermittent and continuous use of IV corticosteroid use is not permitted.
Cough/cold Preparations/Nasal Solutions Containing Vasoconstrictors, Decongestants (Excluding Dextromethorphan)	Y*	Y*	Intranasally-administered decongestants (vasoconstrictors) or saline solution / spray should not be used from 1 hour prior to study drug administration. Pseudoephedrine-containing oral products should not be used within 12 hours prior to study drug administration.
Herbal Supplements (eg, Valerian, St. John's Wort)	N	N	
Mood Stabilizers			
Lithium	N	N	
Non-Opioid Antitussives			
Dextromethorphan	N	N	
Opioids	Y*	Y*	Continuous use of oral opioids may be acceptable for maintenance of stable chronic disease states (eg, sickle cell disease, rheumatologic conditions) but must be discussed with the medical monitor. Illicit use is prohibited if criteria for moderate or severe substance use disorder are met.
Oral Anti-Acne Retinoids			
Isotretinoin	N	Y*	May only be used in consultation with the medical monitor.
Other Psychostimulants			
Armodafanil	N	N	
Modafinil	N	N	
Rauwolfia Alkaloids			
Reserpine	N	N	
Thyroid hormone supplement for treatment of thyroid condition only (not for depression)	N	Y	

Abbreviations: ADHD: attention-deficit/hyperactivity disorder, IM: intramuscular, IV: intravenous, N: Prohibited, Y: permitted, Y*: permitted with restrictions (in the case of "permitted with restrictions", please refer to the column labeled "Comments" for additional guidance or restrictions).

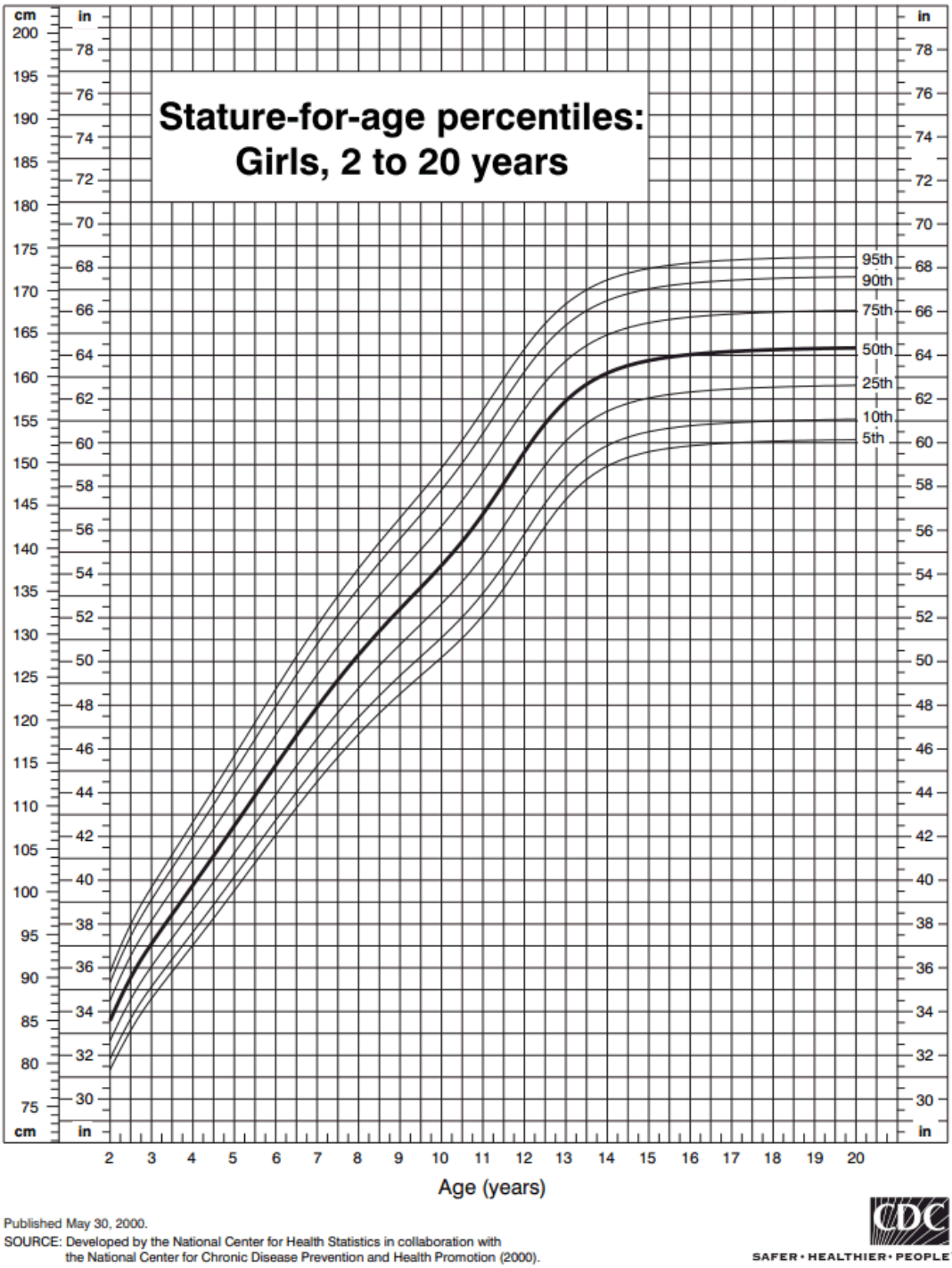
Attachment 2: Growth Charts: Stature-for-Age Percentiles for Use in Blood Pressure Assessments

(Boys, 2 to 20 Years)



To be used to determine individual blood pressure thresholds for eligibility, predose and postdose withdrawal criteria.

Growth Charts: Stature-for-Age Percentiles for Use in Blood Pressure Assessments (Girls, 2 to 20 Years)



To be used to determine individual blood pressure thresholds for eligibility, predose and postdose withdrawal criteria.

Attachment 3: 95th Percentile Blood Pressure Levels For Sex by Age and Height

Blood Pressure Levels and Growth Charts for Boys to be used for Eligibility and Predose

Instructions for Use
1. Use Attachment 2 to determine the height percentile. Subjects who fall below the 5th or above the 95th percentile for their age, sex, and height should be evaluated using the parameters for the 5th or 95th percentile.
2. Measure and record the blood pressure of the child or adolescent.
3. Use the table below to identify the 95th percentile for both systolic and diastolic blood pressure, by sex, according to age and height.

Boys' 95th Percentile Blood Pressure Levels by Age and Height

	Systolic BP (mmHg)								Diastolic BP (mmHg)						
Age (Year)	← Percentile of Height →								← Percentile of Height →						
	5th	10th	25th	50th	75th	90th	95th		5th	10th	25th	50th	75th	90th	95th
9	113	114	116	118	119	121	121		76	77	78	79	80	81	81
10	115	116	117	119	121	122	123		77	78	79	80	81	81	82
11	117	118	119	121	123	124	125		78	78	79	80	81	82	82
12	119	120	122	123	125	127	127		78	79	80	81	82	82	83
13	121	122	124	126	128	129	130		79	79	80	81	82	83	83
14	124	125	127	128	130	132	132		80	80	81	82	83	84	84
15	126	127	129	131	133	134	135		81	81	82	83	84	85	85
16	129	130	132	134	135	137	137		82	83	83	84	85	86	87
17	131	132	134	136	138	139	140		84	85	86	87	87	88	89

95th percentile for blood pressure level is 1.645 SD over the mean.
Adapted from "The fourth report on the diagnosis, evaluation and treatment of high blood pressure in children and adolescents. National Institutes of Health. May 2005."

Blood Pressure Levels and Growth Charts for Girls to be used for Eligibility and Predose

Instructions for Use
1. Use Attachment 2 to determine the height percentile. Subjects who fall below the 5th or above the 95th percentile for their age, sex, and height should be evaluated using the parameters for the 5th or 95th percentile.
2. Measure and record the blood pressure of the child or adolescent.
3. Use the table below to identify the 95th percentile for both systolic and diastolic blood pressure, by sex, according to age and height.

Girls' 95th Percentile Blood Pressure Levels by Age and Height

	Systolic BP (mmHg)								Diastolic BP (mmHg)						
Age (Year)	← Percentile of Height →								← Percentile of Height →						
	5th	10th	25th	50th	75th	90th	95th		5th	10th	25th	50th	75th	90th	95th
9	114	114	115	117	118	119	120		76	76	76	77	78	79	79
10	116	116	117	119	120	121	122		77	77	77	78	79	80	80
11	118	118	119	121	122	123	124		78	78	78	79	80	81	81
12	119	120	121	123	124	125	126		79	79	79	80	81	82	82
13	121	122	123	124	126	127	128		80	80	80	81	82	83	83
14	123	123	125	126	127	129	129		81	81	81	82	83	84	84
15	124	125	126	127	129	130	131		82	82	82	83	84	85	85
16	125	126	127	128	130	131	132		82	82	83	84	85	85	86
17	125	126	127	129	130	131	132		82	83	83	84	85	85	86

95th percentile is 1.645 SD over the mean.
Adapted from "The fourth report on the diagnosis, evaluation and treatment of high blood pressure in children and adolescents. National Institutes of Health. May 2005."

Attachment 4: Postdose Blood Pressure: Withdrawal Criteria Levels for Sex by Age and Height

Postdose Blood Pressure: Withdrawal Criteria Levels for Boys

If, postdose, **either** the systolic or diastolic BP levels are equal to or greater than the age and height values in the table below, measure blood pressure again after at least five minutes of relaxation (ie, sitting or supine). If the values are still equal to or greater than the age and height values in the table, the subject should be withdrawn from the study and appropriate follow-up clinical care should be initiated. Subjects who fall below the 5th or above the 95th percentile for their age, sex, and height should be evaluated using the parameters for the 5th or 95th percentile.

	Blood pressure withdrawal values below represent the 99th percentile for age and height plus 1.28 SD over the mean								Blood pressure withdrawal values below represent the 99th percentile for age and height plus 1.28 SD over the mean						
	Systolic BP (mmHg)								**Diastolic BP (mmHg)**						
Age (Year)	**← Percentile of Height →**								**← Percentile of Height →**						
	5th	**10th**	**25th**	**50th**	**75th**	**90th**	**95th**		**5th**	**10th**	**25th**	**50th**	**75th**	**90th**	**95th**
9	158	159	161	163	164	166	166		111	112	113	114	115	116	116
10	160	161	162	164	166	167	168		112	113	114	115	116	116	117
11	162	163	164	166	168	169	170		113	113	114	115	116	117	117
12	164	165	167	168	170	172	172		113	114	115	116	117	117	118
13	166	167	169	171	173	174	175		114	114	115	116	117	118	118
14	169	170	172	173	175	177	177		115	115	116	117	118	119	119
15	171	172	174	176	178	179	179		116	116	117	118	119	120	120
16	174	175	177	179	180	182	182		117	118	118	119	120	121	122
17	176	177	179	181	183	184	185		119	120	121	122	122	123	124

Adapted from “The fourth report on the diagnosis, evaluation and treatment of high blood pressure in children and adolescents. National Institutes of Health. May 2005.”

Postdose Blood Pressure: Withdrawal Criteria Levels for Girls

If, postdose, **either** the systolic or diastolic BP levels are equal to or greater than the age and height values in the table below, measure blood pressure again after at least five minutes of relaxation (ie, sitting or supine). If the values are still equal to or greater than the age and height values in the table, the subject should be withdrawn from the study and appropriate follow-up clinical care should be initiated. Subjects who fall below the 5th or above the 95th percentile for their age, sex, and height should be evaluated using the parameters for the 5th or 95th percentile.

	Blood pressure withdrawal values below represent the 99th percentile for age and height plus 1.28 SD over the mean								Blood pressure withdrawal values below represent the 99th percentile for age and height plus 1.28 SD over the mean						
	Systolic BP (mmHg)								**Diastolic BP (mmHg)**						
Age (Year)	**← Percentile of Height →**								**← Percentile of Height →**						
	5th	**10th**	**25th**	**50th**	**75th**	**90th**	**95th**		**5th**	**10th**	**25th**	**50th**	**75th**	**90th**	**95th**
9	159	159	160	162	163	164	165		111	111	111	112	113	114	114
10	161	161	162	164	165	166	167		112	112	112	113	114	115	115
11	163	163	165	166	167	168	169		113	113	113	114	115	116	116
12	164	165	166	168	169	170	171		114	114	114	115	116	117	117
13	166	167	168	169	171	172	173		115	115	115	116	117	118	118
14	168	168	170	171	172	174	174		116	116	116	117	118	119	119
15	169	170	171	172	174	175	176		117	117	117	118	119	120	120
16	170	171	172	173	175	176	177		117	117	118	119	120	120	121
17	170	171	172	174	175	176	178		117	118	118	119	120	120	121

Adapted from “The fourth report on the diagnosis, evaluation and treatment of high blood pressure in children and adolescents. National Institutes of Health. May 2005.”

INVESTIGATOR AGREEMENT

JNJ-54135419 (esketamine)

Clinical Protocol ESKETINSUI2002 Amendment 4

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): PPD

Institution: Janssen Research & Development

Signature: PPD PPD Date: _____

(Day Month Year)

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

CONFIDENTIAL – FOIA Exemptions Apply in U.S. 155

Status: Approved, Date: 22 November 2020

Janssen Research & Development *

COVID-19 Appendix

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

Protocol ESKETINSUI2002; Phase 2b

JNJ-54135419 (esketamine)

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen Pharmaceutica 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 study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

EudraCT NUMBER: 2016-004422-42

Status: Approved
Date: 16 July 2020
Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-RIM-100193, 1.0

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS, INCLUDING COUNTRY-SPECIFIC VERSIONS, OF THE PROTOCOL

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

COVID-19 APPENDIX

Guidance on Study Conduct during the COVID-19 Pandemic

This Appendix applies to all current versions, including country-specific versions, of Protocol ESKETINSUI2002.

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

In alignment with recent health authority guidance, the sponsor is providing options for study-related subject management in the event of COVID-related disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgment of the investigator to protect the health and well-being of subjects/guardians and site staff. If, at any time, a subject's safety is considered to be at risk, study participation will be discontinued, and study follow-up will be conducted according to the "**Guidance Specific To This Protocol**" section of this document.

Every effort should be made to adhere to protocol-specified assessments. Modifications addressed in the "**Guidance Specific To This Protocol"** section should be discussed with the subjects/ guardians, and documented as described in section entitled "**Subject Agreement to Modified Study Procedures".**

Additional modifications to protocol-required assessments not addressed in this document may be permitted in response to the pandemic emergency after consultation between the subject/ guardian and investigator, and with the agreement of the sponsor or designee. Missed assessments/visits will be captured as protocol deviations.

If re-consenting of subjects/guardians is required during the COVID-19 pandemic, remote consenting by phone will be acceptable in accordance with local guidance for informed consent.

The sponsor will continue to monitor the conduct and progress of the clinical study in relation to the status of the COVID-19 pandemic, and any changes will be communicated to the sites and to the health authorities according to local guidance. Modifications made to the study conduct as a result of the COVID-19 pandemic will be summarized in the clinical study report.

GUIDANCE SPECIFIC TO THIS PROTOCOL

These provisions are meant to minimize the risk of exposure to COVID-19 and to safely maintain subject study visits while site capabilities and subject / guardian travel limitations are compromised by COVID-19-related restrictions. As restrictions are lifted, sites should revert to original protocol conduct as soon as feasible.

The safety of study subjects and site staff is priority. Each subject's circumstances and potential restrictions should be evaluated by the Principal Investigator. If there is doubt regarding the risk/benefit assessment of the participant in relation to these COVID-related modifications, the investigator should contact the Sponsor's Medical Monitor for discussion and / or discontinue the participant from the study.

All modifications described in this Appendix should be instituted in accordance with applicable (including local) laws, regulations, guidelines, and procedures.

SCREENING AND ENROLLMENT:

- Potential study candidates who are currently known to be positive for the COVID-19 virus will not be screened for the study.
- Potential study candidates who have any symptoms related to the COVID -19 virus or who are suspected to be infected with the COVID -19 virus will not be screened for the study.
- Potential study candidates who have had the COVID-19 virus and have fully recovered may be considered for enrollment following a discussion with the Sponsor's Medical Monitor.
- Prior to enrollment, site should assess current capability for subject / guardian to complete in-person dosing visits (Double-blind Treatment Phase).
  - If known travel / site restrictions constrain or prohibit the completion of the Double-blind Treatment Phase, the potential candidate should not be screened or enrolled.

DOUBLE-BLIND TREATMENT PHASE:

- If needed for COVID-19 mitigation, an enrolled subject may remain as inpatient for the entire 25 days of the Double-blind Treatment Phase provided that:
  - Subject and guardian agree
  - Principal investigator agrees it is in the best interest of the subject
  - Inpatient bed is available

- If subject has been discharged and is an outpatient during the Double-blind Treatment Phase, and subject/guardian is restricted from coming back for dosing visits, OR, if the site cannot conduct a dosing visit, site should consult the Sponsor's Medical Monitor to discuss. General guidelines are as follows:
  - Assess risk/benefit of subject remaining in the study

  - If >14 days elapse since last dose, subject should be discontinued from the study
  - If ≤14 days elapse since last dose, dosing should resume. If possible, all 8 doses should be administered.

- If a dosing visit is missed, the site should call the subject and remotely conduct the following assessments as applicable and feasible for that Visit Day:
  - Suicide Ideation and Behavior Assessment Tool (SIBAT), including both patient modules and clinician modules
  - Children's Depression Rating Scale-Revised (CDRS-R) / Montgomery-Asberg Depression Rating Scale (MADRS)
  - Physician Withdrawal Checklist (PWC-20)
  - International Shopping List Task (ISLT) (from the Cogstate Battery)
  - Children's Depression Inventory (CDI)
  - Evaluation of adverse events (AEs) and concomitant medications

  These assessments should be placed in an "Unscheduled Assessment" folder.

- If a dosing visit is missed, the Study Visit upon return in the Double-blind treatment phase should be resumed as the next visit in the schedule. For example: if Visit Day 8 and Day 11 are missed, , Day 8 would be filled out when the subject returns, and dosing for the remainder of the 8 total doses in the Double-blind Treatment Phase would be administered following the twice-weekly dosing schedule.

- Outpatient standard of care psychological therapy should be initiated/continued per protocol. It is recognized that during this time, standard of care psychological therapy sessions may be constrained or interrupted. Continued psychological therapy remotely via telephone is acceptable/encouraged in this case.

POST-TREATMENT FOLLOW-UP PHASE

The table below provides information on modifications for remote performance of assessments during the Post-treatment Follow-up Phase.

Protocol Procedure	Site / Subject can complete procedures remotely	Comments
Standard of care psychological therapy	Yes* (see comments)	We recognize that during this time, standard of care therapy sessions may be constrained or interrupted. Record in subject source documentation if conducted remotely via telephone
Physical examination	No	
Vital signs	No	
12-lead ECG	No	
Body weight	No	
PWC-20	Yes	
Cogstate computerized cognitive battery	Yes* (see comments)	*International Shopping List Test- Immediate Recall (ISLT - Immediate Recall) is the **only** test within the battery that may be done via phone. Refer to separate Cogstate COVID-19 Remote ISLT Administration Guidelines for ESKETINSUI2002 (Attachment 1).
TLFB	Yes* (see comments)	* TLFB assessment may be done via phone by asking the subject if and how many days they took PCP, ketamine during the look back period and recording only the number in Virgil. The rater does **not** have to complete a paper calendar on the subject's behalf.
SIBAT	Yes* (see comments)	SIBAT PRO should be administered remotely as a clinician -read scale. Process for raters to access this scale is described in separate guidance documents.
CDRS-R (recall: 7 days)	Yes	
MADRS (recall: 7 days)	Yes	
CDRS-R (recall: since last assessment)	Yes	
MADRS (recall: since last assessment)	Yes	
Hematology, Chemistry	Yes* (see comments)	* Investigator to use clinical judgment and assess risk / benefit when considering if subject should have laboratory tests performed locally to assess safety only; site should inform Site Manager and/or Medical Monitor about such cases.
Urinalysis	Yes* (see comments)	
Concomitant therapy	Yes	
Adverse events	Yes	

CDRS-R = Children's Depression Rating Scale-Revised; ClinRo = clinician rated outcome; CGI = Clinical Global Impression; ECG = electrocardiogram; ISLT = International Shopping List Task; MADRS = Montgomery-Asberg Depression Rating Scale; PCP = phencyclidine; PWC-20 = Physician Withdrawal Checklist; SIBAT = Suicide Ideation and Behavior Assessment Tool; TLFB = Timeline Follow-Back

VISIT DAY 200

To accommodate potential restrictions, the window for the Day 200 protocol visit may be extended by an addition of +7 days. The current protocol window is +/-7 days; this effectively allows for a – 7/+14 day visit. If neither an in-person or remote Day 200 visit are feasible within the extended window of +14 days of Day 200 visit, the subject should be discontinued.

GENERAL:

COVID-19 Related:

- If a subject contracts the virus during the **Screening or Double-blind Treatment Phase**:
  - PI should contact the Sponsor's Medical Monitor to discuss the best course of action based on a risk/benefit assessment.
- If a subject contracts the virus during the **Post-Treatment Follow-up Phase**:
  - PI should contact the Sponsor's Medical Monitor; if feasible, the subject, may complete assessments remotely until recovered.

Additional Assessment Information:

- Clinical lab tests that cannot be performed at the site may be performed locally, for safety, per Principal Investigator judgment following a risk/benefit assessment which should be recorded in source documentation.
- ECGs and other physical assessments (eg, PE, body weight, vital signs) that cannot be performed in person at the site will be recorded as 'missing' and documented per conventions.
- At each contact, subjects (and guardians as necessary) will be interviewed to collect AEs and concomitant medication data. Subjects will be questioned regarding their general health status.

Early Withdrawal Information:

- Discontinuation of study treatment and withdrawal from the study due to COVID-19 AEs/ serious adverse events (SAEs) should be documented as discontinuation due to "Adverse Event". The specific COVID-19-related AE should then be chosen from the corresponding AE logline. If a subject dies due to COVID-19, "death" should be selected as the reason for discontinuation and the cause of death should be specified as COVID-19-related. Discontinuations for other COVID-19 reasons should be documented with the prefix "COVID-19-related" in the CRF.

- Early Withdrawal visit assessments should be conducted as feasible, remotely or in-person.

As a reminder, the investigator must ensure the subject is appropriately transitioned and/or followed for any additional care required when a subject discontinues participation in the study for any reason.

Subject Agreement to Modified Study Procedures

Specific guidance provided in this Appendix in response to the global COVID-19 pandemic may influence subject's and legal guardian(s)'s willingness to continue participating in the study. Below is general guidance for an oral consent. Documentation of this should be made within the subject's source documentation (one-time per subject).

General guidance for oral consent is listed below:

- **Who assented / consented:** Name of the study participant and if applicable, the legally authorized representative(s).
- **When they assented / consented:** The time and date the conversation took place.
- **What they were told at the time:** What changes or new aspects of the study were agreed due to the COVID-19 pandemic (example script: *To simplify study participation during the COVID-19 pandemic, some of your previously completed and upcoming scheduled study visits may be conducted by telephone instead of going into the study doctor's office. Your study doctor will explain which visits you can do by phone and which study visits require you to come into the office.*).
- **How they consented:** The consent result (e.g., all subject / legal authorized representative questions were reviewed and answered, they understand and agree to the modifications), the method used (eg, telephone).
- **Who captured the oral / verbal consent:** name and signature of the Investigator or staff member who captured the assent / consent from the subject and legally authorized representative(s).
- **Impartial Witness (if applicable):** Who was present as impartial witness and how the impartial witness was selected.

Sites should refer to their continuity plans and local HA/IRB/EC guidance for appropriate methods of documenting evidence for verbal and/or other alternate consent methods. Additionally, acceptability of alternate consenting methods will vary by country based upon local/country guidance, laws, and regulations, and take precedence over the above general guidance.

Statistical Analysis

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

Attachment 1: Cogstate COVID-19 Remote ISLT Administration Guidelines for ESKETINSUI2002

Cogstate COVID-19 Remote ISLT Administration Guidelines for ESKETINSUI2002

Cogstate

1 Cogstate Phone Administration Guidance

In light of the COVID-19 global pandemic, Cogstate is extending the following guidance for administering certain clinical outcome assessments (COAs) remotely in the event that in-clinic assessments are not possible and/or remote assessment may be required to ensure the safety of study subjects, study partners, and test supervisors participating in the ESKETINSUI2002 study.

Importantly, Cogstate believes that remote assessment will be most feasible for direct report and interview-based assessments. For ESKETINSUI2002, only the International Shopping List Test – Immediate Recall (ISLT) is appropriate for remote administration. Below, we provide specific guidance for collecting these data remotely.

Please note that while remote administration has been deemed feasible for the ISLT in this study, the test itself was not originally designed to be administered remotely and as such Cogstate cannot guarantee that the data are equivalent to what you would collect if the visit was conducted in-clinic. However, in discussions with the Janssen study team, it was determined that using methods other than in-clinic administrations to collect data during this pandemic crisis is preferable to having missing data, provided the form of remote testing selected remains as standardized as possible within the study (e.g., via telephone). The potential for non-equivalence or bias could be evaluated during statistical analysis of the data.

Test Supervisors, please be advised of the following guidelines for remote administration of the ISLT:

1. You should inform the subject that it is important to take the tests in a quiet location, free of distraction, so that they can hear you clearly.
2. After phone contact has been made and rapport established, you should ensure that the subject can hear you clearly.
3. Once it has been established that the subject can hear you clearly, note the expected duration of the testing (estimated time: 5 minutes) and re-iterate that they need to be undisturbed for that length of time.
4. Once you have read the instructions to the subject per the scripts provided (or as shown on screen), please also indicate to the subject that they should not write down any of the words as they are read.
5. Once the subject is ready to begin, proceed with the first round of the test.
6. In addition to reading the instructions to the subject between the second and third rounds, please also ensure that the subject can still hear you clearly and remind them not to write down any of the words as they are read.

Given the ISLT is the first test in the Cogstate software, you will need to abort the software after completion of this test. You would do so by pressing the escape button on the laptop keyboard. You should then proceed re-enter the Cogstate software and upload the data as per usual.

If you have any questions or concerns as to how to do this, please do not hesitate to reach out to Cogstate Site Services via email at PPD

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): PPD

Institution: Janssen Research & Development

Signature: PPD Date: PPD
(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.