Janssen Research & Development *

Clinical Protocol

A Randomized, Double-blind, Multicenter Active-controlled Study to Evaluate the Efficacy, Pharmacokinetics, Safety and Tolerability of Flexible Doses of Intranasal Esketamine Plus an Oral Antidepressant in Adult Subjects with Treatment-resistant Depression

Protocol ESKETINTRD3006; Phase 3
AMENDMENT 2

JNJ-54135419 (esketamine)

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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).

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Prepared by: Janssen Research & Development, LLC
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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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PROTOCOL AMENDMENTS

Protocol Version	Date
Original Protocol	22 May 2017
Amendment 1	23 Aug 2019
Amendment 2	21 Jan 2021

Amendments below are listed beginning with the most recent amendment.

Amendment 2 (21 January 2021)

The overall rationale of the protocol amendment: The overall rationale of the protocol amendment is to change the first key secondary endpoint to a clinically meaningful endpoint for evaluating the rapid reduction of depressive symptoms by intranasal esketamine.

Applicable Section(s)	Description of Change(s)
Rationale: The first key secondary endpoint is being changed to a clinically meaningful endpoint for evaluating the rapid reduction of depressive symptoms by intranasal esketamine. The current key secondary endpoint is being changed to an "Other Secondary Endpoint". Corresponding updates are being made to key secondary and other secondary objectives.	
Synopsis Objectives and Endpoints; 2.1. Objectives and Endpoints	***Key Secondary Objectives*** The key secondary objectives are to assess the effect of intranasal esketamine plus a newly initiated oral antidepressant compared with a newly initiated oral antidepressant (active comparator) plus intranasal placebo on the following parameters in adult subjects with TRD: – Change from baseline in the MADRS total score at 24 hours post first dose ***Other Secondary Objectives*** To assess the effect of intranasal esketamine plus a newly initiated oral antidepressant compared with a newly initiated oral antidepressant (active comparator) plus intranasal placebo on the following parameters in adult subjects with TRD: – Onset of clinical response by Day 2 ***Secondary Endpoints*** • MADRS: The first key secondary endpoint is the change from baseline (Day 1, predose) to 24 hours post first dose in depressive symptoms, as measured by the MADRS total score. ***Other Secondary Endpoints*** • Proportion of subjects showing onset of clinical response (≥50% reduction from baseline in MADRS total score) by Day 2 that is maintained through the end of the 4-week double-blind treatment phase with one excursion allowed.

Applicable Section(s)	Description of Change(s)
Synopsis Efficacy Evaluations; 3.2.5. Efficacy Measures	***MADRS*** In addition to the primary efficacy measure, the change in MADRS total score from baseline (Day 1, prior to randomization) to 24 hours post dose (Day 2) will be included as a key secondary efficacy endpoint to evaluate rapid reduction of depressive symptoms. MADRS will also be used to evaluate a secondary objective assessing the onset of clinical response (ie, antidepressant effect) by Day 2 that is maintained for the duration of the double-blind treatment phase. Onset of clinical response is defined as ≥50% improvement in MADRS total score by Day 2 (ie, the day after taking the first dose of double-blind intranasal medication) that is maintained through the end of the 4-week double-blind treatment phase with one excursion allowed. Additionally, MADRS will be used to evaluate a secondary objective assessing the proportion of subjects in remission (MADRS total score ≤12) at the end of the 4-week double-blind treatment phase; and the proportion who remain in remission (MADRS total score ≤12) through to the end of the follow-up phase.
9.2.1.2. Key Secondary Efficacy Evaluation	***Montgomery-Asberg Depression Rating Scale (MADRS) Total Score*** The MADRS will also be administered using a modified recall period of 24 hours for the key secondary efficacy evaluation related to change from baseline to 24 hours.
Synopsis Statistical Methods: Efficacy Analyses; 11.3. Efficacy Analyses	***Secondary Endpoints*** For the analysis of the first of the two key secondary efficacy endpoints, change from baseline in MADRS total score at 24 hours post first dose (Day 2), will be analyzed using the same model described above for the MADRS total score at Week 4 in the double-blind treatment phase. To strongly control Type I error across the primary and the two key secondary efficacy endpoints, a fixed sequence approach[15,16] will be applied to adjust for multiplicity. The hypotheses will be tested sequentially in the following order: • Change in MADRS total score at the end of the 4-week double-blind treatment phase • Change in MADRS total score at 24 hours post first dose The proportion of subjects showing onset of clinical response by Day 2 (in the event that no MADRS was collected on Day 2, a MADRS collected on Day 3 could be used) that is maintained for the duration of the double-blind treatment phase (≥50% reduction in MADRS total score by the second day after taking the first dose of double-blind medication that continued through the end of the double-blind phase) in esketamine arm will be compared with the active comparator using a Cochran-Mantel-Haenszel chi-square test adjusting for country and class of antidepressant (SNRI or SSRI). Subjects who discontinued the study prior

Applicable Section(s)	Description of Change(s)
	to the end of the double-blind treatment phase will not be considered to have maintained clinical response.
Rationale: Update to footnote "d" of the Time and Events Schedule (screening/prospective observational phase and double-blind treatment phase) to clarify the MADRS assessment at Visit 2.1.	
Time and Events Schedule (screening/prospective observational phase and double-blind treatment phase)	Footnote "d" will be updated as follows: Performed for subjects who require a taper period or who do not require a taper period but their Visit 1.3 and Visit 2.1 occur more than 1 week apart; the result will be considered as the subject's baseline MADRS for the double-blind treatment phase. For all other subjects, the baseline MADRS for the double-blind treatment phase will be the MADRS performed at the end of Week-4 of the screening/prospective observational phase.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 1 (23 August 2019)

The overall rationale of the protocol amendment: The overall rationale of the protocol amendment is to provide updates in line with feedback from investigators and the Human Genetic Resource Administration Office of China (HGRAO), and to provide overall clarification on procedures, wherever applicable.

Applicable Section(s)	Description of Change(s)
Rationale: Correction to criteria for recruiting subjects with major depressive disorder (MDD)	
Synopsis Study Population; 3.2.1. Study Population; 4.1. Inclusion Criteria; 9.1.2. Screening/Prospective Observational Phase	Inclusion criterion No.2 and associated text revised as follows (strikethrough text deleted): At the start of the screening/prospective observational phase, subject must meet the Diagnostic and Statistical Manual of Mental Disorders–Fifth Edition (DSM-5) diagnostic criteria for recurrent MDD or single-episode MDD ~~(if single episode MDD, the duration must be ≥2 years)~~, without psychotic features, based upon clinical assessment and confirmed by the MINI.
Rationale: Clarification that the testing of oral antidepressant levels in blood during the Screening/Prospective Observation Phase is optional.	
4.1. Inclusion Criteria	Inclusion criterion No. 3 revised as follows (bold text added): Clarification that the testing of oral antidepressant levels in blood during the screening/prospective observational phase is optional: – For specific tricyclic antidepressants which are ongoing and being taken at a dose below the MGH-ATRQ minimum therapeutic dose, a blood level that is within the therapeutic (antidepressant) range, is acceptable to establish the adequacy of

Applicable Section(s)	Description of Change(s)
	the antidepressant treatment. **Note: performing the test depends on availability of kit**.
Rationale: Clarification of the criteria for defining clinically significant ECG abnormalities.	
4.2. Exclusion Criteria	Exclusion Criterion No. 10 revised as follows (strikethrough text deleted): Subject has clinically significant ECG abnormalities at the start of the screening/prospective observational phase or on Day 1 of the double-blind treatment phase prior to randomization, defined as: – During screening, a QT interval corrected according to Fridericia's formula (QTcF): ≥470 msec in males and ≥480 msec in females~~; if the QTcF is prolonged on the initial ECG, the average QTcF of three ECGs, recorded 4 minutes apart, must not be ≥450 msec~~. – On Day 1 (predose), a QT interval corrected according to Fridericia's formula (QTcF): ≥470 msec in males and ≥480 msec in females based on the site-evaluated ECG~~; if the QTcF is prolonged on the initial ECG, the average QTcF of three ECGs, recorded 4 minutes apart, must not be ≥450 msec~~.
Rationale: Revised to reflect that there is no evidence to date to support the potential for esketamine to induce liver toxicity, with the cut-off level for alanine aminotransferase (ALT) or aspartate aminotransferase (AST) in serum, as evidence of underlying hepatoxicity in subjects at screening, raised from ≥2 times to ≥3 times the upper limit of normal, and deletion of reference to elevations in bilirubin levels at screening, which are indicative of Gilbert's disease	
4.2. Exclusion Criteria	Exclusion Criterion No. 12 revised as follows (bold text added, strikethrough text deleted): Subject has a history of, or symptoms and signs suggestive of, liver cirrhosis (eg, esophageal varices, ascites, and increased prothrombin time) OR alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values ~~≥2x ≥~~**3x** the upper limit of normal ~~or total bilirubin > 1.5 times the ULN~~ in the screening/prospective observational phase. Repeat of screening test for abnormal ALT and AST is permitted once during the screening period provided per investigator discretion and provided there is an alternative explanation for the out of range value. ~~For elevations in bilirubin, if in the opinion of the investigator and agreed upon by the sponsor's medical officer, the elevation in bilirubin is consistent with Gilbert's disease, the subject may participate in the study.~~

Applicable Section(s)	Description of Change(s)
Rationale: Clarification of the criteria for optional testing of subjects for use of drugs of abuse, at screening or prior to randomization on Day 1 of the Double-blind Treatment Phase.	
4.2. Exclusion Criteria	Exclusion Criterion No. 13 revised as follows (bold text added, strikethrough text deleted): Subject has positive test result(s) for drugs of abuse ~~(including barbiturates, methadone, opiates, cocaine, phencyclicdinee, and amphetamine/methamphetamine)~~ at the start of the screening/prospective observational phase **(including barbiturates, methadone, opiates, cocaine phencyclidine, and amphetamine)** or Day 1 of the double-blind treatment phase prior to randomization **(including cannabinoids, methadone, opiates, cocaine, and amphetamine). Note: performing the test depends on availability of the kit.** – Subjects who have a positive test result at screening due to prescribed psychostimulants (eg, amphetamine, etc.) taken for an indication other than MDD, are permitted to continue to take this medication during the study.
Rationale: Clarification that urine samples will be tested during the Double-blind Treatment Phase for the presence of cocaine only, and that the test is optional.	
4.3. Prohibitions and Restrictions No. 4	The following changes were made (bold text added, strikethrough text deleted): A positive urine drug screen for use of ~~phencyclidine (PCP), 3, 4 methylenedioxy methamphetamine (MDMA), lysergic acid diethylamide (LSD), or~~ cocaine from Day 1 of the double-blind treatment phase through the final visit in the double-blind treatment phase will lead to discontinuation. **Note: performing the test depends on availability of the kit.**
Rationale: Clarification of the criteria for urinalysis during the Screening/Prospective Observational and Double-blind Treatment Phase	
9.5. Safety Evaluations	**Clinical Laboratory Tests** Revised as follows (bold text added, strikethrough text deleted): **Urinalysis** Urine Drug Screen: Barbiturates, methadone, opiates, cocaine, cannabinoids (cannabinoids are only tested at Day 1, predose) phencyclidine, and amphetamine / ~~methamphetamine~~ – **at the start of the Screening/Prospective Observational Phase: barbiturates, methadone, opiates, cocaine, phencyclidine, and amphetamine** – **on Day 1 of the Double-blind Treatment Phase prior to randomization: cannabinoids, methadone, opiates, cocaine, and amphetamine**

Applicable Section(s)	Description of Change(s)
	– **on Day 15 and 25 of the Double-blind Treatment Phase: cocaine**
Rationale: Clarify that the Site-Independent Qualification Assessment to be used in this study is the Clinical Validation Inventory for Study Admission (C-VISA), to ensure enrollment of subjects who have symptoms that reflect the current state of illness.	
Synopsis Study Population; Time and Events Schedule Screening/Prospective Observational Phase and Double-blind Treatment Phase; 3.2.1. Study Population; 4.1. Inclusion Criteria (Criterion No.4); 9.6. Other Evaluations; 15. Study-Specific Materials	Clarify that the Site-Independent Qualification Assessment tool used in this study is the Clinical Validation Inventory for Study Admission (C-VISA).
Time and Events Schedule Screening/Prospective Observational Phase	Footnote (r):C-VISA can be completed prior to randomization.
Rationale: Correction to blood volumes to be collected from subjects in China, to clarify that Biomarkers and Pharmacogenomic evaluations will not be performed.	
9.1.1. Overview	Revised as follows (bold text added): The approximate total blood volume to be collected from subjects in China has been changed to **50 mL** (34 mL for eligibility and safety and 16 mL for PK). No blood will be collected for Biomarkers and Pharmacogenomic evaluations. The "74.5 ml for biomarkers" was deleted. Table 2: Volume of Blood to be Collected from Each Subject The following text was added to footnote (e): "This applies to US sites only, as not applicable for China" Footnote (e) added to the following: Screening/Prospective Observational Phase: Biomarker: DNA Biomarker: RNA The following text (in bold) was added to footnote (g): **50 mL for Chinese subjects and** 108.5 mL for non-Chinese subjects.
Rationale: Correction to footnotes as measurement of HbA1c levels in blood is mandatory.	
9.1.1. Overview	Table 2. Volume of Blood to be Collected from Each Subject Deletion of footnote (c) "as needed, HbA1c will be measured from the sample collected for hematology" Footnotes within the Table renumbered accordingly

Applicable Section(s)	Description of Change(s)
Rationale: Clarification that sections relation to Biomarkers Pharmacogenomic (DNA), and Expression (RNA) Evaluations are not applicable to China	
Synopsis Biomarker, Pharmacogenomic (DNA) and Expression (RNA) Evaluations; Synopsis Statistical Methods: Biomarker and Pharmacogenomic Analyses; Synopsis Exploratory Objectives and Exploratory Endpoints; Time and Events Schedule: Screening/prospective observational phase and double-blind treatment phase; 2.1.1. Objectives; 2.1.2. Endpoints; 3.2.3. Blinding and Randomization; 3.2.9. Biomarker, Pharmacogenomic (DNA) and Expression (RNA) Evaluations; 9.1.1. Overview; 9.4. Biomarker, Pharmacogenomic (DNA) and Expression (RNA) Evaluations; 11.5. Biomarker and Pharmacogenomic Analyses.	Footnote (a) stating that "Not applicable to China" added to text, to clarify that sections relating to Biomarkers, Pharmacogenomic (DNA) and Expression (RNA) evaluations will not be performed in China.
Synopsis Statistical Methods: Biomarker and Pharmacogenomic Analyses; 11.5 Biomarker and Pharmacogenomic Analysis	Addition of following text (bold) to clarify that statistical analysis will not be performed due to insufficient number: Baseline biomarker values and changes from baseline biomarker values to the time points specified in the Time and Events Schedule will be summarized **if available number is sufficient for analyses**.
Rationale: Correction to doses of oral antidepressant available and clarification of responsibility for sourcing study drug.	
14.1. Physical Description of Study Drug(s)	Correction to study drug doses: – Sertraline 25 mg: not available – Venlafaxine XR: 37.5 mg not available
9.1.4. Follow-up Phase	The following text was revised (bold text added): At the start of the follow-up phase, further clinical/standard of care for the treatment of depression will be arranged by the study investigator and/or the subject's treating physician and medication changes are permitted. The decision to continue the antidepressant will be at the discretion of the investigator. **If the subject continues to receive the same antidepressant medication for the duration of the follow-up phase, then the antidepressant will be sourced by the sponsor.**

Applicable Section(s)	Description of Change(s)
Rationale: Addition of a time point during the Double-blind Treatment Phase and Follow-up Phase for dispensing of new oral antidepressant for those subjects who will continue with the same oral antidepressant on entering the Follow-up Phase.	
Time and Events Schedule Screening/Prospective Observational Phase and Double-Blind Treatment Phase; Time and Events Schedule, Follow-up Phase	Study Drug: Dispensing of new oral antidepressant (duloxetine, escitalopram, sertraline, or venlafaxine XR): Addition of a footnote: (q) "For subjects entering the Follow-up phase and continuing with the same oral AD". And an "X" to Visit number 2.10 of the double-blind treatment phase Addition of a row for "Dispensing of oral antidepressant (duloxetine, escitalopram, sertraline, or venlafaxine XR)" and an "X" to Visit number 3.5. of the follow-up phase, Addition of footnote (h) "For subjects continuing with the same oral antidepressant".
Rationale: Clarification that in the event the last visit of the Screening/Prospective Observational Phase and the first visit of the Double-blind Treatment Phase do not occur on the same day, then the baseline MADRS assessment will be performed at the first visit of the Double-blind Treatment Phase	
Time and Events Schedule Screening/Prospective Observational Phase and Double-blind Treatment Phase	Footnote (d) revised as follows (bold text added, strikethrough text deleted): Performed **if Visit 1.3 and Visit 2.1 do not occur on the same day** ~~for subjects requiring a taper period during the screening/prospective observational phase~~; the result will be considered as the subject's baseline MADRS for the double-blind treatment phase. For all other subjects, the baseline MADRS for the double-blind treatment phase will be the MADRS performed at the end of Week 4 of the screening/prospective observational phase.
Rationale: Clarification on performing MADRS assessments during the Screening/Prospective Observational Phase and the Double-blind Treatment Phase	
Time and Events Schedule, Screening/Prospective Observational Phase and Double-blind Treatment Phase; 6.1 Screening/Prospective Observational Phase	Footnote (e) revised as follows: The following text was deleted: "At each "Remote MADRS" visit, site staff will perform the MADRS assessment either at the clinic or remotely by contacting the subject by telephone." The following text was added: "The MADRS interview should be performed in Week 1 (Visit 1.1 or as soon as possible) of the screening/prospective observational phase." Footnote (e) deleted from text "Remote MADRS interview only (RM) at Study Visit 2.2. of the double-blind treatment phase:" Footnote (e) added to text "MADRS (7-day recall) interview performed in Week 1 (Visit 1.1. or as soon as possible) of the screening/prospective observational phase).

Applicable Section(s)	Description of Change(s)
Rationale: Clarification that the C-SSRS assessment will be performed at each Remote Assessment visit.	
Time and Events Schedule, Follow-up Phase	Footnote (b) revised as follows (bold text added): At each "Remote Assessment" visit, site staff will contact the subject by telephone to **perform the C-SSRS and to** obtain information regarding adverse events and concomitant therapies.
Rationale: Clarification of the criteria for treatment blinding	
5. Treatment Allocation and Blinding; 11. Statistical Methods	The following text was deleted: **Blinding** At the end of the double-blind treatment phase the database will be locked for the analysis and reporting of this phase. The subject treatment assignment will be revealed only to sponsor's study staff. The investigators and the site personnel will be blinded to the treatment assignment until all subjects have completed study participation through the follow-up phase.
Rationale: Clarification that Pharmacokinetic analysis will only be performed in Chinese subjects	
9.3. Pharmacokinetics; 11.4 Pharmacokinetic Analysis	Section header edited to clarify that Pharmacokinetic Analysis only applicable to Chinese subjects Section 9.3. Pharmacokinetics **(Chinese subjects only)** Section 11.4. Plasma esketamine concentrations will be tested for all **Chinese** subjects
Rationale: Clarification that only Pharmacokinetic analysis for esketamine levels in serum is mandatory; Pharmacokinetic analysis on all metabolites including noresketamine is optional, and this will not impact on the interpretation of the data.	
Synopsis Pharmacokinetic Evaluations; Statistical Methods; 3.2.8. Pharmacokinetic Assessments; 9.3.1 Evaluations; 9.3.2. Analytical Procedures; 9.3.3. Pharmacokinetic Parameters; 11.4 Pharmacokinetic Analyses	Reference to noresketamine deleted.

Applicable Section(s)	Description of Change(s)
Rationale: Clinically relevant treatment-emergent adverse events of special interest have been updated to reflect changes to the FDA's guidance for industry in assessing abuse potential of drugs.	
3.2.6. Safety Evaluations	Treatment-emergent adverse events (TEAEs) of special interest have been revised as follows (bold text added, strikethrough text deleted): **Clinically relevant** TEAEs of special interest will be examined separately grouped in the following categories **as defined by** the Standardized Medical Dictionary for Regulatory Activities (MedDRA) (version 20.0, or above if applicable) queries (SMQ): ~~Drug abuse dependence and withdrawal~~ **AEs potentially suggestive of abuse**, increased blood pressure, increased heart rate, transient dizziness/vertigo, impaired cognition, anxiety, and cystitis. The following text was added: • The preferred terms used to determine TEAEs potentially suggestive of abuse, as defined by the Food and Drug Administration's Assessment of Abuse Potential of Drugs Guidance for Industry (January 2017), include: Aggression, Confusional state, Decreased activity, Disorientation, Dissociation, Dissociative disorder, Dizziness, Drug tolerance, Euphoric mood, Feeling abnormal, Feeling drunk, Feeling of relaxation, Hallucination, Hallucination, auditory. Hallucination, gustatory, Hallucination, olfactory, Hallucination, synaesthetic, Hallucination, tactile, Hallucination, visual, Hallucinations, mixed, Inappropriate affect, Mental impairment, Product tampering, Psychomotor hyperactivity, Psychotic disorder, Somatic hallucination, Somnolence, Substance use disorder, Substance-induced psychotic disorder, and Thinking abnormal. Narrative descriptions will be provided for deaths, subjects with serious adverse events, and subjects who discontinued study medication due to an adverse event. If applicable, narratives will be prepared for subjects with a TEAE of cystitis, with postdose oxygen saturation <93% for 2 or more consecutive assessments within the same visit, with post-baseline cases of QTcF >500 msec, with clinically significant suicidal ideation (score of 4 or 5 on the C-SSRS) or suicidal behavior (scores 6-10 on the C-SSRS), and for subjects who experienced a motor vehicle accident and/or who had TEAEs potentially suggestive of abuse.
References	The following reference for the Food and Drug Administration's Assessment of Abuse Potential of Drugs Guidance for Industry (January 2017) was added:

Applicable Section(s)	Description of Change(s)
Rationale: Update section on Clinical Studies to include Phase 1 studies performed by the sponsor in healthy volunteers and special populations; recently completed Phase 3 efficacy and safety studies conducted in subjects with treatment resistant depression (TRD); and a Phase 2 proof-of-concept study in subjects with major depressive disorder with suicidal ideation (MDSI).	
1.1.2. Clinical Studies.	The section on Clinical Studies was updated to reflect recently completed studies conducted by the sponsor. Subsections 1.1.2.1. and 1.1.2.2. added to differentiate between studies conducted to investigate the Pharmacokinetics of esketamine and Pharmacodynamic Efficacy and Safety studies conducted in patient populations. The following text was added: The clinical program for esketamine includes: a comprehensive clinical pharmacology program in healthy volunteers and special populations to fully characterize the product's pharmacokinetic (PK) and pharmacodynamic (PD) activity, including Phase 2 studies with IV esketamine and ketamine; a Phase 2 dose response study in adults with TRD; a Phase 2 proof-of-concept study in the related condition of MDD with imminent risk for suicide; and data from 5 completed Phase 3 studies establishing efficacy and safety in adults with TRD, including those 65 years and older. Results from 1 ongoing Phase 2 study and 2 additional ongoing Phase 3 studies in adults with TRD are not available at the time of finalization. **Section 1.1.2.1. Pharmacokinetics** The following Human Pharmacokinetic (PK) and initial tolerability Phase 1 studies were conducted by the sponsor in healthy adult subjects. Further details are available in the Investigator Brochure[34]: • Intravenous and oral dose of radiolabeled esketamine: 54135419TRD1016. • Intravenous, intranasal and oral esketamine: ESKETINTRD1009 • Intranasal esketamine: – Healthy adult non-Asian and Asian subjects: ESKETINTRD1001, ESKETINTRD1002, ESKETINTRD1004, ESKETINTRD1005, ESKETINTRD1006, ESKETINTRD1009, ESKETINTRD1010, ESKETINTRD1013, 54135419TRD1020 (Japanese subjects only). – Healthy elderly and younger adult non-Asian and Asian subjects: ESKETINTRD1003, ESKETINTRD1012, and 54135419TRD1018 (Japanese subjects only). – Subjects with a history of allergic rhinitis: ESKETINTRD1007. – Recreational users of perception-altering drugs: 54135419TRD1015 – Subjects with hepatic impairment: ESKETINTRD1011 – Subjects with renal impairment: 54135419TRD1014 Subjects with MDD; On-Road Driving effects: 54135419TRD1019.

Applicable Section(s)	Description of Change(s)
	Section 1.1.2.2. Efficacy and Safety Studies The following Efficacy and Safety Phase 2a and Phase 3 studies were conducted by the sponsor in subjects with TRD or MDD who are at imminent risk for suicidal ideation. • Phase 2a: Intravenous ketamine or esketamine administered to subjects with TRD: KETIVTRD2002, KETIVTRD2004 and ESKETIVTRD2001, respectively. • Phase 2a: Intranasal esketamine administered to subjects with TRD: ESKETINTRD2003; Intranasal esketamine administered to subjects with MDD who are at imminent risk for suicidal ideation: ESKETINSUI2001. • Phase 3: Intranasal esketamine administered to subjects with TRD: – Short-term studies: ESKETINTRD3001, ESKETINTRD3002, and ESKETINTRD3005 – Long-term studies: ESKETINTRD3003 and ESKETINTRD3004 For the most comprehensive information regarding these clinical studies, refer to the latest version of the Investigator Brochure.[34] Human Pharmacokinetics Metabolism: Include reference to esketamine and update to include a paragraph outlining data obtained on esketamine metabolism and excretion.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

A Randomized, Double-blind, Multicenter Active-controlled Study to Evaluate the Efficacy, Pharmacokinetics, Safety and Tolerability of Flexible Doses of Intranasal Esketamine Plus an Oral Antidepressant in Adult Subjects with Treatment-resistant Depression

Major depressive disorder (MDD), a serious, recurrent, and disabling psychiatric illness, is the second leading cause of years lost to disability worldwide. MDD is associated with excess mortality, and with years of potential life lost. About 30% of patients fail to achieve remission despite treatment with multiple antidepressant medications, and are considered to have treatment-resistant depression (TRD). There is a significant need to develop novel treatments based upon relevant pathophysiologic pathways underlying MDD for the rapid relief of symptoms of depression, especially in patients with TRD.

Esketamine is an *N*-methyl-D-aspartate (NMDA) receptor antagonist. It is the S-enantiomer of racemic ketamine, and has been shown to have approximately 3- to 4 fold stronger binding affinity for the phencyclidine (PCP) site of the N-methyl-D-aspartate (NMDA) receptor than the R-enantiomer. The mechanism of action of ketamine and esketamine is distinct from conventional monoaminergic antidepressant treatments and ketamine profoundly affects fast excitatory glutamate transmission, increases brain-derived neurotrophic factor (BDNF) release, and stimulates synaptogenesis.

Janssen Research & Development (JRD) is developing intranasal esketamine as an antidepressant therapy. A higher NMDA receptor affinity of esketamine allows a lower volume of medication to be administered via the non-invasive, rapidly absorbed intranasal route.

The current study is being conducted to evaluate the efficacy, safety, and tolerability of flexibly dosed intranasal esketamine plus a newly initiated oral antidepressant in adult subjects with TRD. The study will serve as a Phase 3 short-term efficacy and safety study in support of Chinese regulatory agency requirements for registration of intranasal esketamine for the treatment of TRD.

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

Objectives

Primary Objective

The primary objective of this study is to evaluate the efficacy of switching adult subjects with TRD from a prior antidepressant treatment (to which they have not responded) to flexibly dosed intranasal esketamine (56 mg or 84 mg) plus a newly initiated oral antidepressant compared with switching to a newly initiated oral antidepressant (active comparator) plus intranasal placebo, in improving depressive symptoms, as assessed by the change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) total score from Day 1 (pre-randomization) to the end of the 4-week double-blind treatment phase.

Secondary Objectives

Key Secondary Objectives

The key secondary objectives are to assess the effect of intranasal esketamine plus a newly initiated oral antidepressant compared with a newly initiated oral antidepressant (active comparator) plus intranasal placebo on the following parameters in adult subjects with TRD:

- Change from baseline in the MADRS total score at 24 hours post first dose
- Functioning and associated disability

Other Secondary Objectives

To assess the effect of intranasal esketamine plus a newly initiated oral antidepressant compared with a newly initiated oral antidepressant (active comparator) plus intranasal placebo on the following parameters in adult subjects with TRD:

- Onset of clinical response by Day 2
- Depression response rates
- Depression remission rates
- Overall severity of depressive illness
- Anxiety symptoms
- Health-related quality of life and health status

To investigate the safety and tolerability of intranasal esketamine plus a newly initiated oral antidepressant compared with a newly initiated oral antidepressant (active comparator) plus intranasal placebo in adult subjects with TRD, including the following parameters:

- Treatment-emergent adverse events (TEAEs), including AEs of special interest
- Local nasal tolerability
- Effects on heart rate, blood pressure, respiratory rate, and blood oxygen saturation
- Dissociative symptoms
- Potential effects on suicidal ideation/behavior
- Potential withdrawal and/or rebound symptoms following cessation of intranasal esketamine treatment.

To assess the pharmacokinetics (PK) of intranasal esketamine in Chinese adult subjects with TRD receiving intranasal esketamine plus a newly-initiated oral antidepressant.

Exploratory Objectives

For subjects who receive esketamine during the double-blind treatment phase, the proportion of subjects who relapse during the follow-up phase will be evaluated separately for subjects who are remitters (MADRS ≤12) at the end of the 4 week double-blind treatment phase and for subjects who are responders but not remitters (≥50% reduction in MADRS total score, but MADRS >12) at the end of the 4 week double-blind treatment phase.

- Time to relapse during the follow-up phase will be evaluated in esketamine subjects who remitted
- Time to relapse during the follow-up phase will be evaluated in esketamine subjects who are responders but not remitters

To assess the potential relationship of biomarkers with response/non-response to intranasal esketamine or oral antidepressants in adult subjects with TRD.[α]

[α] Not applicable to China

Endpoints

Primary Endpoint

- The primary endpoint is the change in the MADRS total score as measured by the change from baseline (Day 1 prior to randomization) to the end of the 4-week double-blind treatment phase.

Secondary Endpoints

- MADRS: The first key secondary endpoint is the change from baseline (Day 1, predose) to 24 hours post first dose in depressive symptoms, as measured by the MADRS total score.
- Sheehan Disability Scale (SDS): The second key secondary endpoint is the change in SDS total score as measured by the change from baseline (Day 1, prior to randomization) to the end of the 4-week double-blind treatment phase

Other Secondary Endpoints

- Proportion of subjects showing onset of clinical response (≥50% reduction from baseline in MADRS total score) by Day 2 that is maintained through the end of the 4-week double-blind treatment phase with one excursion allowed.
- Proportion of responders (≥50% reduction from baseline in MADRS total score) at the end of the 4-week double-blind treatment phase.
- Proportion of subjects in remission (MADRS ≤12) at the end of the 4-week double-blind treatment phase.
- Proportion of subjects who remain in remission (MADRS ≤12) through to the end of the follow-up phase.
- Change from baseline (Day 1, prior to randomization) to the end of the 4-week double-blind treatment phase in:
  - Severity of depressive illness, using the Clinical Global Impression–Severity (CGI-S);
  - Anxiety symptoms, using the Generalized Anxiety Disorder (GAD-7);
  - Health-related quality of life and health status, as assessed by the EuroQol-5 dimension-5 level (EQ-5D-5L).

Refer to Section 9, Study Evaluations for related evaluations.

Exploratory Endpoints

For subjects who receive esketamine during the double-blind treatment phase, the proportion of subjects who relapse during the follow-up phase will be evaluated separately for subjects who are remitters (MADRS ≤12) at the end of the 4 week double-blind treatment phase and for subjects who are responders but not remitters (≥50% reduction in MADRS total score, but MADRS >12) at the end of the 4 week double-blind treatment phase.

- Time to relapse during the follow-up phase in esketamine subjects who remitted.
- Time to relapse during the follow-up phase in esketamine subjects who are responders but not remitters.

To assess the potential relationship of biomarkers with response/non-response to intranasal esketamine and oral antidepressant.[α]

Hypothesis

The hypothesis for this study is that, in adult subjects with TRD, switching from a failed antidepressant treatment to intranasal esketamine plus a newly initiated oral antidepressant is superior to switching to a newly initiated oral antidepressant treatment (active comparator) plus intranasal placebo in improving depressive symptoms.

OVERVIEW OF STUDY DESIGN

This is a randomized, double-blind, active-controlled, multicenter study in male and female adult subjects with TRD to assess the efficacy, safety, tolerability, and pharmacokinetics of flexibly dosed intranasal esketamine (56 mg or 84 mg) plus a newly initiated oral antidepressant compared with a newly initiated oral antidepressant (active comparator) plus intranasal placebo.

The study has 3 phases;

- Screening/Prospective Observational Phase
- Double-blind Treatment Phase
- Follow-up Phase

Overview of Study Phases

Screening/Prospective Observational phase (4-week duration + optional 3-week taper period)

This phase will prospectively assess treatment response to the subject's current oral antidepressant treatment regimen.

At the start of the screening/prospective observational phase, the subject must have had documented non-response to at least 1 antidepressant treatment (based on Massachusetts General Hospital [MGH]-Antidepressant Treatment Response Questionnaire [ATRQ] [MGH-ATRQ]) in the current episode of depression, and subject is taking a different oral antidepressant treatment (on the MGH-ATRQ) for at least the previous 2 weeks at or above the minimum therapeutic dose. This antidepressant treatment, as well as any other ongoing medications being taken for depression at screening (including adjunctive/augmentation therapies), will continue from the start of Week 1 through the end of Week 4 of the screening/prospective observational phase. Dose adjustment is permitted per clinical judgment, but the oral antidepressant treatment is to remain at or above the minimum therapeutic dose (per the MGH-ATRQ) through the end of Week 4.

After 4 weeks, subjects who are non-responders to their current oral antidepressant treatment (as assessed by independent, remote raters) may be eligible to proceed to the double-blind treatment phase. Non-response at the end of the screening/prospective observational phase is defined as ≤25% improvement in the MADRS total score from Week 1 to Week 4 and a MADRS total score of ≥28 on Week 2 and Week 4.

Eligible subjects who are entering the double-blind treatment phase will discontinue all their current medication(s) being used for depression treatment, including adjunctive/augmentation therapies. Of note, subjects taking benzodiazepines (at dosages equal to or less than the equivalent of 6 mg/day of lorazepam) and/or permitted non-benzodiazepine sleep medications (eg, zolpidem, zaleplon, eszopiclone and ramelteon) during the screening/prospective observational phase, can continue these medications, but no

[α] Not applicable to China

dose increases beyond the equivalent of 6 mg/day of lorazepam or new benzodiazepine medications are permitted during the screening/prospective observational phase. If clinically indicated, a subject's current antidepressant treatment(s) may be tapered and discontinued over an additional, optional period of up to 3 weeks per the local prescribing information or clinical judgment, or discontinued and switched directly to one of the four new oral antidepressant medications on Day 1 of the double-blind treatment phase, per clinical judgment.

Double-blind Treatment Phase (4-week duration)

Approximately 234 eligible subjects (210 Chinese subjects, 24 non-Chinese subjects) with TRD, will be randomly assigned at a 1:1 ratio (n=117 subjects per treatment arm, with approximately 105 Chinese subjects per arm) to receive double-blind treatment with either intranasal esketamine or intranasal placebo. The intranasal treatment sessions (esketamine 56 mg, 84 mg or placebo) will occur twice per week for 4 weeks as a flexible dose regimen at the study site. In addition, all subjects will initiate a new open-label oral antidepressant on Day 1, that will be taken daily for the duration of the double-blind treatment phase. The assigned oral antidepressant will be 1 of 4 oral antidepressant medications (duloxetine, escitalopram, sertraline, or venlafaxine extended release [XR]), that the subject has not previously had a non-response to in the current depressive episode, has not been previously intolerant to (lifetime), and is available in the participating country.

Subjects who were taking benzodiazepines (at dosages equal to or less than the equivalent of 6 mg/day of lorazepam) and/or permitted non-benzodiazepine sleep medications (eg, zolpidem, zaleplon, eszopiclone and ramelteon) during the screening/prospective observational phase can continue these medications during the double-blind treatment phase. No dose increases beyond the equivalent of 6 mg/day of lorazepam or new benzodiazepine medications are permitted during the double-blind treatment phase, with the exception of the use of permitted benzodiazepine rescue medication (eg, alprazolam, clorazepate, triazolam, lorazepam and temazepam).

Refer to the Time and Events Schedule for a list of study evaluations that will be performed during the double-blind treatment phase.

If a subject withdraws from the study before the end of the double-blind treatment phase for reasons other than withdrawal of consent, an Early Withdrawal visit should be conducted within 1 week of the date of discontinuation, followed by the follow-up phase.

Follow-up Phase (8-weeks or until relapse)

The follow-up phase will include all subjects who received at least 1 dose of intranasal study medication in the double-blind treatment phase. No intranasal study medication will be administered during this phase.

At the start of the follow-up phase, further clinical/standard of care for the treatment of depression will be arranged by the study investigator and/or the subject's treating physician and medication changes are permitted. The decision to continue the oral antidepressant in this phase will be at the discretion of the investigator.

This follow-up phase will provide additional information required to assess the course of the subject's major depressive episode over an 8-week period. Safety and tolerability, including potential withdrawal symptoms, following discontinuation of intranasal esketamine will also be assessed.

The follow-up phase is completed at the end of the 8-week period or when a subject meets the criteria below for relapse (in remitters and responders), whichever occurs earlier.

Relapse is defined as any of the following:

- MADRS total score ≥22 for 2 consecutive assessments separated by 5 to 15 days. The date of the second MADRS assessment will be used for the date of relapse.

- Hospitalization for worsening depression or any other clinically relevant event determined per clinical judgment to be suggestive of a relapse of depressive illness such as suicide attempt, completed suicide, or hospitalization for suicide prevention. If hospitalized for any of these events, the start date of hospitalization will be used for the date of relapse. Otherwise the date of the event will be used if the subject is not hospitalized.
- In case more than one relapse criteria are met, the earlier date will be defined as the date of relapse for this subject.

The total duration of a subject's study participation will be up to 19 weeks (including an optional 3-week taper period) for subjects completing the 8-week follow-up phase.

STUDY POPULATION

The study population will consist of approximately 234 subjects (210 Chinese subjects and 24 non-Chinese subjects) with TRD. After giving informed consent, subjects who are 18 to 64 years of age (inclusive), will be screened to determine eligibility for study participation.

Subjects must meet Diagnostic and Statistical Manual of Mental Disorders–Fifth Edition (DSM-5) diagnostic criteria for recurrent MDD or single-episode MDD, without psychotic features, based upon clinical assessment and confirmed by the Mini International Neuropsychiatric Interview (MINI) [DSM-5 diagnostic code 296.23 or 296.33]. An independent rater will conduct the MADRS at screening as well as confirming the diagnosis and the validity of the major depressive episode.

At the start of the screening/prospective observational phase, subjects must have had non-response (ie, lack of clinically meaningful improvement, defined as ≤25% improvement) to ≥1 but ≤5 (if current episode is >2 years or undefinable, upper limit is only applicable to the last 2 years) oral antidepressant treatments, taken at adequate dosage and for adequate duration, as assessed using the MGH-ATRQ and documented by records (eg, medical/pharmacy/prescription records or a letter from treating physician, etc.), for the current episode of depression. In addition, the subject must currently be taking one of a different oral antidepressant treatment (on the MGH-ATRQ) for at least the previous 2 weeks at or above the minimum therapeutic dose. This antidepressant treatment, as well as any other ongoing medications being taken for depression at screening (including adjunctive/augmentation therapies), will continue from the start of Week 1 through the end of Week 4 of the screening/prospective observational phase. Dose adjustment is permitted per clinical judgment, but the oral antidepressant treatment is to remain at or above the minimum therapeutic dose (per the MGH-ATRQ) through the end of Week 4. Antidepressant treatment adherence will be assessed using the PAQ. Subjects who report missing ≥4 days of antidepressant medication treatment(s) in the prior 2-week period will be considered as screen failed due to inadequate adherence.

Non-response at the end of the screening/prospective observational phase is defined as ≤25% improvement from Week 1 to Week 4 in the MADRS total score and a MADRS total score of ≥28 on Week 2 and Week 4.

Treatment-resistant depression is defined as a lack of clinically meaningful improvement after treatment with at least 2 different antidepressant agents prescribed in adequate doses for adequate duration.

The subject's current major depressive episode, depression symptom severity (Week 1 MADRS total score ≥28 required), and antidepressant treatment response in their current depressive episode (retrospectively assessed) must be deemed valid for participation in the clinical study based on a Clinical Validation Inventory for Study Admission (C-VISA). The C-VISA is a tool to facilitate subject selection for MDD clinical studies, with a goal to ensure enrollment of subjects who have symptoms that reflect the current state of illness and that these symptoms can be reliably measured with appropriate measurement tools.

Potential subjects will be excluded from participating in the study if they have previously demonstrated non-response of depressive symptoms to esketamine or ketamine in the current major depressive episode, or to all 4 of the oral antidepressant treatment options available for the double-blind treatment phase (ie, duloxetine, escitalopram, sertraline, and venlafaxine XR) in the current major depressive episode (based

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

DOSAGE AND ADMINISTRATION

During the double-blind treatment phase, subjects will be randomized to receive double-blind intranasal treatment with esketamine (56 mg or 84 mg) or placebo. In addition, subjects will simultaneously initiate a new, open-label oral antidepressant on Day 1 that will be continued for the duration of the 4-week double-blind treatment phase.

Double-Blind Treatment Phase

Intranasal Study Medication

All subjects will self-administer the intranasal study drug (esketamine or placebo) at treatment sessions twice a week for 4 weeks at the study site. The first treatment session will be on Day 1 of the double-blind treatment phase. Intranasal treatment sessions will not take place on consecutive days.

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.

On Day 1, subjects randomized to intranasal esketamine will start with a dose of 56 mg. On any of the subsequent dosing days (Day 4, 8, 11, 15, 18, 22 and 25), the investigator can judge, based on efficacy and tolerance, whether to increase the dose of intranasal esketamine to 84 mg or to maintain the dose at 56 mg. In the event that an increase in dose is poorly tolerated, the investigator may decide to reduce the dose to 56 mg. Food will be restricted for at least 2 hours before each administration of study drug. Drinking of fluids will be restricted for at least 30 minutes before the first nasal spray.

On all intranasal treatment session days, a site staff member with training in cardiopulmonary resuscitation (eg, Basic Life Support course or equivalent course) that is up to date per local regulations, must be present with the subject during the intranasal treatment sessions and the postdose observation period. In addition, equipment for supportive ventilation and resuscitation needs to be present. Subjects must remain at the site until study procedures have been completed and the subject is ready for discharge. At the time of discharge, 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 receiving intranasal study drug.

Oral Antidepressant Study Medication

Starting on Day 1, a new, open-label oral antidepressant treatment will be initiated in all subjects. The oral antidepressant will be 1 of 4 oral antidepressant medications (duloxetine, escitalopram, sertraline, or venlafaxine XR). The antidepressant medication will be assigned by the investigator based on review of MGH-ATRQ and relevant prior antidepressant medication information and will be one that the subject has not previously had a non-response to in the current depressive episode, has not been previously intolerant to (lifetime), and is available in the participating country.

Dosing of the oral antidepressant will begin on Day 1 and will follow a specific titration schedule. The use of the titration schedule is mandatory. Doses are not to exceed the maximum dose defined in the titration schedule. If higher doses are not tolerated, a down-titration is permitted based on clinical judgment.

EFFICACY EVALUATIONS

Primary Efficacy Evaluation and Endpoint

The primary efficacy evaluation will be the MADRS total score. The MADRS will be performed by independent remote raters during the study. The Structured Interview Guide for the Montgomery Asberg Depression Rating Scale (SIGMA: Williams 2008) will be used for each administration.

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

The primary efficacy endpoint will be change from baseline in MADRS total score from Day 1 pre-randomization to the end of the 4-week double-blind treatment phase.

Secondary Efficacy Evaluation and Endpoints

Key Secondary Efficacy Evaluations and Endpoints

- MADRS: The first key secondary endpoint is change from baseline (Day 1, predose) to 24 hours post first dose in depressive symptoms, as measured by the MADRS total score.
- Sheehan Disability Scale (SDS): The SDS is a subject-reported outcome measure that will be used to assess functional impairment and associated disability. The second key secondary endpoint is the change in SDS total score as measured by the change from baseline (Day 1 prior to randomization) to the end of the 4-week double-blind treatment phase.

Other Secondary Efficacy Evaluations and Endpoints

- Proportion of subjects showing onset of clinical response (≥50% reduction from baseline in MADRS total score) by Day 2 that is maintained through the end of the 4-week double-blind treatment phase with one excursion allowed.
- Proportion of responders (≥50% reduction from baseline in MADRS total score) at the end of the 4-week double-blind treatment phase.
- Proportion of subjects in remission (MADRS ≤12) at the end of the 4-week double-blind treatment phase.
- Proportion of subjects who remain in remission (MADRS ≤12) through to the end of the follow-up phase.
- Change from baseline (Day 1, prior to randomization) to the end of the 4-week double-blind treatment phase in:
    - Severity of depressive illness, using the Clinical Global Impression–Severity (CGI-S);
    - Anxiety symptoms, using the Generalized Anxiety Disorder (GAD-7), and
    - Health-related quality of life and health status, as assessed by the EuroQol-5 dimension-5 level (EQ-5D-5L).

Exploratory Efficacy Evaluation and Endpoints

- For subjects who receive esketamine during the double-blind treatment phase, the proportion of subjects who relapse during the follow-up phase will be evaluated separately for subjects who are remitters (MADRS ≤12) at the end of the 4 week double-blind treatment phase and for subjects who are responders but not remitters (≥50% reduction in MADRS total score, but MADRS >12) at the end of the 4 week double-blind treatment phase.
  - Time to relapse during the follow-up phase in esketamine subjects who remitted.
  - Time to relapse during the follow-up phase in esketamine subjects who are responders but not remitters.

See Section 9.2 for further details

PHARMACOKINETIC EVALUATIONS

Pharmacokinetic Venous blood samples of approximately 4 mL will be collected from Chinese subjects at all clinical sites, for measurement of plasma concentrations of esketamine (JNJ-54135419), and other metabolites (if warranted), at the time points specified in the Time and Events Schedule. The exact dates and times of PK blood sampling must be recorded.

BIOMARKER, PHARMACOGENOMIC (DNA) AND EXPRESSION (RNA) EVALUATIONS[α]

Assessment of biomarkers and their potential relationship to intranasal esketamine plus a newly initiated oral antidepressant and to maintenance/stabilization of response, non-response, and relapse will be explored. Blood samples will be collected to measure genetic and epigenetic markers (including but not limited to BDNF allelic variants) and protein markers (including but not limited to growth factors, inflammation, endocrine, or metabolic markers). Samples of deoxyribonucleic acid (DNA) and biomarkers (protein and RNA) may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies. Subjects who agree to participate in the biomarker, pharmacogenomic (DNA) and expression (RNA) component will need to sign a separate written informed consent form.

SAFETY EVALUATIONS

Safety evaluations will include:

Monitoring of Treatment Emergent Adverse Events (TEAEs), clinical laboratory tests (including hematology, serum chemistry, and urinalysis), pregnancy testing (for women of childbearing potential), urine drug screen, 12-lead electrocardiogram (ECG), vital signs, pulse oximetry, physical examination, and body weight measurements.

- Nasal examinations
- Columbia Suicide Severity Rating Scale (C-SSRS), to assess potential suicidal ideation and behavior
- Clinician Administered Dissociative States Scale (CADSS), to assess treatment-emergent dissociative symptoms
- Physician Withdrawal Checklist (20 items; PWC-20) to assess potential withdrawal symptoms following cessation of intranasal esketamine treatment

[α] Not applicable to China

STATISTICAL METHODS

Subject Information

The primary efficacy and safety analysis sets are defined below:

Full Analysis Set: All randomized subjects who receive at least 1 dose of intranasal study medication and 1 dose of oral antidepressant medication in the double-blind treatment phase.

Safety Analysis Set: All randomized subjects who receive at least 1 dose of intranasal study medication or 1 dose of oral antidepressant medication in the double-blind treatment phase.

Sample Size Determination

Assuming a treatment difference for the double-blind treatment phase of 6.5 points in MADRS total score between esketamine plus oral antidepressant compared with oral antidepressant plus intranasal placebo at the Week 4 endpoint, a standard deviation of 12, a one-sided significance level of 0.025, a drop-out rate of 25%, 117 subjects will be randomized to each treatment arm to achieve greater than 90% power and a sample size of 105 Chinese subjects per treatment arm (total n = 210) plus 12 non-Chinese subjects per treatment arm (total of n = 24) will be included. The treatment difference and standard deviation used in this calculation were based on results from Panel A of the ESKETINTRD2003 study and based on clinical judgment.

Efficacy Analyses

Efficacy analyses will be performed on the full analysis set, which will include all randomized subjects who receive at least 1 dose of intranasal study drug and 1 dose of oral antidepressant medication, in the double-blind treatment phase.

Primary Endpoint

The primary estimand, the main clinical quantity of interest to be estimated in the study, is defined by the following 4 components:

- Population: subjects with treatment-resistant depression;
- Variable: change from Day 1 to end of 4-week double-blind treatment phase;
- Intervention Effect: the effect of the initially randomized treatment together with the oral antidepressant medication that would have been observed had all subjects remained on their treatment throughout the double-blind treatment phase;
- Summary Measure: the difference in variable means.

The primary analysis will be based on the full analysis set and the MADRS total scores collected during the double-blind treatment phase.

For the primary efficacy analysis, change from baseline in MADRS total score at Week 4 in the double-blind treatment phase will be analyzed using a mixed-effects model for repeated measures (MMRM). The model will include baseline MADRS total score as a covariate, and treatment, country, class of antidepressant (Serotonin and Norepinephrine Reuptake Inhibitors [SNRI] or Selective Serotonin Reuptake Inhibitor [SSRI]), day, and day-by-treatment interaction as fixed effects. Comparison of the esketamine plus oral antidepressant arm to the active comparator (oral antidepressant plus intranasal placebo) arm will be performed using the appropriate contrast.

Sensitivity analysis for the primary efficacy endpoint to assess the robustness of the results to missing data might be performed. The detailed assumptions and methods will be provided in the statistical analysis plan (SAP).

Secondary Efficacy Endpoint Analysis

For the analysis of the first of the two key secondary efficacy endpoints, change from baseline in MADRS total score at 24 hours post first dose (Day 2), will be analyzed using the same model described above for the MADRS total score at Week 4 in the double-blind treatment phase.

The second key efficacy endpoint, change from baseline in SDS total score at Week 4 in the double-blind treatment phase, will be analyzed using the same models described above for the MADRS total score.

To strongly control Type I error across the primary and the two key secondary efficacy endpoints, a fixed sequence approach will be applied to adjust for multiplicity. The hypotheses will be tested sequentially in the following order:

- Change in MADRS total score at the end of the 4-week double-blind treatment phase
- Change in MADRS total score at 24 hours post first dose
- Change in SDS total score

Further details of this approach will be provided in the SAP.

The proportion of subjects showing onset of clinical response by Day 2 (in the event that no MADRS was collected on Day 2, a MADRS collected on Day 3 could be used) that is maintained for the duration of the double-blind treatment phase (≥50% reduction in MADRS total score by the second day after taking the first dose of double-blind medication that continued through the end of the double-blind phase) in esketamine arm will be compared with the active comparator using a Cochran-Mantel-Haenszel chi-square test adjusting for country and class of antidepressant (SNRI or SSRI). Subjects who discontinued the study prior to the end of the double-blind treatment phase will not be considered to have maintained clinical response.

Response and remission rates will be summarized at each visit.

The proportion of subjects who remain in remission through to the end of the follow-up phase will be presented.

Change from baseline in GAD-7 total scores at the end of the 4-week double-blind treatment phase will be analyzed using an ANCOVA model, with treatment, country and class of antidepressant (SNRI or SSRI) as factors, and the respective baseline score as the covariate.

Ranks of change from baseline in CGI-S scores during the 4-week double-blind treatment phase will be analyzed using the MMRM for repeated measures, as described above for the MADRS and SDS total scores.

Dimension scores of EQ-5D-5L descriptive system, health status index, and the overall health status score will be summarized over time.

Additionally, scores of all efficacy endpoints will be summarized for all visits in the double-blind period. Summaries will be provided to show consistency of effect among relevant subgroups (eg, antidepressant class SSRI [escitalopram, sertraline] and SNRI [duloxetine, venlafaxine]).

For subjects who receive esketamine during the double-blind treatment phase, the proportion of subjects who relapse during the follow-up phase will be summarized separately for subjects who are remitters (MADRS ≤12 at the end of the double-blind treatment phase) and for subjects who are responders but not remitters (≥50% reduction in MADRS total score, but MADRS >12 at the end of the double-blind treatment phase). In addition, the time to relapse during the follow-up phase will be estimated by the Kaplan-Meier method separately for subjects who are remitters, and for subjects who are responders but not remitters. Descriptive statistics (number of relapses, number of censored subjects, and median, 25^{th,} and 75th percentile of time to relapse, if estimable) will be provided.

Pharmacokinetics Analyses

Plasma esketamine concentrations will be listed for all subjects. The plasma concentration-time data of esketamine will be analyzed using population PK modeling. Data may be combined with those of other selected studies to support a relevant structural model. Typical population values of basic PK parameters will be estimated together with the inter-individual variability. Additional pharmacokinetic parameters may be calculated if deemed appropriate. Effects of subject demographics, laboratory parameter values, and other covariates on the PK of esketamine will be explored. The results of the population PK analyses may be reported separately.

Biomarker and Pharmacogenomics Analyses[α]

Baseline biomarker values and changes from baseline biomarker values to the time points specified in the Time and Events Schedule will be summarized if available number is sufficient for analyses. Exploratory biomarker analyses may include comparison of biomarker measures between the treatment groups, correlation with efficacy and other measures, and relationship with clinical response, relapse and non-response.

The analysis plan and summarized results from both biomarker and pharmacogenomics analyses will be reported separately.

Safety Analyses

The primary population for safety analysis will consist of all randomized subjects who receive at least 1 dose of intranasal medication or 1 dose of oral antidepressant in the double-blind treatment phase. The safety data from the follow-up phase will be analyzed separately.

Adverse events (AEs) will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs with onset during the 4-week double-blind treatment phase (ie, TEAEs, and AEs that have worsened from baseline), will be included in the analysis. For each AE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. Subjects who die, or who discontinue treatment due to an adverse event or serious adverse events, will be summarized separately. AEs occurring during the follow-up phase will be summarized separately.

Body weight, vital signs, 12-lead ECG and clinical laboratory test results, and changes from baseline will be tabulated over time by treatment group, using descriptive statistics. Any treatment-emergent abnormalities will be presented.

Changes in findings from the baseline nasal examination will be listed by treatment group. A shift table for changes from double-blind baseline in ratings for each nasal examination will be presented by treatment group.

Descriptive statistics of the CADSS, and changes from baseline will be summarized at each scheduled time point.

Descriptive statistics of the PWC-20 scores and changes and/or percent changes from baseline will be summarized at each scheduled time point.

Suicide-related thoughts and behaviors based on the C-SSRS will be summarized by treatment group in incidence and shift tables.

[α] Not applicable to China

TIME AND EVENTS SCHEDULE (SCREENING/PROSPECTIVE OBSERVATIONAL PHASE AND DOUBLE-BLIND TREATMENT PHASE)

	Screening/ Prospective Observational Phase			Double-blind Treatment Phase										
Visit number	**1.1**	**1.2**	**1.3 [a]**	**2.1 [a]**	**2.2**	**2.3**	**2.4**	**2.5**	**2.6**	**2.7**	**2.8**	**2.9**	**2.10**	**EW [b]**
Week	Week 1	End of Week 2	End of Week 4	1			2		3		4			—
Study day	—	—	—	1 (baseline)	2	4	8	11	15	18	22	25	28	EW
Clinic visit window (in days)	—	±2	±2	—	—	±1	±1	±1	±1	±1	±1	±1	±1	—
Clinic visit (C) or remote MADRS interview only (RM)	C	C	C	C	RM	C	C	C	C	C	C	C	C	C
Screening/Administrative														
Informed consent (ICF)	X													
Medical history, psychiatric history, demographics, employment status	X													
MINI	X													
MGH-ATRQ	X													
C-VISA [r]	X													
Height	X													
Inclusion/exclusion criteria	X			X										
Prestudy therapy	X													
Preplanned surgery/procedures	X													
Study Drug														
Randomization				X										
Dispensing of new oral antidepressant (duloxetine, escitalopram, sertraline, or venlafaxine XR)				X									X[q]	X
Practice session for use of intranasal device				X										
Intranasal esketamine or placebo				X		X	X	X	X	X	X	X		
Drug accountability (intranasal study medication)				X		X	X	X	X	X	X	X		X
Drug accountability (oral antidepressant study medication)				X									X	X
Dispense subject diary for oral antidepressant				X										

	Screening/ Prospective Observational Phase			Double-blind Treatment Phase										
Visit number	**1.1**	**1.2**	**1.3 [a]**	**2.1 [a]**	**2.2**	**2.3**	**2.4**	**2.5**	**2.6**	**2.7**	**2.8**	**2.9**	**2.10**	**EW [b]**
Week	Week 1	End of Week 2	End of Week 4	1			2		3		4			—
Study day	—	—	—	1 (baseline)	2	4	8	11	15	18	22	25	28	EW
Clinic visit window (in days)	—	±2	±2	—	—	±1	±1	±1	±1	±1	±1	±1	±1	—
Clinic visit (C) or remote MADRS interview only (RM)	C	C	C	C	RM	C	C	C	C	C	C	C	C	C
Review subject diary and update (if applicable)						X	X	X	X	X	X	X	X	X
Oral antidepressant adherence check							X		X		X		X	X
Return of subject diary if not entering follow-up phase													X	
Safety Assessments (Clinician)														
Physical examination	X			X									X	X
Nasal examination [c]	X			X									X	X
Vital signs: blood pressure, pulse rate, respiratory rate, temperature [c,l]	X			X		X	X	X	X	X	X	X		X
Vital signs (postdose): blood pressure, pulse, respiratory rate [f,l]				X		X	X	X	X	X	X	X		
Weight	X			X									X	X
12-lead ECG [g,l]	X			X			X					X		X
C-SSRS: Baseline/Screening version	X													
C-SSRS: Since last visit version [l]		X	X	X [m]		X	X	X	X	X	X	X	X	X
Pulse oximetry [h,l]	X			X		X	X	X	X	X	X	X		
CADSS [i,l]				X		X	X		X		X	X		
PWC-20												X		X
Efficacy Assessments (Clinician)														
MADRS (7-day recall; performed by independent, remote raters)	X [e]	X [k]	X [k]	X [d]			X [k]		X [k]		X [k]		X [k]	X
MADRS (24-hr recall; performed by independent, remote raters)					X									
CGI-S [c]	X			X		X	X	X	X		X		X	X
Subject-completed Assessments														
PAQ	X	X	X											
SDS [c]	X			X					X				X	X

	Screening/ Prospective Observational Phase			Double-blind Treatment Phase										
Visit number	**1.1**	**1.2**	**1.3 [a]**	**2.1 [a]**	**2.2**	**2.3**	**2.4**	**2.5**	**2.6**	**2.7**	**2.8**	**2.9**	**2.10**	**EW [b]**
Week	Week 1	End of Week 2	End of Week 4	1			2		3		4			—
Study day	—	—	—	1 (baseline)	2	4	8	11	15	18	22	25	28	EW
Clinic visit window (in days)	—	±2	±2	—	—	±1	±1	±1	±1	±1	±1	±1	±1	—
Clinic visit (C) or remote MADRS interview only (RM)	C	C	C	C	RM	C	C	C	C	C	C	C	C	C
GAD-7 [c]	X			X									X	X
EQ-5D-5L [c]	X			X					X				X	X
Clinical Laboratory Assessments														
TSH, HbA1 [c]	X													
Hematology, Chemistry [c, n]	X			X									X	X
Urine drug screen [c]	X			X					X			X		
Alcohol breath test	X			X										
Urinalysis [c]	X			X					X				X	X
Serum pregnancy test	X													
Urine pregnancy test [c]				X					X				X	X
Pharmacokinetics														
Blood collection [j]												X		
[α] **Biomarker, Pharmacogenomic (DNA), and Expression (RNA) Evaluations [o]**														
Blood sample collection (protein) [c, n]	X			X			X					X		X [p]
Blood collection (DNA) [c, n]	X											X		X [p]
Blood sample collection (RNA) [c, n]	X			X			X					X		X [p]
Ongoing Subject Review														
Concomitant therapy	*Ongoing*													
Adverse events	*Ongoing*													

Footnotes:

Abbreviations: BMI, body mass index; C, clinic visit; CGI-S, Clinical Global Impression – Severity; CADSS, Clinician Administered Dissociative States Scale; C-SSRS, Columbia Suicide Severity Rating Scale; C-VISA, Clinical Validation Inventory for Study Admission; ECG, electrocardiogram; EQ-5D-5L, EuroQol-5 dimension- 5-level; EW, early withdrawal; GAD-7, Generalized Anxiety Disorder, 7-item scale; HbA1c test, glycated hemoglobin test; MADRS, Montgomery-Asberg Depression Rating Scale; MGH-ATRQ, Massachusetts General Hospital - Antidepressant Treatment History Questionnaire; MINI, Mini-International Neuropsychiatric

[α] Not applicable to China

Interview; PAQ, Patient Adherence Questionnaire; PWC-20, Physician Withdrawal Checklist, 20-item scale; SDS, Sheehan Disability Scale; TSH, thyroid-stimulating hormone
Note: On intranasal dosing days, time 0 is defined as the time of the first intranasal spray. Therefore, postdose time points are referenced from this time point.
Note: On intranasal dosing days, food will be restricted for at least 2 hours before each administration of study drug. Drinking of any fluids will be restricted for at least 30 minutes before the first nasal spray.

a) An additional, optional period of up to 3 weeks is permitted to taper and discontinue current antidepressant treatment(s) after completion of the Week 4 (Visit 1.3) assessments, per the local prescribing information or clinical judgment. Subjects who do not require a taper and are thus eligible to immediately proceed to the double-blind treatment phase can have Visit 1.3 and Visit 2.1 occur on the same day or within 1 week of each other (if not occurring the same day, the antidepressant treatment regimen should be continued and discontinued prior to Visit 2.1).
b) If a subject withdraws before the end of the double-blind treatment phase (ie, before completing Visit 2.10/Day 28) for reasons other than withdrawal of consent, an early withdrawal visit should be conducted within 1 week of the date of discontinuation, followed by the follow-up phase. If the early withdrawal visit is conducted on the same day as a scheduled visit, duplicate assessments are not required.
c) Predose (if/when performed on intranasal dosing days). Predose subject-reported outcome assessments should be administered before all other study-related procedures during a clinic visit.
d) Performed for subjects who require a taper period, or who do not require a taper period but their Visit 1.3 and Visit 2.1 occur more than 1 week apart; the result will be considered as the subject's baseline MADRS for the double-blind treatment phase. For all other subjects, the baseline MADRS for the double-blind treatment phase will be the MADRS performed at the end of Week-4 of the screening/prospective observational phase.
e) The MADRS interview should be performed in Week 1 (Visit 1.1 or as soon as possible) of the screening/prospective observational phase.
f) Postdose vital signs will be performed at 40 minutes, 1 hour, and 1.5 hours postdose. Please refer to Section 6.4 for guidance for blood pressure monitoring on intranasal dosing days.
g) Twelve-lead ECG will be performed predose and at t=1 hour postdose at Visit 2.1. Twelve-lead ECG will be performed at t=1 hour postdose only (ie, no predose ECG required) at Visits 2.4 and 2.9. A time window of ±15 minutes is permitted.
h) Pulse oximetry will be performed every 15 minutes from predose to t=1.5 hours postdose (please refer to Section 9.5 for further guidance on timing of pulse oximetry assessments).
i) The CADSS to be performed predose and at 40 minutes and 1.5 hours postdose.
j) Only for Chinese subjects. PK blood collection will be performed at predose, t=40 minutes (30min~50min), t=2 hours (1.5hr ~ 2.5hr) and t=6hr (5.5hr ~ 6.5hr) postdose (where time=0 is defined as the time of the first intranasal spray).
k) The MADRS should be administered no more than 2 days prior to the subject's targeted (not actual) clinic visit date (except Visit 2.10, which is within 1 day prior). If performed on the day of the scheduled clinic visit for an intranasal treatment session, the MADRS must be performed prior to the intranasal treatment session.
l) If intranasal dosing is postponed (but occurs within visit window) due to vital sign results (eg, blood pressure elevation), all assessment time points (including predose) must be performed on the actual intranasal dosing day.
m) The C-SSRS to be performed only if Visit 1.3 and Visit 2.1 do not occur on the same day.
n) Blood samples should be collected prior to dosing. It is preferred that subjects adhere to a low fat diet on the day of sample collection.
o) Only for subjects who give written consent to participate in the biomarker, pharmacogenomic (DNA), and expression (RNA) component of the study.
p) If a subject withdraws after Visit 2.9 of the double-blind treatment phase, the blood collection doesn't need to be repeated at the EW Visit.
q) For subjects entering the Follow-up phase and continuing with the same oral AD.
r) C-VISA can be completed prior to randomization.

TIME AND EVENTS SCHEDULE (Follow-up Phase)

	Follow-up Phase [a]							
Visit number	**3.1**	**3.2**	**3.3**	**3.4**	**3.5**	**3.6**	**3.7**	**3.8** [g]
Weeks after last intranasal dose	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Visit window for clinic visit or remote assessments only (days)	±3	±3	±3	±3	±3	±3	±3	±3
Clinic visit (C) or remote assessments only (RA)	C	C	RA [b]	RA [b]	C	RA [b]	RA [b]	C
Dispensing of oral antidepressant (duloxetine, escitalopram, sertraline, or venlafaxine XR)					X [h]			
Drug accountability								
Drug accountability (oral antidepressant study medication)								X
Return of subject diary								X
Safety Assessments (Clinician-completed)								
Physical examination								X
Vital signs: Blood pressure, pulse, respiratory rate, temperature		X			X			X
Weight								X
C-SSRS: Since last visit version	X [c,d]	X	X	X	X	X	X	X
PWC-20	X [d]	X						
Efficacy Assessments (Clinician-completed)								
MADRS (performed by independent, remote raters)	X [c,d]	X	X	X	X	X	X	X
CGI-S		X			X			X
Efficacy Assessments (Subject-completed)								
SDS		X			X			X
GAD-7		X			X			X
EQ-5D-5L		X			X			X
Clinical Laboratory Assessments								
Hematology, chemistry		X						
Urinalysis		X						
Serum pregnancy test		X						
Urine pregnancy test					X			X
Biomarker and Expression (RNA) Evaluations [e]								
Blood sample collection (protein) [f]		X						
Blood sample collection (RNA) [f]		X						
Ongoing Subject Review								
Concomitant therapy	*Ongoing*							
Adverse events	*Ongoing*							

Footnotes:

Note: No intranasal study medication will be administered during the Follow-up Phase

a) The follow-up phase will begin on Day 28, after completion of all study procedures for the double-blind phase. No intranasal study medication will be administered during the follow-up phase. Clinical visits or telephone contacts will be every week for up to 8 weeks or until relapse.
b) At each "Remote Assessment" visit, site staff will contact the subject by telephone to perform the C-SSRS and to obtain information regarding adverse events and concomitant therapies.
c) Performed only if Visit 2.10 and Visit 3.1 do not occur on the same day.
d) For subjects who withdraw before the end of the double-blind treatment phase, performed only if the EW Visit and Visit 3.1 do not occur on the same day.
e) Only for subjects who give written consent to participate in the biomarker, pharmacogenomic (DNA), and expression (RNA) component of the study.
f) It is preferred that subjects adhere to a low-fat diet on the day of sample collection.
g) For subjects who complete the 8-week Follow-up Phase or meet criteria for relapse or withdraw before the end of the Follow-up Phase for reasons other than withdrawal of consent.
h) For subjects continuing the same oral antidepressant.

ABBREVIATIONS

AE	Adverse Event
AHI	apnea-hypopnea index
ANCOVA	analysis of covariance
AUC	area under the plasma concentration-time curve
BDNF	brain-derived neurotrophic factor
BMI	body mass index
C	clinic visit
CADSS	Clinician Administered Dissociative States Scale
CGI-S	Clinical Global Impression – Severity
C_{max}	maximum plasma concentration
CRF	case report form
C-SSRS	Columbia Suicide Severity Rating Scale
C-VISA	Clinical-Validation Inventory for Study Admission
CYP	cytochrome P450, with any appended letters (2B6, 3A4, etc) indicating subtypes
DBP	diastolic blood pressure
DBS	deep brain stimulation
DNA	deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)
ECG	electrocardiogram
eCRF	electronic case report form
ECT	electroconvulsive therapy
eDC	Electronic Data Capture
EQ-5D-5L	European Quality of Life (EuroQol-5) dimension-5 level
EQ-VAS	EuroQol group: Visual Analogue Scale
EU	European Union
EW	Early Withdrawal
FDA	United States Food and Drug Administration
FT4	free thyroxine
GAD-7	Generalized Anxiety Disorder 7-item scale
GCP	Good Clinical Practice
HbA1c test	glycated hemoglobin test
HPA	hypothalamus pituitary adrenal
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IM	intramuscular
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
IWRS	interactive web response system
LOCF	last observation carried forward
MADRS	Montgomery-Asberg Depression Rating Scale
MAOI	monoamine oxidase inhibitor
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MGH-ATRQ	Massachusetts General Hospital - Antidepressant Treatment Response Questionnaire
MINI	Mini-International Neuropsychiatric Interview (mental status questionnaire)
MMRM	mixed-effects model for repeated measures
NMDA	N-Methyl-D-Aspartate
PAQ	Patient Adherence Questionnaire
PCP	phencyclidine
PD	pharmacodynamics
PK	pharmacokinetics
PQC	product quality complaint
PWC-20	Physician Withdrawal Checklist; 20-item
QTc	QT interval corrected

QTcB	QT interval corrected according to Bazett's formula
QTcF	QT interval corrected according to Fridericia's formula
RM	remote assessments only
RNA	ribonucleic acid
SAEs	serious adverse events
SAP	statistical analysis plan
SDS	Sheehan Disability Scale
SmPC	Summary of Product Characteristics
SMQ	standardized MedDRA queries
SNRI	Serotonin and Norepinephrine Reuptake Inhibitors
SSRI	Selective Serotonin Reuptake Inhibitors
SUSARs	suspected unexpected serious adverse reactions
SBP	systolic blood pressure
TEAEs	treatment-emergent adverse events
TRD	treatment-resistant depression
TSH	thyroid-stimulating hormone
US	United States
US FDA	United States Food and Drug Administration
VNS	vagal nerve stimulation
XR	extended release

1. INTRODUCTION

Major depressive disorder (MDD), a serious, recurrent, and disabling psychiatric illness, is the second leading cause of years lost to disability worldwide. MDD is associated with excess mortality, and with years of potential life lost. About 30% of patients fail to achieve remission despite treatment with multiple antidepressant medications and are considered to have treatment-resistant depression (TRD). There is a significant need to develop novel treatments based upon relevant pathophysiologic pathways underlying MDD for the rapid relief of symptoms of depression, especially in patients with TRD.

Esketamine is an *N*-methyl-D-aspartate (NMDA) receptor antagonist. It is the S-enantiomer of racemic ketamine and has been shown to have approximately 3- to 4-fold stronger binding affinity for the phencyclidine (PCP) site of the N-methyl-D-aspartate (NMDA) receptor than the R-enantiomer. The mechanism of action of ketamine and esketamine is distinct from conventional monoaminergic antidepressant treatments and ketamine profoundly affects fast excitatory glutamate transmission, increases brain-derived neurotrophic factor (BDNF) release, and stimulates synaptogenesis.

Janssen Research & Development (JRD) is developing intranasal esketamine as an antidepressant therapy. A higher NMDA receptor affinity of esketamine allows a lower volume of medication to be administered via the non-invasive, rapidly absorbed intranasal route.

The current study is being conducted to evaluate the efficacy, safety, and tolerability of flexibly dosed intranasal esketamine plus a newly initiated oral antidepressant in adult subjects with TRD. The study will serve as a Phase 3 short-term efficacy and safety study in support of Chinese regulatory agency requirements for registration of intranasal esketamine for the treatment of TRD.

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 following text is quoted from the United States (US) prescribing information for anesthetic Ketalar® (ketamine hydrochloride injection)[37] is provided below: Intravenous Ketalar® produces a fall in arterial blood pressure in the Rhesus monkey and a rise in arterial blood pressure in the dog. In this respect the dog mimics the cardiovascular effect observed in man. The pressor response to Ketalar® injected into intact, anaesthetized dogs is accompanied by a tachycardia, rise in cardiac output and a fall in total peripheral resistance. The pressor response to Ketalar® is reduced or blocked by chlorpromazine (central depressant and peripheral α-adrenergic blockade), by β-adrenergic blockade, and by ganglionic blockade.

Findings from animal studies suggest that the increase in blood pressure produced by ketamine/esketamine is due to selective activation of central cardiac stimulating mechanisms leading to an increase in cardiac output.

In a 3-month repeat-dose toxicity study with intranasally administered esketamine in dogs, no relevant electrocardiogram (ECG) changes were noted up to the highest dose tested, ie, 72 mg/day. Heart rate was slightly increased. The cardiovascular safety of racemic ketamine and esketamine in humans and animals is summarized in the Investigator's Brochure.[34]

Toxicology

Repeat-Dose Toxicity Studies

In repeat-dose toxicity studies with intranasally administered esketamine in rats up to 9 mg/day for 6 months, and dogs up to 72 mg/day for 3 months of duration, the clinical observations mainly related to the central nervous system (eg, changes in activity and gait). No adverse effects were noted up to the highest dose tested, ie, 9 mg/day in rats and 72 mg/day in dogs. These observations reflected the (exaggerated) pharmacology of the test compound. Minor histologic findings were noted in the nasal cavity. These tissue changes were not considered adverse.

In 3- and 9-month repeat-dose toxicity studies with intranasally administered esketamine in dogs, no relevant electrocardiogram (ECG) changes were noted up 72 mg/day. Heart rate was slightly increased.

Further details can be found in the Investigator's Brochure.[34]

Genetic Toxicity

A series of in vitro and in vivo genotoxicity studies was conducted with ketamine and esketamine. The weight of evidence indicates that esketamine poses no genotoxic risk to humans.[34]

Neurotoxicity

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

In studies exploring neurotoxic effects of ketamine on juvenile and prenatal monkeys, neuroapoptosis was observed to be more widespread in fetal brains than in neonatal brains, after administration of ketamine anesthesia IV for 5 hours. In fetal brains, the cerebellum, caudate nucleus, putamen, and nucleus accumbens were most severely affected. In neonatal brains, the cerebellum was not affected; the strongest neuroapoptotic response was noted in the basal ganglia and several thalamic areas.

In juvenile rodents, ketamine induced apoptotic neurodegeneration was observed that was more widespread than in adult rodents, with the developing brain affected in several major regions. Neuronal cell death was induced in the dorsolateral thalamus at blood levels of ketamine of 14 µg/mL (7 times the human anesthetic blood level of approximately 2 µg/mL).

No significant neurotoxic effects occurred in juvenile Rhesus monkeys if the anesthesia was administered by IM induction followed by IV maintenance for a duration of 3 hours. Ketamine infusion for 9 or 24 hours increased neuronal cell death in the frontal cortex, but no significant changes were noted in the hippocampus, thalamus, striatum, or amygdala. Cognitive impairments were observed beginning around 10 months of age, and persisted at 3.5 years of age.

The clinical studies will exclude neonates, infants, children, pregnant women, and breastfeeding women. Therefore, ketamine's neurotoxicity in juvenile animals does not represent a safety risk to eligible adult subjects. Moreover, the large dosages and prolonged treatment durations associated with neurotoxicity in juvenile animals do not suggest a concern.

Chronic treatment with ketamine at high dose levels affected the brain of adolescent monkeys, as evidenced by histopathologic lesions and functional impairment.

The neurotoxicity of ketamine in adult animals is also associated with high dose levels, in contrast to the relatively low dose levels of esketamine associated with antidepressant efficacy in humans. In single-dose and 14-day repeated-neurotoxicity studies with intranasally administered esketamine in rats, no histopathologic brain lesions were noted even upon high exposures, as achieved at 54 mg/day in the 14-day study. In the 6-month rat and 9-month dog repeat-dose toxicology studies with intranasally administered esketamine, where the animals were of adolescent age at initiation of treatment, and in the pre- and post-natal developmental toxicity study in rats, no evidence of neurotoxicity was found. Consequently, the risk of neurotoxicity associated with intranasal administration of esketamine to adult and adolescent patients is considered low.[34]

Abuse Potential

Animal studies with ketamine suggest that it would have abuse potential in humans. These studies included self-administration and withdrawal experiments in several species.[34]

Reproductive Toxicity

In a rat fertility and early embryonic developmental toxicity study with intranasally administered esketamine, no adverse effects on fertility or reproductive capacity or performance were found.

Rat and rabbit embryo-fetal developmental toxicity studies with intranasally administered racemic ketamine did not reveal evidence of reproductive toxicity. However, when monkey fetuses were exposed in utero to high dose levels of racemic ketamine, neurotoxicity was observed.

Intranasally administered esketamine did not affect pre- and postnatal development in rats. However, high dose levels of racemic ketamine induced neurotoxicity in early postnatal rat pups.[34]

Considering the neurotoxic potential of ketamine and esketamine, and the fact that no threshold for these effects has been demonstrated, female subjects of childbearing potential should be adequately protected from becoming pregnant and pregnant women should not be enrolled.

Cardiovascular toxicity

In guinea pig tissues, ketamine-induced negative inotropic effects and shortening of action potential duration at the 0-mV level was observed, likely as a result of the suppression of inward calcium current, whereas in rat left atria ketamine-induced positive inotropic effects and prolongation of action potential duration at the 0-mV level was observed, likely as a result of a decrease in calcium-insensitive transient outward current.[20] The inhibitory action on membrane currents may partly explain the species and tissue differences in inotropic responses to ketamine.

Blood pressure responses to ketamine also vary with the laboratory species and with experimental conditions. Blood pressure is increased in normotensive and renal hypertensive rats with and without adrenalectomy and under pentobarbital anesthesia. The US prescribing information for the anesthetic Ketalar® (ketamine hydrochloride [HCl] for injection) provides the following guidance.

Intravenous Ketalar® produces a fall in arterial blood pressure in the Rhesus monkey and a rise in arterial blood pressure in the dog. In this respect the dog mimics the cardiovascular effect observed in man. The pressor response to Ketalar® injected into intact, unanesthetized dogs is accompanied by a tachycardia, rise in cardiac output and a fall in total peripheral resistance. It causes a fall in perfusion pressure following a large dose. The tachycardia and increase in myocardial contractile force seen in intact animals does not appear in isolated hearts. These observations support the hypothesis that the hypertension produced by Ketalar® is due to selective activation of central cardiac stimulating mechanisms leading to an increase in cardiac output.

The dog would be considered the most predictive species in terms of ketamine's cardiovascular effects in humans, but the antidepressant effects of ketamine were studied only in rodent models. The myocardial contractility effects and blood pressure responses to ketamine vary between species.[34] Consequently, a margin of safety could not be reliably derived from the available animal data.

Overall Conclusion

The currently available nonclinical safety studies support chronic intranasal administration of esketamine in human subjects up to a dosage of 84 mg/day.

Further details can be found in the Investigator's Brochure.[34]

1.1.2. Clinical Studies

The clinical program for esketamine includes: a comprehensive clinical pharmacology program in healthy volunteers and special populations to fully characterize the product's pharmacokinetic (PK) and pharmacodynamic (PD) activity, including Phase 2 studies with IV esketamine and ketamine; a Phase 2 dose response study in adults with TRD; a Phase 2 proof-of-concept study in the related condition of MDD with imminent risk for suicide; and data from 5 completed Phase 3

studies establishing efficacy and safety in adults with TRD, including those 65 years and older. Results from 1 ongoing Phase 2 study and 2 ongoing Phase 3 studies in adults with TRD are not available at the time of finalization.

1.1.2.1. Pharmacokinetics

The following Human Pharmacokinetic (PK) and initial tolerability Phase 1 studies were conducted by the sponsor in healthy adult subjects. Further details are available in the Investigator Brochure[34]:

- Intravenous and oral dose of radiolabeled esketamine: 54135419TRD1016.
- Intravenous, intranasal and oral esketamine: ESKETINTRD1009
- Intranasal esketamine:
  - Healthy adult non-Asian and Asian subjects: ESKETINTRD1001, ESKETINTRD1002, ESKETINTRD1004, ESKETINTRD1005, ESKETINTRD1006, ESKETINTRD1009, ESKETINTRD1010, ESKETINTRD1013, 54135419TRD1020 (Japanese subjects only).
  - Healthy elderly and younger adult non-Asian and Asian subjects: ESKETINTRD1003, ESKETINTRD1012, and 54135419TRD1018 (Japanese subjects only).
  - Subjects with a history of allergic rhinitis: ESKETINTRD1007.
  - Recreational users of perception-altering drugs: 54135419TRD1015
  - Subjects with hepatic impairment: ESKETINTRD1011
  - Subjects with renal impairment: 54135419TRD1014
  - Subjects with MDD; On-Road Driving effects: 54135419TRD1019.

Human Pharmacokinetics Metabolism

Ketamine (and esketamine) undergoes extensive metabolism by hepatic cytochrome P450 (CYP). In humans, N-demethylation to norketamine is the major route of metabolism, which can undergo further metabolism to form hydroxynorketamine. Ketamine and norketamine are extensively hydroxylated to a series of 6 hydroxynorketamine metabolites and 2 hydroxyketamine metabolites.[75] Like ketamine, norketamine is a noncompetitive antagonist at the NMDA receptor.[19] Norketamine has a half-life in plasma of approximately 5 hours.[38] The major human hepatic CYPs that catalyze ketamine and esketamine N-demethylation in vitro are CYP2B6 and CYP3A4.[29,31,78] The CYP enzymes responsible for the formation of norketamine metabolites include CYP2A6 and CYP2B6.[53] Published results of a clinical pharmacokinetics (PK) study indicate that esketamine does not invert to the R-enantiomer.[26]

Excretion

Racemic ketamine and its metabolites have been previously shown to be predominantly excreted in the urine. An average of 91% and 3% of a tritium-labeled dose (1 mg/kg) administered to 6 healthy subjects was recovered in urine and feces, respectively.[4] Less than 3% of an administered dose was excreted in urine as parent drug.[75]

Following oral administration of radiolabeled esketamine, approximately 86% and 2% of administered radioactivity was recovered in urine and feces, respectively. The recovered radioactivity consisted primarily of esketamine metabolites. For the IV and oral routes of administration, <1% of the dose was excreted in the urine as unchanged drug.

A summary of the PK of esketamine administered by the IV and intranasal routes is provided below.

Intravenous Esketamine

Subjects with TRD received 0.2 mg/kg or 0.4 mg/kg esketamine as a 40-minute IV infusion during Study ESKETIVTRD2001.[9] Maximum concentrations of esketamine were observed at the end of the infusion. Mean values for maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC) increased with an increase in the esketamine dose administered (80.9 and 135 ng/mL, respectively, and 150 and 218 ng*h/mL, respectively, for 0.2 mg/kg and 0.4 mg/kg esketamine). The mean plasma clearance of esketamine was high (109 L/h and 141 L/h for the 0.2 mg/kg and 0.4 mg/kg doses, respectively), as it was similar to or exceeded hepatic blood flow in humans.[8] The large volume of distribution suggests that esketamine distributes widely into tissues (236 L and 303 L, respectively). The half-life of esketamine in plasma was 2.14 and 2.65 hours, respectively, for the 2 doses.

Intranasal Esketamine

Plasma esketamine PK results from Studies ESKETINTRD1001, ESKETINTRD1002, ESKETINTRD1003, and the double-blind phase of Panel A of the ESKETINTRD2003 that inform dose selection for the Phase 3 program are described below.[5,6,7,10] The results demonstrate that plasma esketamine concentrations produced by effective IV regimens (0.2 mg/kg and 0.4 mg/kg as 40 minute infusions) may be achieved by the intranasal route.

Study ESKETINTRD1001 included 3 cohorts of subjects who were healthy male and female subjects.[5] The intranasal esketamine treatments were self-administered under the direct supervision of the investigator or designee. Subjects in Cohorts 1 and 3 received esketamine doses that ranged from 28 to 112 mg. The regimens were self-administered in the upright position. No instructions were given with regards to sniffing after administration. The reported median time for C_{max} values of esketamine ranged from 0.37 to 0.83 hours from the time the first spray was administered (ie, 0.33 to 0.5 hours after the last spray was administered). The doses of 28 to 112 mg produced mean C_{max} values ranging from 63.3 to 151 ng/mL, whereas mean area under the plasma concentration-time curve from time 0 to infinite time (AUC_{∞}) values ranged from 164 to 565 ng*h/mL. Mean C_{max} and AUC values of esketamine increased in a less than dose-proportional manner across the dose regimens. Furthermore, there was substantial overlap in the range of individual C_{max} and AUC values among the 3 doses. The mean terminal half-life of esketamine ranged from 5.86 to 9.83 hours across all treatments. Subjects in Cohort 2 received 84 mg in a semi-reclined position and were instructed to sniff after each spray. Higher mean C_{max} and AUC_{∞} values were observed in this cohort (174 ng/mL and 437 ng*h/mL, respectively) compared with the same esketamine dose self-administered by subjects in Cohort 1 (107 ng/mL and 400 ng*h/mL, respectively). The semi-reclined position of the head and the instruction to subjects to sniff gently

following intranasal dosing are believed to be the cause for the increase in exposure observed in Cohort 2 compared with Cohort 1. As a result, the instructions for self-administration of intranasal esketamine were adapted to include the semi-reclined position of the head and sniffing following dosing for all future studies.

During the Phase 1 study ESKETINTRD1002, healthy Japanese and Caucasian subjects received single intranasal doses of esketamine 28 mg, 56 mg, and 84 mg in a crossover manner.[6] On average, plasma esketamine C_{max} and AUC values were up to 48% higher in Japanese subjects compared with Caucasian subjects. In study ESKETINTRD1008, healthy Japanese, Chinese, Korean, and Caucasian subjects received a single intranasal dose of 56 mg esketamine. The mean esketamine C_{max} and AUC values were approximately 40% higher in Japanese subjects compared to Caucasian subjects. In general, smaller differences in esketamine and noresketamine exposure were observed when comparing other Asian subjects (Hans Chinese and Korean) to Caucasian subjects. Mean esketamine C_{max} and AUC_{∞} values were 14% and 33% higher, respectively, in Han Chinese subjects compared to Caucasian subjects. The incidence and type of treatment-emergent adverse events most frequently reported, as defined by system-organ-class, were comparable for subjects in all 4 population cohorts. Study ESKETINTRD1003 compared the PK, safety, and tolerability of intranasally administered esketamine in healthy elderly (≥65 years of age) and younger adult subjects (18 to 55 years of age, inclusive).[7] Subjects received a single intranasal treatment of esketamine 28 mg. The T_{max} of esketamine was approximately 30 minutes for both age groups. The geometric means of C_{max} and AUC_{∞}, for esketamine were approximately 21% and 17% higher, respectively, in the elderly compared with younger adult subjects.

Study ESKETINTRD2003, is a recently completed 2-panel, doubly randomized, double-blind, placebo-controlled, multicenter study.[55] Panel A was conducted in the United States and Belgium and Panel B in Japan. Panel A assessed the efficacy and safety of 3 dose strengths of intranasal esketamine (28, 56, and 84 mg) administered twice a week in subjects with TRD. Panel B was designed to assess the efficacy and safety of 14 mg and 56 mg dose strengths. Results of a preliminary analysis of data from the double-blind phase of Panel A indicate mean (standard deviation) esketamine concentrations at 40 minutes postdose were 36.4 ng/mL (16.4), 58.1 ng/mL (24.5), and 72.5 ng/mL (34.2), respectively, for the 3 doses (data on file). The mean esketamine concentrations in plasma samples collected on Days 1 and 11 were similar, suggesting that the PK are consistent after repeated administration.[10]

1.1.2.2. Efficacy and Safety Studies

The following Efficacy and Safety Phase 2a and Phase 3 studies were conducted by the sponsor in subjects with TRD or MDD who are at imminent risk for suicidal ideation.

- Phase 2a: Intravenous ketamine or esketamine administered to subjects with TRD: KETIVTRD2002, KETIVTRD2004 and ESKETIVTRD2001, respectively.
- Phase 2a: Intranasal esketamine administered to subjects with TRD: ESKETINTRD2003; Intranasal esketamine administered to subjects with MDD who are at imminent risk for suicidal ideation: ESKETINSUI2001.

- Phase 3: Intranasal esketamine administered to subjects with TRD:
  - Short-term studies: ESKETINTRD3001, ESKETINTRD3002, and ESKETINTRD3005
  - Long-term studies: ESKETINTRD3003 and ESKETINTRD3004

For the most comprehensive information regarding these clinical studies, refer to the latest version of the Investigator Brochure.[34]

Pharmacodynamics and Efficacy

The efficacy of subanesthetic doses (0.5 mg/kg IV administered over 40 minutes) of IV ketamine has been evaluated in approximately 192 subjects with MDD (cases and controls), and 2 studies in bipolar depressed subjects (meta-analyses).[25] This recent meta-analysis of studies suggests that IV administered ketamine has a rapid onset (within 1 day) of antidepressant efficacy, including in those who have not benefitted from other antidepressant treatments, used as monotherapy or in combination with oral antidepressant treatments.

Esketamine (0.2 and 0.4 mg/kg administered over 40 minutes) has similar, rapid, and robust antidepressant effects as that seen with IV ketamine. A double-blind, double-randomization, placebo-controlled study (ESKETIVTRD2001) enrolled 30 adult subjects with TRD: 10 in the IV placebo group, 9 in the IV esketamine 0.20 mg/kg group, and 11 in the IV esketamine 0.40-mg/kg group (based on Day 1 randomization).[9] The intent-to-treat (ITT) analysis of the primary efficacy variable (change in Montgomery-Asberg Depression Rating Scale [MADRS] total score from baseline [Day 1] to Day 2) indicated that the improvement in both IV esketamine dose groups were statistically significant (1-sided p-value=0.001 in both dose groups) compared with the placebo group. The mean (standard deviation) change from baseline [Day 1] to Day 2 in MADRS total score was -4.9 (4.72) in the placebo group, -16.8 (10.12) in the IV esketamine 0.20 mg/kg group, and -17.8 (9.45) in the IV esketamine 0.40 mg/kg group.

The studies listed above assessed the efficacy of IV ketamine or IV esketamine after a single dose as the primary endpoint. The average duration of response to a single dose of ketamine (0.5 mg/kg) was approximately 5 days. An open-label study demonstrated that the response to the first dose could be maintained by multiple infusions 3 times a week over 2 weeks. The duration of response lasted for approximately 19 days.[1]

The KETIVTRD2002 study assessed whether multiple doses of IV ketamine given twice a week would also maintain the antidepressant response; the data from this study suggest that IV ketamine (0.50 mg/kg over 40 minutes) administered twice a week was sufficient for maintaining the initial effect over a 4 week treatment period.[11]

As noted above, Study ESKETINTRD2003 is a 2-panel, doubly randomized, double-blind, placebo-controlled, multicenter study.[10] Panel A was conducted in the United States and Belgium and Panel B in Japan. Panel A assessed the efficacy and safety of 3 dose strengths of intranasal esketamine (28, 56, and 84 mg) administered twice a week in subjects with TRD. Panel B was designed to assess the efficacy and safety of 14 mg and 56 mg dose strengths. In Panel A, subjects in period 1 (1-week duration) were randomly assigned in a 3:1:1:1 ratio to placebo (33 subjects),

esketamine 28 mg (11 subjects), esketamine 56 mg (11 subjects), or esketamine 84 mg (12 subjects). Data from the double-blind phase of Panel A indicates that of the 67 subjects randomized in Period 1, 63 entered Period 2 (1-week duration), in which 28 placebo subjects who were eligible for re-randomization at the end of Period 1, were randomly assigned in a 1:1:1:1 ratio to placebo (N=6), esketamine 28 mg (N=8), esketamine 56 mg (N=9), or esketamine 84 mg (N=5). Subjects eligible for re-randomization had to have a Quick Inventory of Depressive Symptomatology – Self Report (QIDS-SR_{16}) total score >11 at the end of Period 1.

The improvement (with respect to change in MADRS total score from baseline Day 1 to Day 8) in all 3 intranasal esketamine dose groups reached statistical significance (p=0.021, p=0.001, and p<0.001 for esketamine 28 mg, 56 mg, and 84 mg, respectively) compared with placebo. The results of the 2 periods were consistent. The mean differences from placebo on Day 8 (after 1 week of treatment), estimated using data from the combined periods, were:

- Esketamine 28 mg: -4.2 (SE 2.09)
- Esketamine 56 mg: -6.3 (SE 2.07)
- Esketamine 84 mg: -9.0 (SE 2.13)

The effect sizes in Period 1 for esketamine compared with placebo were:

- Esketamine 28 mg: 0.43 (CI -0.259-1.118)
- Esketamine 56 mg: 0.92 (CI 0.201-1.621)
- Esketamine 84 mg: 1.19 (CI 0.473-1.883)

The duration of effect with the 28-mg dose appears to be shorter, with the MADRS total score higher on Day 8 than on Day 2. The duration of effect for the 56- and 84-mg doses appears to support twice-a-week dosing.

In Panel B, a significant improvement in symptoms of depression as measured by the MADRS total score was detected in the esketamine 56 mg treatment group compared with the placebo group (-3.7 [SE 2.81]; p=0.096) during Period 1. Smaller improvements in MADRS total score were detected in the esketamine 14 mg group compared with the placebo group (+1.8 [SE 2.62]) during Period 1.

These data with intranasal esketamine support the hypotheses that intranasal esketamine is effective as a treatment for depression, that it has rapid onset of effect within 2 hours, and that multiple repeated sessions dose-dependently show sustained response throughout the study duration. A clear dose response was seen in the double-blind data in Panel A, and the point estimates and confidence intervals suggest a high effect size (Cohen's D) with the 56 mg and 84 mg dose groups, supporting further development.

Safety and Tolerability

Ketamine is a rapidly acting general anesthetic that is approved and widely used intravenously or intramuscularly for the induction and maintenance of anesthesia in children and adults at a dose of 1 to 3 mg/kg given as a bolus. Ketamine is marketed as a racemic mixture and in Europe also as the S-enantiomer, esketamine. Ketamine was first introduced as an anesthetic in 1963 and is considered to have an excellent medical safety profile (Ketalar® Summary of Product Characteristics [SmPC] 2011; Ketanest®S SmPC 2011).[28,36]

Within the US prescribing information for ketamine HCl for injection and the SmPC for esketamine HCl for injection, the following adverse reactions were listed as very common, common, or frequent occurrences: Emergence or recovery reactions, elevated blood pressure and pulse rate, stimulation of respiration, nausea, and vomiting. See the table below for details.

Adverse reactions Listed as very Common, Common, or Frequent Occurrences in the Product Information of Anesthetic Ketamine and Esketamine

System Organ Class	"Frequent" Adverse Reactions Per Anesthetic Ketamine USPI[37a]	"Very Common" or "Common" Reactions Per Anesthetic Esketamine SmPC[73b]
Psychiatric disorders	Frequency: Emergence reactions occurred in approximately 12% of patients. Characteristics: Severity varied from pleasant dreamlike states, vivid imagery, hallucinations, and emergence delirium. Some states were accompanied by confusion, excitement, and irrational behavior, which some patients recalled as an unpleasant experience.	Frequency: Recovery reactions were common. When esketamine was the sole anesthetic, up to 30% of patients displayed dose-dependent recovery reactions. Characteristics: Reactions included vivid dreams (including nightmares), nausea and vomiting, increased salivation, blurred vision, dizziness, and motor restlessness [c]
Cardiac disorders	Blood pressure and pulse rate were frequently elevated after administration. However, hypotension and bradycardia have been observed. Arrhythmia has also occurred.	Common occurrences were temporary tachycardia and increase in blood pressure and heart rate (approximately 20% of the initial value was typical).
Respiratory, thoracic, and mediastinal disorders	Although stimulation of respiration was a frequently observed effect, severe depression of respiration or apnea also could occur after rapid intravenous administration of high doses.	Common effects were increase in vascular resistance in pulmonary circulation and increase in mucus secretion. Increased oxygen consumption, laryngospasms, and temporary respiratory depression were common; the risk of respiratory depression was noted to depend on dose and injection speed.
Gastro-intestinal disorders	No gastrointestinal effects were listed as frequent, but the USPI stated that anorexia, nausea, and vomiting have been observed.	Common effects included nausea and vomiting.

Abbreviations: SmPC, Summary of Product Characteristics; USPI, United States Prescribing Information

a. "Frequent" was not defined numerically, except in the case of emergence reactions (12%). The terms "very common" and "common" did not appear in the adverse effects section of the USPI.

b. "Very common" was defined in the SmPC as ≥1/10 and "common" was defined as ≥1/100 to <1/10.

c. The incidence of these events can be greatly reduced by the administration of a benzodiazepine.

Source: Investigator's Brochure for esketamine (JNJ-54135419).[34]

Adverse Events Associated with Short-term Use of Intranasal Esketamine in Patients with MDD

Esketamine has not yet been approved by the FDA for intranasal delivery. Within the SmPC for intravenous esketamine,[38] the following are reported as common adverse effects: transient tachycardia, vivid dreams (including nightmares), nausea and vomiting, increased blood pressure, increased salivation, blurred vision, dizziness, motor unrest, increase in vascular resistance in pulmonary circulation and increase in mucus secretion, increased oxygen consumption, laryngospasms, and temporary respiratory depression. It is reported that the risk of respiratory depression typically depends on the dosage and injection speed.[36]

Administration of intranasal esketamine is associated with adverse events, all of which are transient in nature and typically resolve within 2 hours or less from the start of drug administration. In Panel A of the Phase 2 study with intranasal esketamine (ESKETINTRD2003), the most common TEAEs (>10% of subjects in the pooled esketamine treatment groups) during the double-blind phase were: Dizziness, headache, dissociation, dysgeusia (metallic taste), nausea, dissociative disorder, and oral hypoesthesia.[10] Dissociative symptoms were the most typical of these adverse events observed post dose and were characterized by feeling unreal or detached from reality or by perceptual changes. Transient perceptual changes (dissociation), dizziness, and nausea were typically seen immediately after drug administration, resolving by 2 hours.

No deaths were reported in the double-blind or open-label phases of ESKETINTRD2003. There was one death (placebo/esketamine 14 mg/OL esketamine treatment group) due to completed suicide in Panel B on Study Day 45 during the follow-up phase of the study, 20 days after the subject received the last dose of study medication. The investigator considered the event to be 'not related' to study medication. A total of 3 subjects experienced at least one serious adverse event (SAE) during the study. In Panel A, one subject (placebo/placebo treatment group) experienced a SAE of esophagitis on Study Day 15 during the double-blind phase that was considered by the investigator to be 'not related' to study medication; one subject (esketamine 56 mg/esketamine 56 mg/OL esketamine treatment group), experienced a SAE of ectopic pregnancy on Study Day 40 during the open-label phase, which led to withdrawal of study medication. The subject subsequently experienced another SAE of general physical health deterioration on study Day 44 of the follow-up phase after cessation of study medication. The investigator considered that both events were 'not related' to study medication. In Panel B, one subject experienced a SAE of confusional state during the follow-up phase, 10 days after receiving the last dose of study medication. The sponsor considered the event 'not related' to study medication based on the short half-life of esketamine and the time of onset of the TEAE. A total of 4 subjects in Panel A experienced TEAEs which led to withdrawal of study medication. Three subjects withdrew during the double-blind phase because of TEAEs. One subject in the esketamine 28 mg group experienced a TEAE of syncope of severe intensity on Study Day 2 (Period 1), 1 day after receiving the first dose of study medication. The investigator considered the event to be 'possibly related' to study medication; the sponsor considered the event 'not related' to study medication based on the short half-life of esketamine and the onset of the TEAE of syncope. One subject in the placebo/esketamine 56 mg group experienced a TEAE of headache of moderate intensity on Day 11 (Period 2). The investigator considered the event to be 'very likely' related to

the study agent. One subject in the esketamine group (84 mg/esketamine 84 mg) experienced a TEAE of dissociative disorder of moderate intensity on Study Day 8 (Period 2). The investigator considered the event to be very likely related to the study agent. One subject experience an SAE of ectopic pregnancy (considered by the investigator as 'not related' to study medication; see above).[63]

Dissociative symptoms measured on the Clinician Administered Dissociative States Scale (CADSS)[3] were dose-dependent, with significant reductions in severity observed on multiple dosing, over the 2 weeks. No psychotic symptoms were seen. Transient increases in mean blood pressure (systolic and diastolic) were observed post dose following the intranasal esketamine administration.

The mean (standard deviation; SD) peak systolic blood pressure after the first administration in each dose group was:

- Placebo: 124.2 (11.51) mmHg; an increase of 5.4 (7.84) mmHg
- Esketamine 28 mg: 131.8 (15.49) mmHg; an increase of 10.4 (10.44) mmHg
- Esketamine 56 mg: 130.4 (18.64) mmHg; an increase of 11.2 (15.01) mmHg
- Esketamine 84 mg: 146.1 (19.9) mmHg; an increase of 17.1 (15.5) mmHg

Mean (SD) peak diastolic blood pressure after the first administration in each dose group was:

- Placebo: 81.2 (8.36) mmHg; an increase of 3.8 (7.99) mmHg
- Esketamine 28 mg: 85.7 (9.16) mmHg; an increase of 6.5 (7.00) mmHg
- Esketamine 56 mg: 86.5 (11.34) mmHg; an increase of 7.2 (9.67) mmHg
- Esketamine 84 mg: 87.8 (10.62) mmHg; an increase of 8.1 (9.12) mmHg

The blood pressure increase typically resolved within 2 hours. Unlike dissociative symptoms, the blood pressure changes observed do not appear to attenuate over time with multiple doses. Transient increases in heart rate were also observed in parallel with blood pressure change. There was no clinically meaningful change in blood oxygen level.

Adverse Events Associated with Chronic Use of Ketamine

There are no controlled studies of long-term use with esketamine/ketamine in patients with MDD. Much of the literature on chronic use of ketamine comes from data gathered from street/illegal use of the drug, rather than systematically conducted clinical studies. Data therefore should be interpreted with caution, as in many cases, no baseline pre-drug data are available and drug exposure is poorly documented.

In a 1-year longitudinal study, 150 subjects were divided into 5 groups of 30 subjects each: Frequent ketamine users (more than 4 times per week), infrequent ketamine users (at least once a month), abstinent users (abstinent for at least 1 month), polydrug controls, and non-users of illicit drugs.[48] Eighty percent of the participants were retested at the end of 1 year. Cognitive deficits (including impairment in spatial working memory, pattern recognition memory and category

fluency) were mainly observed in frequent users and not with the infrequent users. Short-lasting, dose-dependent effects of psychosis were associated with ketamine users. There was no increase in symptoms over time, and symptoms were completely reversible upon stopping use of ketamine. As noted, these data should be interpreted with caution, as baseline data predating drug use were not available. Furthermore, in their recent review, Morgan and Curran report that there is little evidence of any link between chronic, heavy use of ketamine and diagnosis of a psychotic disorder.[47]

The principal action of ketamine is at the NMDA receptor, and the consequences of ketamine use on cognition have been widely investigated. Several studies have examined cognitive function in infrequent and frequent ketamine users.[13,46,48,50] Overall, infrequent or recreational ketamine use does not appear to be associated with long-term cognitive impairment.[48] The most robust findings are that frequent ketamine users (more than 5 times a week) exhibit impairments in both short- and long-term memory.[46] Although dosages have varied, 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 TRD. Memory impairments may be reversible when individuals stop using the drug, as they were not found in a group of 30 ex-ketamine users who had been abstinent for at least a year.[46,47]

Ketamine-induced ulcerative cystitis is a recently identified complication.[47] The most common symptoms are frequency and urgency of urination, dysuria, urge incontinence, and occasionally painful hematuria (blood in urine). Computerized tomography scans revealed a marked thickening of the bladder wall, a small bladder capacity, and perivesicular stranding consistent with severe inflammation. At cystoscopy, all patients had severe ulcerative cystitis. Biopsies in 4 of these cases found denuded urothelial mucosa with thin layers of reactive and regenerating epithelial cells, and ulcerations with vascular granulation tissue and scattered inflammatory cells. Cessation of ketamine use provided some relief of symptoms. Most of the described cases are in near-daily users of ketamine for recreational purposes. The prevalence is difficult to determine, as it is seen in recreational users who often do not seek help. The majority of cases resolve after stopping ketamine use, one-third remaining static.

Abuse Liability, Dependence, and Withdrawal

There are a number of reports of ketamine dependence in the literature[33,35,45,52] but no large-scale studies, and so the incidence of ketamine dependence is largely unknown.[47] An interview study of 90 ketamine users found that 57% of frequent users, 43% of infrequent users, and 60% of ex-users expressed concerns about ketamine addiction.[49] The majority of frequent users in that study reported using the drug without stopping until supplies ran out, so compulsive patterns of behavior are also a concern. Oral ketamine has also been evaluated as a positive control in human abuse potential studies, with dosages of 65 mg and 110 mg reported as appropriate for use as positive controls for future abuse potential studies of compounds with a similar mechanism of action or with possible perception-altering effects.[68] There is conflicting evidence of the existence of a "withdrawal syndrome" after cessation of ketamine use.[47] Cravings seem to be a key problem in frequent users: 28 of the 30 daily users in 1 study reported having tried to stop taking the drug but failed; all reported ketamine cravings as the reason for failure.[47] The same study found that 12 of the 30 daily users reported withdrawal symptoms characterized by anxiety, shaking, sweating, and

palpitations when they stopped using. A few published case studies also show craving and somatic and psychological aspects of anxiety as withdrawal symptoms.[12,42] However, a specific ketamine withdrawal syndrome has not yet been described.[47]

Please refer to the Investigator's Brochure for a summary of the adverse events reported in ketamine and esketamine studies.[34]

1.2. Active Comparator

This study will evaluate the efficacy of switching adult subjects with TRD from a prior antidepressant treatment (to which they have not responded) to a flexible dose regimen of intranasal esketamine (56 mg or 84 mg) plus a newly initiated oral antidepressant, compared with switching to a newly initiated oral antidepressant (active comparator) plus intranasal placebo.

In the double-blind treatment phase, subjects will be assigned to receive 1 of 4 commercially available oral antidepressant medications from 2 different classes of antidepressant medications, selective serotonin reuptake inhibitors (SSRIs: Escitalopram or Sertraline), or serotonin and norepinephrine reuptake inhibitors (SNRIs: Duloxetine or Venlafaxine extended release [XR]), that the subject has not previously had a non-response to, in the current major depressive episode, and has not been previously intolerant to (lifetime).

The indications and safety information provided below for each oral antidepressant are from the US prescribing information.[17,21,65,71] For further information, please refer to the appropriate package insert applicable to the local country in which the study is being conducted.

In the US, all oral antidepressants include a black box warning in the prescribing information regarding suicidality and antidepressant drugs. In China, a similar warning is included in the label. The black box warning informs the prescriber that antidepressant treatment(s) increase the risk compared with placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of MDD and other psychiatric disorders. It states that anyone considering using the antidepressant in this population must balance the risk with the clinical need. Refer to the US and Chinese prescribing information for the entire content of the black box warning.[17,21,65,71]

1.2.1. Selective Serotonin Reuptake Inhibitors

1.2.1.1. Escitalopram

Escitalopram is indicated in adults for acute and maintenance treatment of MDD and acute treatment of generalized anxiety disorder.[21]

The starting dosage for MDD in the US prescribing information is 10 mg once daily, and in China, the commonly used dosage is 10 mg once daily, with a maximum of 20 mg once daily for both countries. If the dosage is increased to 20 mg, this should occur after a minimum of 1 week. No additional benefits have been seen at 20 mg/day dose.

In adult MDD subjects treated with escitalopram, the most commonly observed adverse reactions with escitalopram (incidence of approximately 5% or greater and approximately twice the incidence in placebo subjects) were insomnia, ejaculation disorder (primarily ejaculatory delay), nausea, sweating increased, fatigue, and somnolence.

Contraindications to the use of escitalopram include serotonin syndrome and monoamine oxidase inhibitor (MAOI) use (concomitant use with MAOIs intended to treat psychiatric disorders, linezolid, or IV methylene blue; use within 14 days of stopping treatment with an MAOI intended to treat psychiatric disorders [in addition, an MAOI should not be used within 14 days of stopping escitalopram]); concomitant use with pimozide; and known hypersensitivity to escitalopram or citalopram or any of the inactive ingredients.

As with most SSRIs, a gradual reduction in the dosage rather than abrupt cessation of escitalopram treatment is recommended whenever possible.

1.2.1.2. Sertraline

Sertraline hydrochloride is indicated in adults for the treatment of MDD, obsessions and compulsions in patients with obsessive compulsive disorder, panic disorder (with or without agoraphobia), post-traumatic stress disorder, premenstrual dysphoric disorder, and social anxiety disorder.[65]

According to both the US and China prescribing information, sertraline should be administered at a dose of 50 mg once daily for the treatment of MDD. While a relationship between dose and effect has not been established for MDD, obsessive compulsive disorder, panic disorder, post-traumatic stress disorder, or social anxiety disorder, patients were dosed in a range of 50-200 mg/day in the clinical trials demonstrating the effectiveness of sertraline for the treatment of these indications. Consequently, a dose of 50 mg, administered once daily, is recommended as the initial therapeutic dose. Patients not responding to a 50 mg dose may benefit from dose increases up to a maximum of 200 mg/day. Given the 24-hour elimination half-life of sertraline, dose changes should not occur at intervals of less than 1 week. The maximum dose of sertraline in the current study is 200 mg/day.

Contraindications to the use of sertraline include serotonin syndrome and MAOI use (concomitant use with MAOIs intended to treat psychiatric disorders, linezolid, or IV methylene blue; use within 14 days of stopping treatment with an MAOI intended to treat psychiatric disorders); concomitant use with pimozide; and known hypersensitivity to sertraline or any of the inactive ingredients.

In adult subjects, the most common TEAEs associated with the use of sertraline (incidence of at least 5% for sertraline or at least twice that for placebo within at least one of the indications) were ejaculation failure, dry mouth, increased sweating, somnolence, tremor, dizziness, fatigue, pain, malaise, abdominal pain, anorexia, constipation, diarrhea/loose stools, dyspepsia, nausea, agitation, insomnia, and decreased libido.

As with most SSRIs, a gradual reduction in the dosage rather than abrupt cessation treatment is recommended whenever possible.

1.2.2. Serotonin and Norepinephrine Reuptake Inhibitors

1.2.2.1. Duloxetine

Duloxetine is indicated in adults for MDD, generalized anxiety disorder, diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain.[17]

The starting dosage for MDD in both the US and China prescribing information is 40 to 60 mg/day. The dosage for acute treatment is 40 to 60 mg/day, with maintenance treatment at 60 mg/day. For some patients, it may be desirable to start at 30 mg once daily for 1 week, to allow patients to adjust to the medication before increasing to 60 mg once daily.[74]

In the current study, subjects should be initiated with 60 mg/day. Subjects that have in the past shown increased sensitivity towards SSRI/SNRIs can, at the discretion of the treating physician, be started on a 30 mg dose and up-titrated into the therapeutic range of 60 mg by the start of Week-2 of the double-blind treatment phase.

The maximum dosage is 120 mg/day, although there is no evidence that dosages greater than 60 mg/day confer any additional benefits. The maximum dose to be used in this study is 60 mg/day.

For pooled studies for all approved indications, the most commonly observed adverse reactions in duloxetine-treated subjects (incidence of at least 5% and at least twice the incidence in placebo subjects) were nausea, dry mouth, somnolence, fatigue, constipation, decreased appetite, and hyperhidrosis. As observed in diabetic peripheral neuropathy studies, duloxetine treatment worsens glycemic control in some subjects with diabetes.

Contraindications to the use of duloxetine include use of an MAOI concomitantly or within 2 weeks of MAOI use; and use in patients with uncontrolled narrow-angle glaucoma.

A gradual reduction in the dosage rather than abrupt cessation is recommended whenever possible.

1.2.2.2. Venlafaxine Extended-release

Venlafaxine XR is indicated in adults for MDD and social anxiety disorder.[71]

The starting dosage for MDD in both the US and China prescribing information is 75 mg/day (in some patients, 37.5 mg/day for 4 to 7 days), with a dosage increase by 75 mg/day at intervals of 4 days or longer, and a maximum dosage of 225 mg/day.

Dosage reductions are recommended for hepatic impairment (including mild) and renal impairment.

Contraindications to the use of venlafaxine XR include serotonin syndrome and MAOI use (concomitant use with MAOIs intended to treat psychiatric disorders, linezolid, or IV methylene blue; use within 14 days of stopping treatment with an MAOI intended to treat psychiatric disorders); concomitant use with pimozide; and known hypersensitivity to venlafaxine XR or any of the inactive ingredients.

In adult subjects with MDD, adverse events in short-term studies that occurred in at least 5% of the subjects receiving venlafaxine hydrochloride XR capsules and at a rate at least twice that of the placebo group were abnormal ejaculation, gastrointestinal complaints (nausea, dry mouth, and anorexia), central nervous system complaints (dizziness, somnolence, and abnormal dreams), and sweating.

Sustained hypertension is noted within the Warnings and Precautions section. Preexisting hypertension should be controlled before treatment with venlafaxine XR. It is recommended that patients receiving venlafaxine XR tablets have regular monitoring of blood pressure. For patients who experience a sustained increase in blood pressure while receiving venlafaxine XR, either dosage reduction or discontinuation should be considered.

Across most indications, a dose-related increase in supine systolic and diastolic blood pressure was evident in venlafaxine XR-treated patients. Across all clinical studies, 1.4% of subjects in the venlafaxine XR-treated groups experienced a ≥15-mmHg increase in supine diastolic blood pressure, with blood pressure ≥105 mmHg, compared with 0.9% of subjects in the placebo groups. Similarly, 1% of subjects in the venlafaxine XR-treated groups experienced a ≥20 mmHg increase in supine systolic blood pressure, with blood pressure ≥180 mmHg, compared with 0.3% of subjects in the placebo groups.

A gradual dosage reduction, individualized as necessary, is recommended to avoid discontinuation symptoms.

1.3. Overall Rationale for the Study

The current study is being conducted to evaluate the efficacy, safety, tolerability and pharmacokinetics of flexible doses of intranasal esketamine (56 mg or 84 mg) plus a newly initiated oral antidepressant in adult subjects with TRD. The study will serve as a Phase 3 efficacy and safety study in support of regulatory agency requirements in China for registration of intranasal esketamine for the treatment of TRD.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

2.1.1. Objectives

Primary Objective

The primary objective of this study is to evaluate the efficacy of switching adult subjects with TRD from a prior antidepressant treatment (to which they have not responded) to flexibly dosed intranasal esketamine (56 mg or 84 mg) plus a newly initiated oral antidepressant compared with switching to a newly initiated oral antidepressant (active comparator) plus intranasal placebo, in improving depressive symptoms, as assessed by the change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) total score from Day 1 (pre-randomization) to the end of the 4-week double-blind treatment phase.

Secondary Objectives

Key Secondary Objectives

The key secondary objectives are to assess the effect of intranasal esketamine plus a newly initiated oral antidepressant compared with a newly initiated oral antidepressant (active comparator) plus intranasal placebo on the following parameters in adult subjects with TRD:

- Change from baseline in the MADRS total score at 24 hours post first dose
- Functioning and associated disability

Other Secondary Objectives

To assess the effect of intranasal esketamine plus a newly initiated oral antidepressant compared with a newly initiated oral antidepressant (active comparator) plus intranasal placebo on the following parameters in adult subjects with TRD:

- Onset of clinical response by Day 2
- Depression response rates
- Depression remission rates
- Overall severity of depressive illness
- Anxiety symptoms
- Health-related quality of life and health status

To investigate the safety and tolerability of intranasal esketamine plus a newly initiated oral antidepressant compared with a newly initiated oral antidepressant (active comparator) plus intranasal placebo in adult subjects with TRD, including the following parameters:

- Treatment-emergent adverse events (TEAEs), including AEs of special interest
- Local nasal tolerability
- Effects on heart rate, blood pressure, respiratory rate, and blood oxygen saturation
- Dissociative symptoms
- Potential effects on suicidal ideation/behavior
- Potential withdrawal and/or rebound symptoms following cessation of intranasal esketamine treatment.

To assess the pharmacokinetics (PK) of intranasal esketamine in Chinese adult subjects with TRD receiving intranasal esketamine plus a newly-initiated oral antidepressant.

Exploratory Objectives

For subjects who receive esketamine during the double-blind treatment phase, the proportion of subjects who relapse during the follow-up phase will be evaluated separately for subjects who are remitters (MADRS ≤12) at the end of the 4 week double-blind treatment phase and for subjects

who are responders but not remitters (≥50% reduction in MADRS total score, but MADRS >12) at the end of the 4 week double-blind treatment phase.

- Time to relapse during the follow-up phase will be evaluated in esketamine subjects who remitted
- Time to relapse during the follow-up phase will be evaluated in esketamine subjects who are responders but not remitters
- To assess the potential relationship of biomarkers with response/non-response to intranasal esketamine or oral antidepressant in adult subjects with TRD.[α]

2.1.2. Endpoints

Primary Endpoint

- The primary endpoint is the change in the MADRS total score as measured by the change from baseline (Day 1, prior to randomization) to the end of the 4-week double-blind treatment phase.

Secondary Endpoints

- MADRS: The first key secondary endpoint is the change from baseline (Day 1, predose) to 24 hours post first dose in depressive symptoms, as measured by the MADRS total score.
- Sheehan Disability Scale (SDS): The second key secondary endpoint is the change in SDS total score as measured by the change from baseline (Day 1, prior to randomization) to the end of the 4-week double-blind treatment phase

Other Secondary Endpoints

- Proportion of subjects showing onset of clinical response (≥50% reduction from baseline in MADRS total score) by Day 2 that is maintained through the end of the 4-week double-blind treatment phase with one excursion allowed.
- Proportion of responders (≥50% reduction from baseline in MADRS total score) at the end of the 4-week double-blind treatment phase.
- Proportion of subjects in remission (MADRS ≤12) at the end of the 4-week double-blind treatment phase.
- Proportion of subjects who remain in remission (MADRS ≤12) through to the end of the follow-up phase.
- Change from baseline (Day 1, prior to randomization) to the end of the 4-week double-blind treatment phase in:
  - Severity of depressive illness, using the Clinical Global Impression–Severity (CGI-S);
  - Anxiety symptoms, using the Generalized Anxiety Disorder (GAD-7);

[α] Not applicable to China

- Health-related quality of life and health status, as assessed by the EuroQol-5 dimension-5 level (EQ-5D-5L).

Exploratory Endpoints

- For subjects who receive esketamine during the double-blind treatment phase, the proportion of subjects who relapse during the follow-up phase will be evaluated separately for subjects who are remitters (MADRS ≤12) at the end of the 4-week double-blind phase and for subjects who are responders but not remitters (≥50% reduction in MADRS total score, but MADRS >12) at the end of the 4-week double-blind treatment phase.
  - Time to relapse during the follow-up phase in esketamine subjects who remitted.
  - Time to relapse during the follow-up phase in esketamine subjects who are responders but not remitters.
- To assess the potential relationship of biomarkers with response/non-response to intranasal esketamine and oral antidepressant.[α]

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

2.2. Hypothesis

The hypothesis for this study is that, in adult subjects with TRD, switching from a failed antidepressant treatment to intranasal esketamine plus a newly initiated oral antidepressant is superior to switching to a newly initiated oral antidepressant treatment (active comparator) plus intranasal placebo in improving depressive symptoms.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a randomized, double-blind, active-controlled, multicenter study in male and female adult subjects with TRD to assess the efficacy, safety, tolerability, and pharmacokinetics of flexibly dosed intranasal esketamine (56 mg or 84 mg) plus a newly initiated oral antidepressant compared with a newly initiated oral antidepressant (active comparator) plus intranasal placebo.

The study has 3 phases;

- Screening/Prospective Observational Phase
- Double-blind Treatment Phase
- Follow-up Phase

[α] Not applicable to China

3.1.1. Overview of Study Phases

Screening/Prospective Observational phase (4-week duration + optional 3-week taper period)

This phase will prospectively assess treatment response to the subject's current oral antidepressant treatment regimen.

At the start of the screening/prospective observational phase, the subject must have had documented non-response to at least 1 antidepressant treatment (based on Massachusetts General Hospital–Antidepressant Treatment Response Questionnaire [MGH-ATRQ]) in the current episode of depression, and subject is taking a different oral antidepressant treatment (on the MGH-ATRQ) for at least the previous 2 weeks at or above the minimum therapeutic dose. This antidepressant treatment, as well as any other ongoing medications being taken for depression at screening (including adjunctive/augmentation therapies), will continue from the start of Week 1 through the end of Week 4 of the screening/prospective observational phase. Dose adjustment is permitted per clinical judgment, but the oral antidepressant treatment is to remain at or above the minimum therapeutic dose (per the MGH-ATRQ) through the end of Week 4. Antidepressant treatment adherence will be assessed using the PAQ. Subjects who report missing ≥4 days of antidepressant medication treatment(s) in the prior 2-week period will be considered as screen failed due to inadequate adherence.

After 4 weeks, subjects who are non-responders to their current oral antidepressant treatment (as assessed by independent, remote raters) may be eligible to proceed to the double-blind treatment phase. Non-response at the end of the screening/prospective observational phase is defined as ≤25% improvement in the MADRS total score from Week 1 to Week 4 and a MADRS total score of ≥28 on Week 2 and Week 4.

Eligible subjects who are entering the double-blind treatment phase will discontinue all of their current medication(s) being taken for depression (including adjunctive/augmentation therapies), and any other prohibited psychotropic medications (including adjunctive atypical antipsychotics). Subjects taking benzodiazepines (at dosages equal to or less than the equivalent of 6 mg/day of lorazepam) and/or permitted non-benzodiazepine sleep medications (eg, zolpidem, zaleplon, eszopiclone and ramelteon) during the screening/prospective observational phase, can continue these medications during the treatment phase No dose increases beyond the equivalent of 6 mg/day of lorazepam or new benzodiazepine medications are permitted during the screening/prospective observational phase. If clinically indicated, a subject's current antidepressant treatment(s) may be tapered and discontinued over an additional, optional period of up to 3 weeks per the local prescribing information or clinical judgment, or discontinued and switched directly to one of the four new oral antidepressant medications on Day 1 of the double-blind treatment phase, per clinical judgment.

Double-blind Treatment Phase (4-week duration)

Approximately 234 eligible subjects (210 Chinese subjects, 24 non-Chinese subjects) with TRD, will be randomly assigned at a 1:1 ratio (n=117 subjects per treatment arm, with approximately 105 Chinese subjects per arm) to receive double-blind treatment with either intranasal esketamine or intranasal placebo. The intranasal treatment sessions (esketamine 56 mg, 84 mg or placebo) will occur twice per week for 4 weeks as a flexible dose regimen at the study site. In addition, all subjects will initiate a new open-label oral antidepressant on Day 1, that will be taken daily for the duration of the double-blind treatment phase. The assigned oral antidepressant will be 1 of 4 oral antidepressant medications (duloxetine, escitalopram, sertraline, or venlafaxine extended release [XR]), that the subject has not previously had a non-response to in the current depressive episode, has not been previously intolerant to (lifetime), and is available in the participating country.

Subjects who were taking benzodiazepines (at dosages equal to or less than the equivalent of 6 mg/day of lorazepam) and/or permitted non-benzodiazepine sleep medications (eg, zolpidem, zaleplon, eszopiclone and ramelteon) during the screening/prospective observational phase can continue these medications during the double-blind treatment phase. No dose increases beyond the equivalent of 6 mg/day of lorazepam or new benzodiazepine medications are permitted during the double-blind treatment phase, with the exception of the use of permitted benzodiazepine rescue medication (eg, alprazolam, clorazepate, triazolam, lorazepam and temazepam).

Intranasal Treatment Sessions:

All subjects will self-administer the intranasal study medication (esketamine or placebo) at treatment sessions occurring twice a week for 4 weeks at the clinical site. Treatment is assigned by the Interactive Web Response System (IWRS). Table 1 in Section 6.2 describes how each treatment session will be administered in the double-blind treatment phase.

On Day 1, subjects randomized to intranasal esketamine will start with a dose of 56 mg. On any of the subsequent dosing days (Day 4, 8, 11, 15, 18, 22 and 25), the investigator can judge, based on efficacy and tolerability, whether to increase the dose of intranasal esketamine to 84 mg or to maintain the dose at 56 mg. In the event that an increase in dose is poorly tolerated, the investigator may decide to reduce the dose to 56 mg.

Oral Antidepressant Treatment:

Starting on Day 1 of the double-blind treatment phase, a new open-label oral antidepressant treatment will be initiated in all subjects. The oral antidepressant selected will be 1 of the 4 oral antidepressant medications allowed (duloxetine, escitalopram, sertraline, or venlafaxine extended release [XR]). The antidepressant medication will be assigned by the investigator based on review of MGH-ATRQ and relevant prior antidepressant medication information and will be one that the subject has not previously had a non-response to, in the current major depressive episode, has not been previously intolerant to (lifetime), and is available in participating country.

Dosing of the oral antidepressant will begin on Day 1 and follow a protocol specific titration schedule (Attachment 3). The use of the titration schedule provided in the protocol is mandatory. Doses are not to exceed the maximum dose defined in the titration schedule. If higher doses are not tolerated, a down-titration is permitted based on clinical judgment.

Refer to the Time and Events Schedule for a list of study evaluations that will be performed during the double-blind treatment phase.

If a subject withdraws from the study before the end of the double-blind treatment phase for reasons other than withdrawal of consent, an Early Withdrawal visit should be conducted within 1 week of the date of discontinuation, followed by the follow-up phase.

Follow-up Phase (8-weeks or until relapse)

The follow-up phase will include all subjects who received at least 1 dose of intranasal study medication in the double-blind treatment phase. No intranasal study medication will be administered during this phase.

At the start of the follow-up phase, further clinical/standard of care for the treatment of depression will be arranged by the study investigator and/or the subject's treating physician and medication changes are permitted. The decision to continue the oral antidepressant in this phase will be at the discretion of the investigator.

This follow-up phase will provide additional information required to assess the course of the subject's major depressive episode over an 8-week period. Safety and tolerability, including potential withdrawal symptoms, following discontinuation of intranasal esketamine will also be assessed.

The follow-up phase is completed at the end of the 8-week period or when a subject meets criteria below for relapse (in remitters and responders), whichever occurs first.

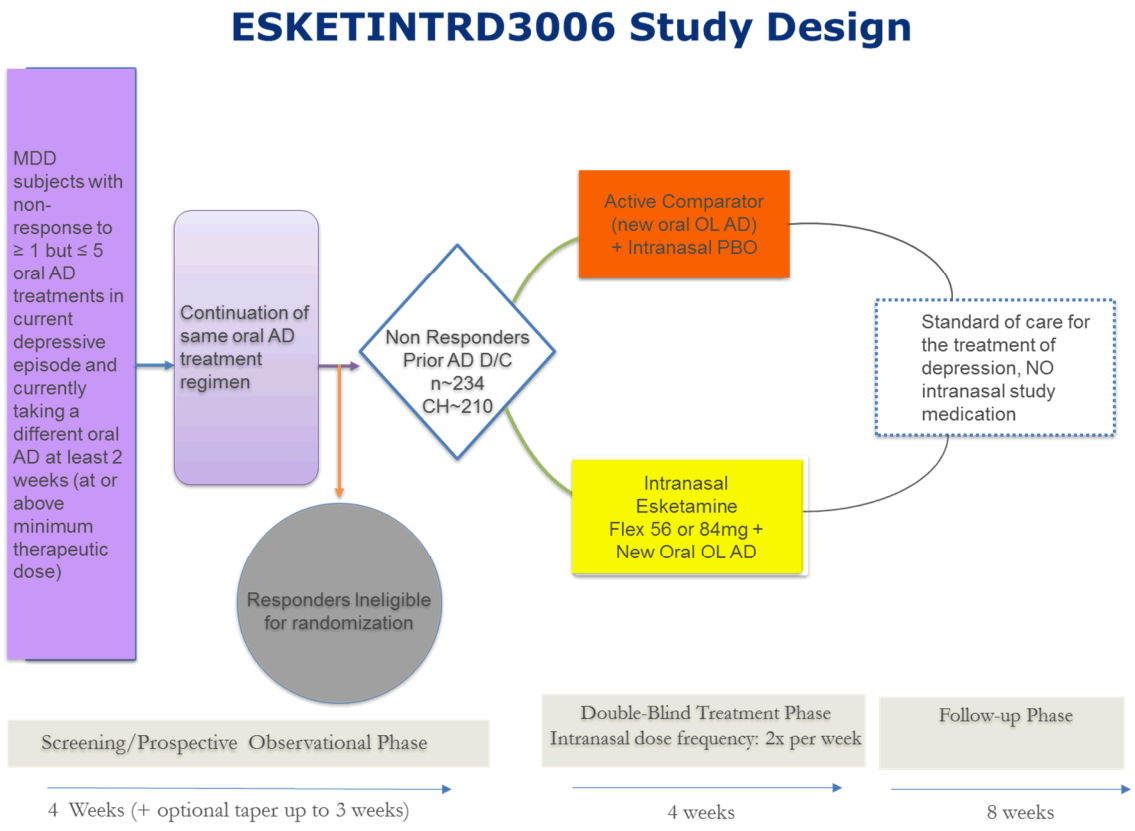
Relapse is defined as any of the following:

- MADRS total score ≥22 for 2 consecutive assessments separated by 5 to 15 days. The date of the second MADRS assessment will be used for the date of relapse.
- Hospitalization for worsening depression or any other clinically relevant event determined per clinical judgment to be suggestive of a relapse of depressive illness such as suicide attempt, completed suicide, or hospitalization for suicide prevention. If hospitalized for any of these events, the start date of hospitalization will be used for the date of relapse. Otherwise the date of the event will be used if the subject is not hospitalized.
- In case more than one relapse criteria are met, the earlier date will be defined as the date of relapse for this subject.

The total duration of a subject's study participation will be up to 19-weeks (including an optional 3-week taper period) for subjects completing the 8-week follow-up phase.

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

Figure 1: Schematic Overview of the Study



AD = antidepressant; CH = Chinese subjects; D/C = discontinue; MDD = major depressive disorder; OL = open-label; PBO = placebo.
The study will end after 8 weeks follow-up clinical/standard of care for treatment of depression, or following relapse, whichever is earlier.

3.2. Study Design Rationale

3.2.1. Study Population

The study population will consist of approximately 234 subjects (210 Chinese subjects, 24 non-Chinese subjects) with TRD. After giving informed consent, subjects who are 18 to 64 years of age (inclusive), will be screened to determine eligibility for study participation.

Subjects must meet Diagnostic and Statistical Manual of Mental Disorders–Fifth Edition (DSM-5) diagnostic criteria for recurrent MDD or single-episode MDD, without psychotic features, based upon clinical assessment and confirmed by the Mini International Neuropsychiatric Interview (MINI) [DSM-5 diagnostic code 296.23 or 296.33]. An independent rater will conduct the MADRS at screening as well as confirming the diagnosis and the validity of the major depressive episode.[81]

Treatment-resistant depression is defined as a lack of clinically meaningful improvement after treatment with at least 2 different antidepressant agents prescribed in adequate doses for adequate duration. At the start of this study, subjects must have had non-response (ie, lack of clinically meaningful improvement, defined as ≤25% improvement) to ≥1 but ≤5 (if current episode is >2 years or undefinable, upper limit is only applicable to the last 2 years) oral antidepressant treatments, taken at adequate dosage and for adequate duration, as assessed using the MGH-ATRQ and documented by records (eg, medical/pharmacy/prescription records or a letter from treating physician, etc.) for the current episode of depression. Subjects who have had some initial response but then lose the response (eg, tolerance effects/bradyphylaxis) to an antidepressant treatment will not be considered to have failed that antidepressant treatment. The use of historical data to define non-response to treatment prior to patient enrollment in a treatment study is considered practical and valid. The MGH-ATRQ is a validated tool assessing treatment response.

In addition, at the start of the screening/prospective observational phase, subjects must currently be taking one of a different oral antidepressant treatment (on the MGH-ATRQ) for at least the previous 2 weeks at or above the minimum therapeutic dose. This antidepressant treatment, as well as any other ongoing medications being taken for depression at screening (including adjunctive/ augmentation therapies), will continue from the start of Week-1 through the end of Week-4 of the screening/prospective observational phase. Dose adjustment is permitted per clinical judgment, but the oral antidepressant treatment is to remain at or above the minimum therapeutic dose (per the MGH-ATRQ) through the end of Week-4. Antidepressant treatment adherence will be assessed using the PAQ. Subjects who report missing ≥4 days of antidepressant medication treatment(s) in the prior 2-week period will be considered as screen failed due to inadequate adherence.

Non-response at the end of the screening/prospective observational phase is defined as ≤25% improvement in the MADRS total score from Week 1 to Week 4 and a MADRS total score of ≥28 on Week 2 and Week 4.

The subject's current major depressive episode, depression symptom severity (Week 1 MADRS total score ≥28 required), and antidepressant treatment response in their current depressive episode (retrospectively assessed) must be deemed valid for participation in the clinical study based on a C-VISA. The C-VISA is a tool to facilitate subject selection for MDD clinical studies, with a goal to ensure enrollment of subjects who have symptoms that reflect the current state of illness and that these symptoms can be reliably measured with appropriate measurement tools, as well as to help reduce placebo response.

Potential subjects will be excluded from participating in the study if they have previously demonstrated non-response of depressive symptoms to esketamine or ketamine in the current major depressive episode, or to all 4 of the oral antidepressant treatment options available for the double-blind treatment phase (ie, duloxetine, escitalopram, sertraline, and venlafaxine XR) in the current major depressive episode (based on MGH-ATRQ), or an adequate course of treatment with electroconvulsive therapy (ECT) in the current major depressive episode, defined as at least 7 treatments with unilateral/ bilateral ECT. Subjects, who in the current depressive episode have received vagal nerve stimulation (VNS) or who have received deep brain stimulation (DBS), will be excluded. Subjects will also be excluded if they have a current or prior DSM-5 diagnosis of a

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

3.2.2. Study Phases

The Company sponsored phase 3 esketamine studies (ESKETINTRD3001, ESKETINTRD3002, ESKETINTRD3003, ESKETINTRD3004 and ESKETINTRD3005)[56,57,58,59,60] in subjects with treatment resistant depression, all consist of a 4 week screening/prospective observational phase plus an optional 3 week taper, and a 4 week induction or treatment phase. The follow-up phase is of variable duration.

The 4-week duration of the screening/prospective observational phase will provide adequate time to assess subject eligibility according to the study entry criteria while also allowing for a prospective confirmation of non-response to the current antidepressant treatment(s) that is continued for the duration of this phase. This method of recruitment allows subjects to enter the study on a variety of different antidepressant medications that they had been taking, which mimics clinical practice and yet allows for prospective demonstration of treatment resistance to the current antidepressant treatment. Even though there is no depression rating score available at the start of the antidepressant treatment, subjects at screening will have to meet criteria for moderate to severe depression. After 4 weeks of prospective observation of continuation of the current antidepressant treatment and assessment of treatment response, subjects who meet the predefined non-response criteria and are eligible to enter the double-blind treatment phase will discontinue all of the current antidepressant treatments, including adjunctive/augmentation therapies, prior to starting the next phase. Non-responders who are eligible to enter the double-blind treatment phase are permitted to have up to 3 additional weeks to taper and discontinue their current antidepressant treatment prior to entry into the double-blind treatment phase per the local prescribing information or clinical judgment (eg, tolerability concerns). The optional taper period of up to 3 weeks is expected to provide an adequate amount of time for taper and discontinuation.

As described in Section 1.1.2, the duration of the 4-week double-blind treatment phase was selected based upon the onset of effect of typical antidepressant treatments and that the duration is considered to be sufficiently long to show the antidepressant effects of the active comparator. Preliminary findings from an analysis of antidepressant treatments were presented recently, as well as a completed analysis of 24 recent MDD studies that compared study durations of 4, 6, and 8 weeks. Exploratory analyses were conducted for each of the study durations using mixed effects model for repeated measures (MMRM) but excluding data beyond the duration of interest. These preliminary findings suggest that it is plausible to shorten the study duration down to 4 weeks.[40,79] Similarly, it has been demonstrated that improvement of ≥25% on the Hamilton Depression

17-item rating scale on Day 14 was a significant cutoff value to predict response after 5 weeks of treatment and a lack of improvement (ie, <25%) by Day 14 predicted poor response after 5 weeks of treatment.[51] All together, these results suggest that a 4-week duration should be adequate to assess antidepressant response.

For subjects entering the follow-up phase, the 8-week duration following the last dose of intranasal study medication will allow sufficient time to assess safety and tolerability after cessation of intranasal study medication. Given the frequency of esketamine administration, the 8-week follow-up should be sufficient to assess potential withdrawal symptoms and reversibility of any drug related adverse events and/or laboratory abnormalities. It will provide additional information required to assess the course of the subject's major depressive episode over an 8-week period. During this phase, the subject may continue to receive oral antidepressant treatment or follow clinical/standard of care, as judged by the study investigator and/or the subject's treating physician.

3.2.3. Blinding and Randomization

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

An intranasal placebo control will be used in the double-blind treatment phase to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of intranasal active treatment.

Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. The randomization will be stratified by country, class of antidepressant (SNRI or SSRI) and consent to biomarker evaluation[α] (Yes or No) with an allocation ratio of 1:1 to placebo or esketamine. The stratification is aimed at balancing treatment groups across two countries, class of antidepressant and whether subjects consent to biomarker evaluation.

3.2.4. Treatment Groups and Dose Selection

The 2 treatment groups in the double-blind treatment phase are:

- Active comparator (open-label new oral antidepressant) plus intranasal placebo
- Intranasal esketamine (56 mg or 84 mg) plus open-label new oral antidepressant

During the double-blind treatment phase, subjects will be randomized to receive intranasal treatment with esketamine (56 mg or 84 mg) or placebo. In addition, subjects will simultaneously initiate a new, open-label oral antidepressant on Day 1 that will be continued for the duration of the 4-week double-blind treatment phase.

[α] Not applicable to China

The treatment groups will allow for evaluation of the efficacy, safety, and tolerability of flexibly dosed intranasal esketamine plus a newly initiated oral antidepressant, as compared with a newly initiated oral antidepressant treatment (active comparator) plus intranasal placebo, in adult subjects with TRD.

Intranasal Study Drug

The dose selection (56 mg and 84 mg) and administration interval (2 treatment sessions per week for 4 weeks) for this study were based on the sponsor's previous clinical data, notably results from Studies ESKETIVTRD2001, KETIVTRD2002, ESKETINTRD1001, and Panel A of Study ESKETINTRD2003, described above in Section 1.1.2.

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

Small differences were observed in the pharmacokinetic profile of esketamine between healthy Chinese and Caucasian subjects who were administered a single 56 mg intranasal dose of esketamine (ESKETINTRD1008)[8]. The mean plasma C_{max} and AU_{∞} of esketamine were approximately 15% and 33% higher, respectively, in Chinese subjects as compared to Caucasian subjects. The mean terminal half-life was slightly longer in Chinese subjects (8.8 hours) than in Caucasians (6.8 hours). Intranasally administered esketamine 56 mg was well tolerated in both cohorts. Based on comparable responses of the two population cohorts to the 56 mg dose, and on data from the Caucasian population (ESKETINTRD2003)[10], we expected the 84 mg dose to be both efficacious and tolerated in the Chinese population.

The use of flexible dosing, rather than using a fixed dose, of intranasal esketamine is considered to facilitate improved tolerability by gradually increasing to a higher dose and will also inform clinical practice, as many clinicians prefer to gradually increase, and then adjust as clinically required, the dose of an antidepressant medication.

Oral Antidepressant

On Day 1 of the double-blind treatment phase, a new, open-label oral antidepressant treatment will be initiated in all subjects. Each subject will be assigned to receive 1 of 4 oral antidepressant medications from 2 different classes of antidepressant treatments, an SSRI (escitalopram or sertraline) or an SNRI (duloxetine or venlafaxine XR). The oral antidepressant medication selected are all recommended as standard-of-care treatments for depression, and therefore expected to show comparable efficacy.

The antidepressant medication will be assigned by the investigator based on review of MGH-ATRQ and relevant prior antidepressant medication information.

These 2 classes were selected because they are the most commonly prescribed antidepressant classes in this population and are generally well-tolerated. The oral antidepressant treatment assigned will be one that the subject has not previously had a non-response to in the current depressive episode, has not been previously intolerant to (lifetime), and is available in the participating country. Dosing of the oral antidepressant will begin on Day 1 and will follow a specific titration schedule (Attachment 3). The use of the titration schedule is mandatory. Doses are not to exceed the maximum dose defined in the titration schedule. If higher doses are not tolerated, a down-titration is permitted based on clinician's judgment.

3.2.5. Efficacy Measures

MADRS

The 10-item clinician-administered MADRS was designed to be used in subjects with MDD to measure the overall severity of depressive symptoms.[43,44] The MADRS scale has been selected as the primary efficacy measure for this study because it is validated, reliable, and acceptable to regulatory health authorities as a primary scale to determine efficacy in major depression. The MADRS has been validated in Chinese subjects with MDD.[81]

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

In addition to the primary efficacy measure, the change in MADRS total score from baseline (Day 1, prior to randomization) to 24 hours post dose (Day 2) will be included as a key secondary efficacy endpoint to evaluate rapid reduction of depressive symptoms.

In this study, subjects in any of the 2 treatment groups who respond to the study medication (ie, responders) are defined as subjects who meet the criterion for response defined as ≥50% reduction in the MADRS total score from baseline (Day 1, pre-randomization) to the end of the 4-week double-blind treatment phase.

MADRS will also be used to evaluate a secondary objective assessing the onset of clinical response (ie, antidepressant effect) by Day 2 that is maintained for the duration of the double-blind treatment phase. Onset of clinical response is defined as ≥50% improvement in MADRS total score by Day 2 (ie, the day after taking the first dose of double-blind intranasal medication) that is maintained through the end of the 4-week double-blind treatment phase with one excursion allowed. Additionally, MADRS will be used to evaluate a secondary objective assessing the proportion of subjects in remission (MADRS total score ≤12) at the end of the 4-week double-blind treatment phase; and the proportion who remain in remission (MADRS total score ≤12) through to the end of the follow-up phase.

The proportion of subject who relapse during the follow-up phase will be evaluated separately for subjects who are remitters (MADRS total score ≤12) at the end of the 4-week double-blind treatment phase and for subjects who are responders but not remitters (≥50% reduction in MADRS total score, but MADRS total score >12) at the end of the 4-week double-blind treatment phase.

Sheehan Disability Scale (SDS)

The SDS is a subject-reported outcome measure and is included as an assessment of functional impairment and associated disability.[41,67] The SDS assessment has been used for many years in psychiatric clinical trials in China, and its validity and reliability are well established. Please refer to Section 9.2.1.2 for additional information regarding SDS.

Clinical Global Impression–Severity (CGI-S)

The CGI-S is included to rate the severity of the subject's illness at the time of assessment, relative to the clinician's past experience with subjects who have the same diagnosis and improvement with treatment.[27] The CGI-S is widely used in clinical trials in psychiatry in China and has demonstrated validity and reliability in Chinese subjects with MDD. Please refer to Section 9.2.1.3.1 for additional information regarding CGI-S.

Generalized Anxiety Disorder 7-item Scale (GAD-7)

GAD-7 is included as a brief and validated measure of overall anxiety.[69] The GAD-7 has been validated in Chinese subjects with MDD.[30,80] Please refer to Section 9.2.1.3.2 for additional information regarding GAD-7.

EuroQol-5 Dimension-5 Level (EQ-5D-5L)

The EQ-5D-5L is included as a standardized subject-completed instrument for use as a measure of health-related quality of life and health status.[23,24] The EQ-5D-5L has been validated in Chinese subjects with MDD.[77] Please refer to Section 9.2.1.3.2 for additional information regarding EQ-5D-5L.

3.2.6. Safety Evaluations

Physical examination, body weight, vital signs (including blood pressure, pulse rate, respiratory rate and temperature measurements), 12-lead ECG, pulse oximetry, clinical laboratory tests (including hematology, serum chemistry, and urinalysis), pregnancy testing (for women of childbearing potential) will be performed throughout the study to monitor subject safety.

- 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 6.4 (Guidance on Blood Pressure Monitoring on Intranasal Treatment Session Days).

Treatment-emergent adverse events (TEAEs) will be evaluated throughout the course of the study.

Clinically relevant TEAEs of special interest will be examined separately grouped in the following categories as defined by the Standardized Medical Dictionary for Regulatory Activities (MedDRA) (version 20.0, or above if applicable) queries [(SMQ): AEs potentially suggestive of abuse, increased blood pressure, increased heart rate, transient dizziness/vertigo, impaired cognition, anxiety, and cystitis.

- The preferred terms used to determine TEAEs potentially suggestive of abuse, as defined by the Food and Drug Administration's Assessment of Abuse Potential of Drugs Guidance for Industry (January 2017) [a], include: Aggression, Confusional state, Decreased activity, Disorientation, Dissociation, Dissociative disorder, Dizziness, Drug tolerance, Euphoric mood, Feeling abnormal, Feeling drunk, Feeling of relaxation, Hallucination, Hallucination, auditory. Hallucination, gustatory, Hallucination, olfactory, Hallucination, synaesthetic, Hallucination, tactile, Hallucination, visual, Hallucinations, mixed, Inappropriate affect, Mental impairment, Product tampering, Psychomotor hyperactivity, Psychotic disorder, Somatic hallucination, Somnolence, Substance use disorder, Substance-induced psychotic disorder, and Thinking abnormal.

Narrative descriptions will be provided for deaths, subjects with serious adverse events, and subjects who discontinued study medication due to an adverse event. If applicable, narratives will be prepared for subjects with a TEAE of cystitis, with postdose oxygen saturation <93% for 2 or more consecutive assessments within the same visit, with post-baseline cases of QTcF >500 msec, with clinically significant suicidal ideation (score of 4 or 5 on the C-SSRS) or suicidal behavior (scores 6-10 on the C-SSRS), and for subjects who experienced a motor vehicle accident and/or who had TEAEs potentially suggestive of abuse.

The following safety evaluations will be performed:

- Nasal Examination
- Columbia Suicide Severity Rating Scale (C-SSRS), to assess suicidal ideation and behavior
- Clinician Administered Dissociative States Scale (CADSS), to assess treatment-emergent dissociative symptoms
- Physician Withdrawal Checklist (20-item; PWC-20), to assess potential withdrawal symptoms after cessation of esketamine treatment.

On all intranasal dosing days, subjects must remain at the site until study procedures have been completed and the subject is ready for discharge and 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 receiving intranasal study drug.

A list of prohibited medications is provided in Attachment 1 as general guidance for the investigator (but is not all inclusive).

3.2.7. Other Assessments

Patient Adherence Questionnaire

During the screening/prospective observational phase, the subject-reported Patient Adherence Questionnaire (PAQ) will be used to assess how often the subject has taken, and whether he or she has made any changes to, his or her antidepressant treatment regimen in the last 2 weeks. This

[a] Federal Disease Associations Assessment of Abuse Potential of Drugs Guidance for Industry. https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm198650.pdf.

assessment will provide confirmation of medication adherence when evaluating antidepressant treatment response. Subjects who report missing ≥4 days of antidepressant medication treatment(s) during a 2 week recall period will be considered as screen failed due to inadequate adherence.

3.2.8. Pharmacokinetic Assessments

Serial pharmacokinetic blood samples (4 mL, each) will be collected from Chinese subjects at all clinical sites, at the time points specified in the Time and Events Schedule. Concentration time data will allow estimation of individual PK parameters for esketamine, using a population PK modeling approach. The timing of PK sample collections was chosen to gather maximal information about the PK properties of esketamine while minimizing subject burden. The exact dates and times of PK blood sampling must be recorded. The concentrations of esketamine will be measured in plasma using a validated liquid chromatography coupled to tandem mass spectrometry (LC MS/MS) achiral method. The concentration of other esketamine metabolites may be measured in plasma, if required.

3.2.9. Biomarker, Pharmacogenomic (DNA), and Expression (RNA) Evaluations[α]

Assessment of biomarkers (protein and RNA) and their potential relationship to the different treatment groups and to maintenance/stabilization of response, non-response, and relapse will be explored. Blood samples will be collected to measure genetic and epigenetic markers (including but not limited to BDNF allelic variants) and protein markers (including but not limited to growth factors, inflammation, endocrine, or metabolic). Samples of deoxyribonucleic acid (DNA) and biomarkers may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

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 or subgroups that are more susceptible to relapse. In addition, pharmacogenomics research may allow for the identification of genetic factors that influence the PK, PD, efficacy, safety, or tolerability of the different treatment groups, and for the identification of genetic factors associated with TRD or MDD. Specifically, genetic and epigenetic changes in genes known to be in pathways relevant to depression (eg, hypothalamic pituitary adrenal [HPA] axis, inflammation, growth factors, monoamine transporters, ion channels, and circadian rhythm) will be evaluated.

Protein, metabolite, and ribonucleic acid (RNA) biomarkers may aid in the elucidation of the mechanism of action of the different treatment groups or help to explain inter-individual variability in clinical outcomes or may help to identify population subgroups that respond differently to a drug or may help to identify subgroups that are more susceptible to relapse. The goal of the

[α] Not applicable to China

biomarker analyses is to evaluate the PD of the different treatment groups, and aid in evaluating the drug-clinical response relationship.

On the day of biomarker sample collection, it is preferred that subjects adhere to a low fat diet (as an alternative to fasting) to reduce the level of postprandial lipemia in blood samples, since moderately or grossly lipemic specimens may interfere with assay results.

Subjects who agree to participate in the biomarker, pharmacogenomic (DNA) and expression (RNA) component will need to sign a separate written informed consent form.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed within a period of at least 28 days before administration of the study drug.

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

For a discussion of the statistical consideration 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. At the time of signing the informed consent form (ICF), subject must be a man or woman 18 (or older if the minimum legal age of consent in the country in which the study is taking place is >18) to 64 years of age, inclusive.

2. Criterion modified per Amendment 1

   2.1 At the start of the screening/prospective observational phase, subject must meet the Diagnostic and Statistical Manual of Mental Disorders–fifth edition (DSM-5) diagnostic criteria for recurrent MDD or single-episode MDD, without psychotic features, based upon clinical assessment and confirmed by the MINI.

3. Criterion modified per Amendment 1

   3.1 At the start of the screening/prospective observational phase, subject must have had non-response (≤25% improvement) to ≥1 but ≤5 (if current episode is >2 years or not definable, upper limit is applicable to only the last 2 years) oral antidepressant treatments in the current episode of depression, assessed using the MGH-ATRQ and confirmed by documented records (eg, medical/ pharmacy/prescription records or letter from a treating physician, etc.). In addition, the subject is taking a different oral

antidepressant treatment (on the MGH-ATRQ) for at least the previous 2 weeks at or above the minimum therapeutic dose.

- For specific tricyclic antidepressants which are ongoing and being taken at a dose below the MGH-ATRQ minimum therapeutic dose, a blood level that is within the therapeutic (antidepressant) range, is acceptable to establish the adequacy of the antidepressant treatment. Note: performing the test depends on availability of the kit.
- Subjects must be adherent to the continued oral antidepressant treatment medication(s) through the screening/prospective observational phase, as documented on the Patient Adherence Questionnaire (PAQ). Missing ≥4 days of antidepressant medication in the prior 2-week period will be considered as screen failed due to inadequate adherence.
- Subjects who are non-responders to their current oral antidepressant medication(s) from the screening/prospective observational phase (as assessed by independent, remote raters) may be eligible for randomization if all other entry criteria are met. Non-response at the end of the screening/prospective observational phase is defined as ≤25% improvement in the MADRS total score from Week 1 to Week 4 and a MADRS total score of ≥28 on Week 2 and Week 4.

4. Criterion modified per Amendment 1

   4.1 The subject's current major depressive episode, depression symptom severity (Week 1 MADRS total score ≥28 required), and antidepressant treatment response in the current depressive episode, must be confirmed using a C-VISA.

5. Subject must be medically stable on the basis of physical examination, medical history, vital signs (including blood pressure), pulse oximetry, and 12-lead ECG performed in the screening/prospective observational phase. If there are any abnormalities that are not specified in the inclusion and exclusion criteria, they must be consistent with the underlying illness in the study population. This determination must be recorded in the subject's source documents and initialed or signed by the investigator.

6. Subject must be medically stable on the basis of clinical laboratory tests performed in the screening/prospective observational phase. 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 or to be appropriate and reasonable for the population under study. This determination must be recorded in the subject's source documents and initialed or signed by the investigator.

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

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

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

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

A woman must be either:

a. Not of childbearing potential defined as:

- postmenopausal
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy, however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- permanently sterile
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

b. Of childbearing potential and

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

Examples of highly effective contraceptives include

– user-independent methods:

  implantable progestogen-only hormone contraception associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); vasectomized partner; sexual abstinence (s*exual abstinence is considered a highly effective method* ***only*** *if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.*)

– user-dependent methods:

  combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, and transdermal; progestogen-only hormone contraception associated with inhibition of ovulation: oral and injectable.

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

Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method.

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

Note: If the childbearing potential changes after start of the study (eg, woman who is not heterosexually active becomes active), a woman must begin a highly effective method of birth control, as described throughout the inclusion criteria.

9. A woman of childbearing potential must have a negative serum (β-human chorionic gonadotropin [β-hCG]) at the start of the screening/prospective observational phase and a negative urine pregnancy test must be obtained before the first dose of study drug on Day 1 of the double-blind phase prior to randomization.

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

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

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

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

12. Each subject must sign an ICF indicating that he or she understands the purpose of and procedures required for the study and is willing to participate in the study.

13. For Chinese subjects, the primary spoken language must be Mandarin or subjects must be capable of communication fluently in Mandarin.

4.2. Exclusion Criteria

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

1. The subject's depressive symptoms have previously demonstrated non-response to:

   - Esketamine or ketamine in the current major depressive episode per clinical judgment, or
   - All of the oral antidepressant treatment options available in the respective country for the double-blind phase (ie, duloxetine, escitalopram, sertraline, and venlafaxine XR) in the current major depressive episode (based on MGH-ATRQ), or
   - An adequate course of treatment with electroconvulsive therapy (ECT) in the current major depressive episode, defined as at least 7 treatments with unilateral/bilateral ECT.

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

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

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

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

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

6. Subjects with a current or past history of seizures (uncomplicated childhood febrile seizures with no sequelae are not exclusionary).

7. Subject has one of the following cardiovascular-related conditions:

   - Cerebrovascular disease with a history of stroke or transient ischemic attack.
   - Aneurysmal vascular disease (including intracranial, thoracic, or abdominal aorta, or peripheral arterial vessels).
   - Coronary artery disease with myocardial infarction, unstable angina, or revascularization procedure (eg, coronary angioplasty or bypass graft surgery) within 12 months before the start of the screening/prospective observational phase. Subjects who have had a revascularization performed >12 months prior to screening and are clinically stable and symptom-free, per investigator's clinical judgment, can be included.
   - Hemodynamically significant valvular heart disease such as mitral regurgitation, aortic stenosis, or aortic regurgitation.
   - New York Heart Association (NYHA) Class III-IV heart failure of any etiology.

8. Subject has a history of uncontrolled hypertension despite diet, exercise, or antihypertensive therapy, any past history of hypertensive crisis, or ongoing evidence of uncontrolled hypertension defined as a supine systolic blood pressure (SBP) >140 mmHg or diastolic blood pressure (DBP) >90 mmHg, during the screening/prospective observational phase, which continues to be above this range with repeated testing during this phase. [Note: On Day 1 of the double-blind treatment phase prior to randomization a supine SBP >140 mm Hg or DBP >90 mmHg is exclusionary].

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

9. Subject has a current or past history of significant pulmonary insufficiency/condition or with an arterial blood oxygen saturation (SpO_2) of <93% at the start of the screening/prospective observational phase or Day 1 prior to randomization.

10. Criterion modified per Amendment 1

    10.1 Subject has clinically significant ECG abnormalities at the start of the screening/prospective observational phase or on Day 1 of the double-blind treatment phase prior to randomization, defined as:

    - During screening, a QT interval corrected according to Fridericia's formula (QTcF): ≥470 msec in males and ≥480 msec in females.

- On Day 1 (predose), a QT interval corrected according to Fridericia's formula (QTcF): ≥470 msec in males and ≥480 msec in females based on the site-evaluated ECG.
- Evidence of 2nd and 3rd degree AV block, complete left bundle branch block (LBBB), or complete right bundle branch block (RBBB).
- Features of new ischemia.
- Arrhythmia (except premature atrial contractions [PACs] and premature ventricular contractions [PVCs]).

11. Subject has a history of additional risk factors for Torsades de Pointes (eg, heart failure, hypokalemia, family history of Long QT Syndrome).

12. Criterion modified per Amendment 1

    12.1 Subject has a history of, or symptoms and signs suggestive of, liver cirrhosis (eg, esophageal varices, ascites, and increased prothrombin time) OR alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values ≥3x the upper limit of normal in the screening/prospective observational phase.

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

13. Criterion modified per Amendment 1

    13.1 Subject has positive test result(s) for drugs of abuse at the start of the screening/prospective observational phase (including barbiturates, methadone, opiates, cocaine, phencyclidine, and amphetamine) or Day 1 of the double-blind treatment phase prior to randomization (including cannabinoids, methadone, opiates, cocaine, and amphetamine). Note: performing the test, depends on availability of the kit.

    - Subjects who have a positive test result at screening due to prescribed psychostimulants (eg, amphetamine, etc.) taken for an indication other than MDD, are permitted to continue to take this medication during the study.
    - Otherwise, subjects who have a positive test result at screening due to prescribed/over-the-counter opiates or barbiturates may be permitted to continue in the screening/prospective observational phase if the medication is discontinued at least 1 week or 5 half-lives, whichever is longer, before Day 1 of the double-blind treatment phase (prior to randomization). The result of the Day 1 (prior to randomization) test for drugs of abuse must be negative for the subject to be randomized.
    - Retesting is not permitted for positive test result(s), except for reasons stated above.

- Prior intermittent use of cannabinoids prior to the start of the screening/prospective observational phase is not exclusionary as long as the subject does not meet the criteria for substance use disorder. A positive test for cannabinoids at the start of the screening/prospective observational phase is not exclusionary however a positive test result for cannabinoids predose on Day 1 of the double-blind treatment phase is exclusionary.

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

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

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

17. Subject has known allergies, hypersensitivity, intolerance, or contraindications to esketamine/ketamine and/or its excipients or all of the available oral antidepressant treatment options for the double-blind treatment phase.

18. Subject has taken any prohibited therapies that would not permit dosing on Day 1.

19. Subject is taking a total daily dose of benzodiazepines greater than the equivalent of 6 mg/day of lorazepam at the start of the screening/prospective observational phase.

20. Subject has an obstructive sleep apnea (eg, apnea-hypopnea index [AHI] must be <30). A subject with obstructive sleep apnea can be included if he or she is using a positive airway pressure device or other treatment/therapy that is effectively treating (ie, AHI <30) his or her sleep apnea.

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

22. Subject is a woman who is pregnant, breast-feeding, or planning to become pregnant while enrolled in this study or within 6 weeks after the last dose of intranasal study drug.

23. Subject is a man who plans to father a child while enrolled in this study or within 12 weeks after the last dose of study drug.

24. Subject has a diagnosis of acquired immunodeficiency syndrome (AIDS). Human immunodeficiency virus (HIV) testing is not required for this study.

25. Subject has any condition or situation/circumstance 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.

28[a]. Subject has had major surgery, (eg, requiring general anesthesia) within 12 weeks before the start of the screening/prospective observational phase, or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study.

Note: Subjects with planned surgical procedures to be conducted under local anesthesia may participate.

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

30. Subject has severe renal impairment (creatinine clearance <30 ml/min).

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 9.1.2, Screening/Prospective Observational Phase describes options for retesting. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

The sponsor will evaluate and approve/reject requests to rescreen an individual subject on a case-by-case basis.

[a] In the original protocol the numbering of the exclusion criteria inadvertently skipped 26 and 27. These numbers are not being used.

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 8 (Concomitant Therapy) and Attachment 1 (Prohibited Concomitant Medications for Intranasal Study Medication [Esketamine or Placebo]) for details regarding prohibited and restricted therapy during the study.
2. Agree to follow all requirements that must be met during the study as noted in the Inclusion Criteria (Section 4.1) and Exclusion Criteria (Section 4.2; eg, contraceptive requirements)
3. Subjects who were taking benzodiazepines at dosages equal to or less than the equivalent of 6 mg/day of lorazepam and/or permitted non-benzodiazepine sleep medications (eg, zolpidem, zaleplon, eszopiclone, and ramelteon) during the screening/prospective observational phase can continue these medications during the double-blind treatment phase. No dose increases beyond the equivalent of 6 mg/day of lorazepam or new benzodiazepine medications are permitted during the double-blind treatment phase, with the exception of the use of permitted benzodiazepine rescue medication (eg, alprazolam, clorazepate, triazolam, lorazepam and temazepam). Benzodiazepines and non-benzodiazepine sleeping medication (eg, zolpidem, zaleplon, eszopiclone, and ramelteon) are prohibited within 12 hours prior to the start of each intranasal treatment session.
4. A positive urine drug screen for use of cocaine from Day 1 of the double-blind treatment phase through the final visit in the double-blind treatment phase will lead to discontinuation. Note: performing the test depends on availability of the kit
5. Subjects must abstain from using alcohol within 24 hours before and after each intranasal treatment session. If a subject appears intoxicated, dosing should not occur (delayed per the permitted visit window; see the Time and Events Schedule).
6. On all intranasal study drug dosing days, all subjects must remain at the clinical study site until study procedures have been completed and the subject is ready for discharge. 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.
7. ECT, DBS, transcranial magnetic stimulation (TMS), and VNS are prohibited from study entry through the end of the double-blind treatment phase.
8. Subjects receiving psychotherapy (including cognitive behavioral therapy; CBT) can continue receiving psychotherapy; however, CBT must have been ongoing for the last 3 months prior to the screening/prospective observational phase. With the exception of new CBT, which is prohibited, new psychotherapy is allowed during this study. Any change in existing therapy or new therapy must be documented on the concomitant therapies form.

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

Procedures for Randomization

Central randomization will be implemented in this study. Subjects will be randomly assigned to 1 of 2 treatment groups in a 1:1 ratio based on a computer-generated randomization schedule

prepared before the study by or under supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by country, class of oral antidepressant (SNRI or SSRI) and consent to biomarker evaluation (Yes or No) to be initiated in the double-blind treatment phase. The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kits for the subject. After the investigator selects the oral antidepressant treatment for the double-blind treatment phase, the site will enter this information into IWRS. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject.

Blinding

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

Data that may potentially unblind the treatment assignment (eg, intranasal 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 and time of the unblinding will be documented by the IWRS, and reason for the unblinding must be documented by 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 withdrawal and follow up visits.

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

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

6. DOSAGE AND ADMINISTRATION

6.1. Screening/Prospective Observational Phase (4-week duration + optional 3-week taper period)

This phase will prospectively assess treatment response to the subject's current oral antidepressant treatment regimen.

At the start of the screening/prospective observational phase, the subject must have had documented non-response to at least 1 antidepressant treatment (based on Massachusetts General Hospital–Antidepressant Treatment Response Questionnaire [MGH-ATRQ]) in the current episode of depression, and subject is taking a different oral antidepressant treatment (on the MGH-ATRQ) for at least the previous 2 weeks at or above the minimum therapeutic dose. This antidepressant treatment, as well as any other ongoing medications being taken for depression at screening (including adjunctive/augmentation therapies), will continue from the start of Week 1 through the end of Week 4 of the screening/prospective observational phase. Dose adjustment is permitted per clinical judgment, but the oral antidepressant treatment is to remain at or above the minimum therapeutic dose (per the MGH-ATRQ) through the end of Week 4. Antidepressant treatment adherence will be assessed using the PAQ. Subjects who report missing ≥4 days of antidepressant medication treatment(s) in the prior 2-week period will be considered as screen failed due to inadequate adherence.

The sponsor will not supply these antidepressant medication(s).

After 4 weeks, subjects who are non-responders to their current oral antidepressant treatment (as assessed by independent, remote raters) may be eligible to proceed to the double-blind treatment phase. Non-response at the end of the screening/prospective observational phase is defined as ≤25% improvement in the MADRS total score from Week 1 to Week 4 and a MADRS total score of ≥28 on Week 2 and Week 4.

The MADRS interview should be performed in Week 1 (Visit 1.1 or as soon as possible) of the screening/prospective observational phase.

Eligible subjects who are entering the double-blind treatment phase will discontinue all current medication(s) being used for depression treatment (including adjunctive/augmentation therapies), and any other prohibited psychotropic medications (including adjunctive atypical antipsychotics). Subjects taking benzodiazepines (at dosages equal to or less than the equivalent of 6 mg/day of lorazepam) and/or permitted non-benzodiazepine sleep medications (eg, zolpidem, zaleplon, eszopiclone and ramelteon) during the screening/prospective observational phase, can continue these medications during the treatment phase. No dose increases beyond the equivalent of 6 mg/day of lorazepam or new benzodiazepine medications are permitted during the screening/prospective observational phase. If clinically indicated, a subject's current antidepressant treatment(s) may be tapered and discontinued over an additional optional period of up to 3 weeks per the local prescribing information or per clinical judgment or discontinued and switched directly to one of the four new oral antidepressant medications on Day 1 of the double-blind treatment phase, per clinical judgment.

6.2. Double-blind Treatment Phase (4-week duration)

Approximately 234 eligible subjects (210 Chinese subjects, 24 non-Chinese subjects) with TRD, will be randomly assigned at a 1:1 ratio (n=117 subjects per treatment arm, with approximately 105 Chinese subjects per arm) to receive double-blind treatment with either intranasal esketamine or intranasal placebo. The intranasal treatment sessions (esketamine 56 mg, 84 mg or placebo) will occur twice per week for 4 weeks as a flexible dose regimen at the study site. In addition, all subjects will initiate a new open-label oral antidepressant on Day 1, that will be taken daily for the duration of the double-blind treatment phase. The assigned oral antidepressant will be 1 of 4 oral antidepressant medications (duloxetine, escitalopram, sertraline, or venlafaxine extended release [XR]), that the subject has not previously had a non-response to in the current depressive episode, has not been previously intolerant to (lifetime), and is available in the participating country.

Subjects who were taking benzodiazepines (at dosages equal to or less than the equivalent of 6 mg/day of lorazepam) and/or permitted non-benzodiazepine sleep medications (eg, zolpidem, zaleplon, eszopiclone and ramelteon) during the screening/prospective observational phase can continue these medications during the double-blind treatment phase. No dose increases beyond the equivalent of 6 mg/day of lorazepam or new benzodiazepine medications are permitted during the double-blind treatment phase, with the exception of the use of permitted benzodiazepine rescue medication (eg, alprazolam, clorazepate, triazolam, lorazepam and temazepam).

Intranasal Treatment Sessions:

All subjects will self-administer the intranasal study medication (esketamine or placebo) at treatment sessions occurring twice a week for 4 weeks at the clinical site. Treatment is assigned by the Interactive Web Response System (IWRS). The table below describes how each treatment session will be administered in the Double-Blind Treatment Phase.

Table 1: Intranasal Treatment Sessions in the Double-Blind Treatment Phase

Intranasal Treatment	Time of Administration (Time 0 is defined as the time of the first 100-µL spray)		
	0 [a]	5 minutes	10 minutes
Intranasal Device [b,c]	1st	2nd	3rd
Placebo	1 spray of placebo to each nostril	1 spray of placebo to each nostril	1 spray of placebo to each nostril
Esketamine 56 mg	1 spray of esketamine to each nostril	1 spray of esketamine to each nostril	1 spray of placebo to each nostril
Esketamine 84 mg	1 spray of esketamine to each nostril	1 spray of esketamine to each nostril	1 spray of esketamine to each nostril

a. Time 0 is defined as the time of administration of the first intranasal spray to one nostril from the first intranasal device.
b. One device will be used at each time point. Each individual intranasal device contains 2 sprays. The intranasal devices containing esketamine deliver 14 mg per spray, for a total of 28 mg per individual device (ie, 2 sprays).
c. The 3 intranasal devices for each intranasal treatment session should be administered in the medication kit order provided by the IWRS

Instructions for use documents (subject and healthcare provider versions) for intranasal study drug administration will be provided as separate documents. Details regarding study drug administration will be recorded in the source documents and the electronic case report form (eCRF).

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 intranasal study drug (esketamine or placebo) at treatment sessions twice a week for 4 weeks at the study site. The first treatment session will be on Day 1. Intranasal treatment sessions should not take place on consecutive days.

On Day 1, subjects randomized to intranasal esketamine will start with a dose of 56 mg. On any of the subsequent dosing days (Day 4, 8, 11, 15, 18, 22 and 25), the investigator can judge, based on efficacy and tolerance, whether to increase the dose of intranasal esketamine to 84 mg or to maintain the dose at 56 mg. In the event that an increase in dose is poorly tolerated, the investigator may decide to reduce the dose to 56 mg. Food will be restricted for at least 2 hours before each administration of study drug. Drinking of any fluids will be restricted for at least 30 minutes before the first nasal spray.

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

On all intranasal treatment sessions, subjects must remain at the clinical site until study procedures have been completed and the subject is ready for discharge. On all intranasal treatment session days, a site staff member with training in cardiopulmonary resuscitation (eg, Basic Life Support course or equivalent course) that is up to date per local regulations, must be present with the subject during the intranasal treatment sessions and the postdose observation period. In addition, equipment for supportive ventilation and resuscitation needs to be present. Subjects must remain at the site until study procedures have been completed and the subject is ready for discharge. At the time of discharge, 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 receiving intranasal study drug.

On intranasal dosing days, it is recommended that the oral antidepressant medication not be taken until at least 3 hours after an intranasal treatment session, thus providing sufficient time for potential side-effects related to esketamine (including dissociation, increase in blood pressure) to have resolved.

Oral Antidepressant Treatment:

Starting on Day 1 of the double-blind treatment phase, a new open-label oral antidepressant treatment will be initiated in all subjects. The oral antidepressant selected will be 1 of the 4 oral antidepressant medications allowed (duloxetine, escitalopram, sertraline, or venlafaxine extended release [XR]). The antidepressant medication will be assigned by the investigator based on review of MGH-ATRQ and relevant prior antidepressant medication information and will be one that the subject has not previously had a non-response to, in the current depressive episode, has not been previously intolerant to (lifetime), and is available in the participating country.

Dosing of the oral antidepressant will begin on Day 1 and follow a protocol specific titration schedule (Attachment 3). Doses are not to exceed the maximum dose defined in the titration schedule. If higher doses are not tolerated, a down-titration is permitted based on clinical judgment.

Refer to the Time and Events Schedule for a list of study evaluations that will be performed during the double-blind treatment phase.

If a subject withdraws from the study before the end of the double-blind treatment phase for reasons other than withdrawal of consent, an Early Withdrawal visit should be conducted within 1 week of the date of discontinuation, followed by the follow-up phase.

6.3. Follow-up Phase (8-weeks or until relapse)

The follow-up phase will include all subjects who receive at least 1 dose of intranasal study medication in the double-blind treatment phase. No intranasal study medication will be administered during this phase.

At the start of the follow-up phase, further clinical/standard of care for the treatment of depression will be arranged by the study investigator and/or the subject's treating physician and medication changes are permitted. The decision to continue the oral antidepressant in this phase will be at the discretion of the investigator.

This follow-up phase will provide additional information required to assess the course of the subject's major depressive episode over an 8-week period. Safety and tolerability, including potential withdrawal symptoms, following discontinuation of intranasal esketamine will also be assessed.

The follow-up phase is completed at the end of the 8-week period or when a subject meets criteria below for relapse (in remitters and responders), whichever occurs earlier.

- Relapse is defined as any of the following:
  - MADRS total score ≥22 for 2 consecutive assessments separated by 5 to 15 days. The date of the second MADRS assessment will be used for the date of relapse.
  - Hospitalization for worsening depression or any other clinically relevant event determined per clinical judgment to be suggestive of a relapse of depressive illness such as suicide attempt, completed suicide, or hospitalization for suicide prevention. If hospitalized for any of these events, the start date of hospitalization will be used for the date of relapse. Otherwise the date of the event will be used if the subject is not hospitalized.
  - In case more than one relapse criteria are met, the earlier date will be defined as the date of relapse for this subject.

The total duration of a subject's study participation will be up to 19 weeks for subjects completing the follow-up phase.

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

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

- If subsequent to fulfilling the inclusion and exclusion criteria on Day 1 (ie, applicable for all other intranasal treatment session days after Day 1), a subject's pre-dose systolic blood pressure (SBP) is >140 mmHg and/or diastolic blood pressure (DBP) is >90 mmHg, it is recommended to repeat the blood pressure measurement after subject rests in sitting or recumbent position. If after rest and repeated measurements, pre-dose SBP is >140 mmHg and/or DBP is >90 mmHg, then dosing should be postponed, and the subject scheduled to return on the following day or within the given visit window. If the blood pressure elevation still persists on the next visit, the subject will be scheduled for a consultation by cardiologist, other specialist, or primary care physician, prior to further dosing.
- If at any postdose time point on the dosing day, the SBP is ≥180 mmHg but <200 mmHg and/or the DBP is ≥110 mmHg but <120 mmHg, further intranasal dosing should be interrupted and the subject should be referred to a cardiologist, other specialist, or primary care physician for a follow-up assessment.
  - After the assessment by a cardiologist, other specialist, or primary care physician, if recommended by the referring doctor and considered appropriate according to the clinical judgment for the subject to continue in the study, the subject may continue with intranasal dosing if the pre-dose blood pressure at the next scheduled visit is within the acceptable range (see bullet point above).
- If at any postdose time point on the dosing day the SBP is ≥200 mmHg and/or the DBP is ≥120 mmHg, the subject must discontinue from further dosing and the subject should be referred to a cardiologist, other specialist or primary care physician for a follow-up assessment.

During the double-blind treatment phase, at 1.5 hours postdose, if the SBP is ≥160 mmHg and/or the DBP ≥100 mmHg, assessments should continue every 30 minutes until:

- the blood pressure is <160 mmHg SBP and <100 mmHg DBP, or
- in the investigator's clinical judgment, the subject it is clinically stable and can be discharged from the study site, or
- the subject is referred for appropriate medical care, if clinically indicated, or
- if the blood pressure remains ≥180 mmHg SBP and/or ≥110 mmHg DBP, 2 hours after dosing, the subject should be referred for immediate medical treatment.

7. TREATMENT COMPLIANCE

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

Subjects will receive instructions on compliance with the oral antidepressant treatment. During the course of the study, the investigator or designated study-site personnel will be responsible for providing additional instruction to re-educate any subject to ensure compliance with taking the oral antidepressant. A subject diary will be provided to capture oral antidepressant study medication use.

Antidepressant treatment adherence during the screening/prospective observational phase will be assessed using the PAQ. Missing ≥4 days of antidepressant medication in the prior 2-week period will be considered screen failed due to inadequate adherence.

Antidepressant treatment compliance during the double-blind treatment and follow-up phases will be assessed by performing pill counts (ie, compliance check) and drug accountability.

All doses of intranasal study drug will be self-administered by the subjects at the study site under the direct supervision of the investigator or designee and will be recorded.

8. PRESTUDY AND CONCOMITANT THERAPY

Prestudy non-antidepressant therapies administered up to 30 days before the start of the screening/prospective observational phase must be recorded at the start of this phase.

All antidepressant treatment(s), including adjunctive treatment for MDD, taken during the current depressive episode (ie, including those taken more than 30 days prior to the start of the screening/prospective observational phase) will be recorded at the start of the screening/prospective observational phase. In addition, information will also be obtained regarding any history of intolerance to any of the 4 antidepressant choices (ie, duloxetine, escitalopram, sertraline, and venlafaxine XR). Antidepressant treatments which are not listed on the MGH-ATRQ but were used, or currently being used, as antidepressant treatment in the current depressive episode must be recorded in the 'Concomitant Therapy' eCRF.

Any medication that is listed on the MGH-ATRQ and is being taken at the start of the screening/prospective observational phase for an indication other than depression (eg, insomnia) should be continued during the screening/prospective observational phase but must be discontinued before the start of the double-blind treatment phase.

Concomitant therapies must be recorded throughout the study, beginning with signing of the informed consent and continuing up to the last visit. Information on concomitant therapies should also be obtained beyond this time only in conjunction with new or worsening adverse events until resolution of the event.

Subjects should continue to take their permitted concomitant medications (eg, antihypertensive medications) at their regular schedule; however, restrictions as outlined in Section 4.3 (Prohibitions and Restrictions) and Attachment 1, should be taken into account. Of note, if a subject has routinely taken his/her oral antihypertensive medications in the morning on dosing days, the morning dose should be taken prior to intranasal dosing.

Subjects receiving psychotherapy (including cognitive behavioral therapy; CBT) can continue receiving psychotherapy; however, CBT must have been ongoing for the last 3 months prior to the start of the screening/prospective observational phase. With the exception of new CBT, which is prohibited, new psychotherapy is allowed during the study. Any change in existing therapy or new therapy must be documented on the concomitant therapies form.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; nonpharmacologic therapies, such as psychotherapy, electrical stimulation, acupuncture, special diets, and exercise regimens) different from the study drug must be recorded in the eCRF. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a subject into the study, unless permitted by protocol (eg, adjustment of blood pressure medications.

Rescue Medications

Rescue medications will not be supplied by the sponsor. In case of treatment-emergent adverse events that cannot be resolved by stopping further administration of intranasal esketamine/placebo, the following rescue medications may be considered:

- For agitation or anxiety: As required, midazolam (maximum dose 2.5 mg orally or IM) or short acting benzodiazepine (eg, alprazolam, clorazepate, triazolam, lorazepam and temazepam)
- For nausea: As required, ondansetron 8 mg sublingually, metoclopramide (10 mg orally or IV or IM) or dimenhydrinate (25 to 50 mg, IV or IM)
- Unless clinically indicated, it is recommended that transient increases in blood pressure not be treated, as the blood pressure typically returns to predose values in 2 hours. The effect of any treatment may result in hypotension.

Prohibited Medications

A list of prohibited medications is provided in Section 4.3 and Attachment 1 as general guidance for the investigator (but is not all inclusive).

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 and pharmacogenomics[α], health economic, and safety measurements applicable to this study.

[α] Not applicable to China

With the exception of postdose assessments, visit-specific subject-reported outcomes assessments should be conducted or completed before any tests, procedures, or other consultations for that clinic visit to prevent influencing subject perceptions. A recommended order of study procedures will be provided to sites as a separate document.

If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: Collection of urine samples for Clinical laboratory assessments and blood samples for PK assessments should be kept as close to the specified time as possible. Other measurements may be done earlier than specified timepoints if needed. Actual dates and times of assessments will be recorded in the source documentation and eCRF.

The approximate total blood volume to be collected will be 50 mL from each Chinese subject (34 mL for eligibility and safety, and 16 mL for PK) and 108.5 mL from each non-Chinese subject (34 mL for eligibility and safety, and 74.5 mL for biomarker) (Table 2). The biomarker blood sample including protein, DNA and RNA will only be collected from those subjects who give separate written informed consent to participate in the biomarker, pharmacogenomic (DNA) and expression (RNA) component of the study. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or as required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

Table 2: Volume of Blood to Be Collected from Each Subject

Type of Sample	Volume per Sample (mL)	No. of Samples per Subject	Total Volume of Blood (mL) [a]
Screening/Prospective Observational Phase			
Serum chemistry [b]	2.5	1	2.5
TSH	3.5	1	3.5
Hematology	2	1	2
Biomarker: protein [e]	10	1	10
Biomarker: DNA [e]	6	1	6
Biomarker: RNA [e]	2.5	1	2.5
Tricyclic Antidepressant Blood level [c]	9	1	9
FT4 [d]	3.5	1	3.5
Double-blind Treatment Phase			
Serum chemistry	2.5	2	5
Hematology	2	2	4
Pharmacokinetics [f]	4	4	16
Biomarker: protein [e]	10	3	30
Biomarker: DNA [e]	6	1	6
Biomarker: RNA [e]	2.5	3	7.5
Follow-up Phase			
Serum chemistry	2.5	1	2.5
Hematology	2	1	2
Biomarker: protein [e]	10	1	10
Biomarker: RNA [e]	2.5	1	2.5
Approximate volume of blood collected during the study			**124.5 mL [g]**

Abbreviations: DNA, deoxyribonucleic acid; RNA: Ribonucleic Acid; FT4, free thyroxine; TSH, thyroid-stimulating hormone

a. Calculated as number of samples multiplied by amount of blood per sample.
b. Serum chemistry includes serum β-hCG pregnancy tests (for women of childbearing potential) and lipid panel.
c. For specific tricyclic antidepressants which are being taken at a dose below the MGH-ATRQ minimum therapeutic dose, a blood level that is within therapeutic (antidepressant) range, is acceptable to establish the adequacy of the antidepressant treatment.
d. For any subject (regardless of thyroid history), if the TSH value is out of range, a free thyroxine (FT4) will be conducted.
e. Only for subject who has consented to participate in the biomarker, pharmacogenomic (DNA) and expression (RNA) component of the study. This applies to US sites only, as not applicable for China.
f. Only for Chinese subjects.
g. 50 mL for Chinese subjects and 108.5 mL for non-Chinese subjects.

Note: An indwelling IV cannula may be used for blood sample collection.
Note: Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples.

9.1.2. Screening/Prospective Observational Phase

Prior to conducting any study procedure, the investigator (or designated study personnel) will review and explain the written ICF to each subject. After signing the ICF, subjects who are 18 (or older if the minimum legal age of consent in the country in which the study is taking place is >18) to 64 years of age (inclusive) will be screened to determine eligibility for study participation (please refer to the study entry criteria listed in Section 4).

Subjects must meet DSM-5 diagnostic criteria for recurrent MDD or single-episode MDD, without psychotic features, based upon clinical assessment and confirmed by the MINI. An independent blinded rater will conduct the MADRS at screening as well as confirming the diagnosis and the validity of the major depressive episode.

Treatment-resistant depression is defined as a lack of clinically meaningful improvement after treatment with at least 2 different antidepressant agents prescribed in adequate dose for adequate duration. At the start of the screening/prospective observational phase, subjects must have had non-response (ie, lack of clinically meaningful improvement, defined as ≤25% improvement) to ≥1 but ≤5 (if current episode is >2 years or undefinable, upper limit is applicable to only the last 2 years) oral antidepressant treatments taken at adequate dosage and for adequate duration, as assessed using the MGH-ATRQ and documented by records (eg, medical/ pharmacy/prescription records or a letter from treating physician, etc.) for the current episode of depression. In addition, at the start of the screening/prospective observational phase, the subject is taking a different oral antidepressant treatment (on the MGH-ATRQ) for at least the previous 2 weeks at or above the minimum therapeutic dose. This antidepressant treatment, as well as any other ongoing medications being taken for depression (including adjunctive/augmentation therapies), will continue from the start of Week 1 through the end of Week 4 of the screening/prospective observational phase to confirm non-response prospectively. Dose adjustment is permitted per clinical judgment, but the oral antidepressant treatment is to remain at or above the minimum therapeutic dose (per the MGH-ATRQ) through the end of Week 4. Antidepressant treatment adherence will be assessed using the PAQ. Subjects who report missing ≥4 days of antidepressant medication treatment(s) in the prior 2-week period will be considered as screen failed due to inadequate adherence.

After 4 weeks, subjects who are non-responders to the current oral antidepressant treatment (as assessed by independent, remote raters) may be eligible to proceed to the double-blind treatment phase. Non-response at the end of the screening/prospective observational phase is defined as ≤25% improvement in the MADRS total score from Week 1 to Week 4 and a MADRS total score of ≥28 on Week 2 and Week 4.

Eligible subjects who are entering the double-blind treatment phase will discontinue all current medication(s) being taken for depression (including adjunctive/augmentative therapies), and any other prohibited psychotropic medications (including adjunctive atypical antipsychotics). Subjects taking benzodiazepines (at dosages equal to or less than the equivalent of 6 mg/day of lorazepam) and/or permitted nonbenzodiazepine sleep medications (eg, zolpidem, zaleplon, eszopiclone and ramelteon) during the screening/prospective observational phase can continue these medications during the treatment phase. No dose increases beyond the equivalent of 6 mg/day of lorazepam or new benzodiazepine medications are permitted during the screening/prospective observational phase. If clinically indicated, a subject's current antidepressant treatment(s) may be tapered and discontinued over an additional, optional period of up to 3 weeks per the local prescribing information or clinical judgment or discontinued and switched directly to one of the four new oral antidepressant medications on Day 1 of the double-blind treatment phase, per clinical judgment.

All other subjects who do not proceed to the double-blind treatment phase will end study participation at this time. No further study visits or follow-up is required.

Optional Antidepressant Taper Period

Since all non-responder subjects will be starting a new oral antidepressant during the double-blind treatment phase, no washout or drug-free period is required after discontinuing the current antidepressant treatment. However, an additional, optional period of up to 3 weeks is permitted to taper and discontinue the current antidepressant treatment(s) after completion of the Week 4 assessments, per the local prescribing information or clinical judgment. Subjects who do not require a taper are eligible to immediately proceed to the double-blind treatment phase.

The taper period should not start until after the completion of 4 weeks of prospective antidepressant treatment and assessment of the antidepressant treatment response.

9.1.3. Double-Blind Treatment Phase

During this phase, all subjects will self-administer the intranasal study medication esketamine (56 mg or 84 mg) or placebo, at treatment sessions occurring twice a week for 4 weeks at the study site, using a flexible dosing regimen. Treatment is assigned by the Interactive Web Response System (IWRS). Table 1 in Section 6.2 describes how each treatment session will be administered in the double-blind treatment phase.

Approximately 234 eligible subjects (210 Chinese subjects, 24 non-Chinese subjects) with TRD, will be randomly assigned at a 1:1 ratio (n = 117 subjects per treatment arm, with approximately 105 Chinese subjects per arm) to receive double-blind treatment with either intranasal esketamine or intranasal placebo. The intranasal treatment sessions (esketamine 56 mg, esketamine 84 mg or placebo) will occur twice per week for 4 weeks as a flexible dose regimen at the study site.

In addition, all subjects will simultaneously initiate a new, open-label oral antidepressant (please refer to Section 6, Dosage and Administration), on Day 1, that will be taken daily for the duration of the double-blind treatment phase. The assigned oral antidepressant will be 1 of 4 oral antidepressant medications (duloxetine, escitalopram, sertraline, or venlafaxine XR). The antidepressant medication assigned by the investigator (based on review of the MGH-ATRQ and relevant prior antidepressant treatment information) will be one that the subject has not previously had a non-response to in the current depressive episode, has not been previously intolerant to (lifetime), and is available in the participating country.

Dosing of the oral antidepressant will begin on Day 1 and follow a protocol specific titration schedule (Attachment 3). The use of the titration schedule provided is mandatory. Doses are not to exceed the maximum dose defined in the titration schedule. If higher doses are not tolerated, a down-titration is permitted based on clinical judgment.

Subjects who were taking benzodiazepines (at dosages equal to or less than the equivalent of 6 mg/day of lorazepam) and/or permitted non-benzodiazepine sleep medications (eg, zolpidem, zaleplon, eszopiclone and ramelteon) during the screening/prospective observational phase can continue these medications during the double-blind treatment phase. No dose increases beyond the equivalent of 6 mg/day of lorazepam or new benzodiazepine medications are permitted during the

double-blind treatment phase, with the exception of the use of permitted benzodiazepine rescue medication (eg, alprazolam, clorazepate, triazolam, lorazepam and temazepam).

For information obtained via telephone contact, written documentation of the communication must be available for review in the source documents. During telephone contact visits with the subject by site personnel, adverse event and concomitant therapy information will be obtained. In addition, specified clinician-administered assessments will be performed by appropriately qualified staff.

At the end of the double-blind treatment phase, subjects will proceed into the follow-up phase.

Early Withdrawal

If a subject withdraws from the study before the end of the double-blind treatment phase for reasons other than withdrawal of consent, an Early Withdrawal visit should be conducted within 1 week of the date of discontinuation, followed by the follow-up phase. If the Early Withdrawal visit occurs on the same day as a scheduled visit, the early withdrawal visit can be performed on the same day and duplicate assessments are not required.

Further clinical/standard of care for the treatment of depression will be arranged by the study investigator and/or the subject's treating physician. The study investigator and/or treating physician will determine whether or not the current oral antidepressant medication will continue.

9.1.4. Follow-up Phase

The follow-up phase will include all subjects who received at least 1 dose of intranasal study medication in the double-blind treatment phase. No intranasal study medication will be administered during this phase.

At the start of the follow-up phase, further clinical/standard of care for the treatment of depression will be arranged by the study investigator and/or the subject's treating physician and medication changes are permitted. The decision to continue the antidepressant will be at the discretion of the investigator. If the subject continues to receive the same antidepressant medication for the duration of the follow-up phase, then the antidepressant will be sourced by the sponsor.

This follow-up phase will provide additional information required to assess the course of the subject's major depressive episode over an 8-week period. Safety and tolerability, including potential withdrawal symptoms, following discontinuation of intranasal esketamine will be assessed.

The follow-up phase is completed at the end of the 8-week period or when a subject meets criteria below for relapse (in remitters and responders), whichever occurs earlier.

Relapse is defined as any of the following:

- MADRS total score ≥22 for 2 consecutive assessments separated by 5 to 15 days. The date of the second MADRS assessment will be used for the date of relapse.

- Hospitalization for worsening depression or any other clinically relevant event determined per clinical judgment to be suggestive of a relapse of depressive illness such as suicide attempt, completed suicide, or hospitalization for suicide prevention. If hospitalized for any of these events, the start date of hospitalization will be used for the date of relapse. Otherwise the date of the event will be used if the subject is not hospitalized.
- In case more than one relapse criteria are met, the earlier date will be defined as the date of relapse for this subject.

The total duration of a subject's study participation will be up to 19-weeks (including an optional 3-week taper period) for subjects completing the 8-week follow-up phase.

Clinic visits and remote assessment visits will be performed as specified in the Time and Events Schedule.

Telephone contact or clinic visit will be made to determine safety and efficacy assessments and any reported adverse events every week for up to 8 weeks after the last dose of study drug, unless the subject has died, is lost to follow-up, or has withdrawn consent. If the information is obtained via telephone contact, written documentation of the communication must be available for review in the source documents. If the subject has died, the date and cause of death will be collected and document on the CRF.

Any clinically significant abnormalities persisting at the End of the Study/Early Withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached. All adverse events and special reporting situations, whether serious or non-serious, will be reported until completion of the subject's last study-related procedure.

9.2. Efficacy Evaluations

9.2.1. Evaluations

It is recommended that the various subject-reported outcome assessments be completed prior to other procedures.

9.2.1.1. Primary Efficacy Evaluation

The primary efficacy evaluation will be the MADRS total score. The MADRS will be performed by independent remote raters during the study. The Structured Interview Guide for the Montgomery Asberg Depression Rating Scale (SIGMA: Williams 2008)[76] will be used for each administration.

The MADRS is a clinician-rated scale designed to measure depression severity and detects changes due to antidepressant treatment. The scale consists of 10 items, each of which is scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), for a total possible score of 60. Higher scores represent a more severe condition. The MADRS evaluates apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, inability to feel (interest level), pessimistic thoughts, and suicidal thoughts. The test exhibits high inter-rater reliability. The MADRS has been validated in Chinese subjects with MDD.[81]

The typical recall period for the MADRS is 7 days and will be used for the primary efficacy evaluation.

9.2.1.2. Key Secondary Efficacy Evaluation

Montgomery-Asberg Depression Rating Scale (MADRS) Total Score

The MADRS will also be administered using a modified recall period of 24 hours for the key secondary efficacy evaluation related to change from baseline to 24 hours. The feasibility of this shortened recall period has been confirmed with patients, and physicians, and there are data supporting the psychometric properties of this shortened recall period (data on file).

Sheehan Disability Scale (SDS)

The SDS will be used to assess the secondary objective of functional impact and associated disability. The SDS is a subject-reported outcome measure that consists of a 5-item questionnaire which has been widely used and accepted for assessment of functional impairment and associated disability.[41,67] The first three items assess disruption of (1) work/school, (2) social life, and (3) family life/home responsibilities using a 0-10 rating scale. The score for the first three items are summed to create a total score of 0-30 where a higher score indicates greater impairment. It also has one item on days lost from school or work and one item on days when underproductive. The recall period for this study is 7 days.

9.2.1.3. Other Secondary Efficacy Evaluations

9.2.1.3.1. Other Secondary Efficacy Evaluations (Clinician-completed)

Clinical Global Impression–Severity (CGI-S)

The CGI-S provides an overall clinician-determined summary measure of the severity of the subject's illness that takes into account all available information, including knowledge of the subject's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the subject's ability to function.[27] The CGI-S evaluates the severity of psychopathology on a scale of 0 to 7. Considering total clinical experience, a subject is assessed on severity of mental illness at the time of rating according to: 0=not assessed; 1=normal (not at all ill); 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among the most extremely ill patients. The CGI-S permits a global evaluation of the subject's condition at a given time.

9.2.1.3.2. Other Secondary Efficacy Evaluations (Patient-reported Outcomes)

Generalized Anxiety Disorder (GAD-7)

The 7-item subject-reported GAD-7 will be used to measure the secondary objective of symptoms of anxiety. The GAD-7 is a brief and validated measure of overall anxiety. Each item is rated on a 4-point scale (0=not at all; 1=several days; 2=more than half the days; 3=nearly every day).[69] Item responses are summed to yield a total score (range of 0 to 21), with higher scores indicating more anxiety. The recall period is 2 weeks.

EuroQol-5 dimension-5 level (EQ-5D-5L)

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

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

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

9.3. Pharmacokinetics (Chinese subjects only)

Whole blood samples will be used to evaluate the PK of esketamine (JNJ-54135419). 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 blood samples. Subject confidentiality will be maintained.

9.3.1. Evaluations

Venous blood samples of approximately 4 mL will be collected from Chinese subjects at all clinical sites, for measurement of plasma concentrations of esketamine (JNJ-54135419), (and other metabolites, if warranted), at the time points specified in the Time and Events Schedule. The exact dates and times of PK blood sampling must be recorded.

9.3.2. Analytical Procedures

Pharmacokinetics

Serial pharmacokinetic blood samples (4 mL, each) will be collected from Chinese subjects at all study sites, at the time points specified in the Time and Events Schedule. Concentration time data will allow estimation of individual PK parameters for esketamine using a population PK modeling approach. The exact dates and times of PK blood sampling must be recorded. Plasma samples will be analyzed to determine concentrations of esketamine using a validated, specific, and sensitive liquid chromatography-tandem 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 other analytes (eg, circulating metabolites or denatonium) 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 clinical study report as an appendix.

9.3.3. Pharmacokinetic Parameters

The plasma concentration-time data of esketamine will be analyzed using population PK modeling. Typical population values of basic PK parameters (eg, esketamine clearance and distribution volumes) will be estimated together with the inter-individual variability. Effects of subject demographics, laboratory parameter values, and other covariates on the PK of esketamine will be explored. The results of the population PK analyses may be reported separately.

9.4. Biomarker, Pharmacogenomic (DNA), and Expression (RNA) Evaluations[α]

During the study, blood will be collected for the assessment of biomarkers at the time points indicated in the Time and Events schedule. The biomarker blood samples should be collected prior to dosing. It is preferred that subjects adhere to a low-fat diet on the day of sample collection.

In blood, biomarkers (protein, metabolite, and ribonucleic acid [RNA]) related to (but not limited to) the immune system activity, hypothalamus pituitary adrenal (HPA) axis activation, neurotrophic factors, and metabolic factors will be investigated. 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.

The biomarker data obtained from this study may also be included in an ongoing cross-study analysis to investigate the relationship between depression severity and phenotypes and biomarkers.

Blood samples for DNA analyses will be collected at the time points indicated in the Time and Events Schedule for the assessment of genetic and epigenetic variation in genes in pathways relevant to depression (eg, HPA axis, inflammation, growth factors, monoamine transporters, ion channels, and circadian rhythm).

Genotyping will be conducted only on the screening sample; pharmacogenomic and epigenetic evaluations may be performed on any/all collected samples.

DNA samples will be used for research related to esketamine, oral antidepressants, TRD, or MDD. They may also be used to develop tests/assays related to esketamine, oral antidepressants, TRD, or MDD. Pharmacogenomic research may consist of the analysis of 1 or more candidate genes or of the analysis of genetic markers throughout the genome (as appropriate) in relation to esketamine, oral antidepressants, TRD, or MDD clinical endpoints.

Further information regarding handling, shipment, and labeling of biological samples will be provided in a separate laboratory manual.

[α] Not applicable to China

9.5. Safety Evaluations

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.

There may be instances where a subject has started a scheduled clinic visit in which an intranasal treatment session is planned, but due to predose vital sign measurements (eg, blood pressure value), a decision has been made to postpone/delay the intranasal treatment session within the visit window permitted per protocol. In such cases, all time points (including predose) of the following assessments must be repeated on the actual intranasal treatment session day: vital sign (ie, blood pressure, pulse, respiratory rate, and temperature), 12-lead ECG, C-SSRS (since last visit), pulse oximetry, and CADSS.

Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

TEAEs of special interest will be examined separately (please refer to Section 3.2.6, Safety Evaluations and Section 11.6, Safety Analyses).

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 report, 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.

The use of local laboratories is allowed in cases where initiation of treatment or safety follow-up is time-critical and the central laboratory results are not expected to be available before the need to begin dosing or if actions need to be taken for safety reasons.

The following tests will be performed by the central laboratory, unless noted otherwise:

- 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)
  -alkaline phosphatase
  -creatine phosphokinase (CPK)
  -calcium
  -phosphate
  -albumin
  -total protein
  -total bilirubin

- Urinalysis

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

  Sediment (if dipstick result is abnormal)
  -red blood cells
  -white blood cells
  -epithelial cells
  -crystals
  -casts
  -bacteria

  If dipstick result is abnormal, flow cytometry or microscopy 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.

The following tests will be done at time points specified in the Time and Events Schedule or as required based on subject status (noted below):

- Serum and urine pregnancy testing (for women of childbearing potential only)
- Urine Drug Screen: barbiturates, methadone, opiates, cocaine, cannabinoids (cannabinoids are only tested at Day 1 predose), phencyclidine, and amphetamine
  - at the start of the Screening/Prospective Observational Phase: barbiturates, methadone, opiates, cocaine, phencyclidine, and amphetamine
  - on Day 1 of the Double-blind Treatment Phase prior to randomization: cannabinoids, methadone, opiates, cocaine, and amphetamine
  - on Day 15 and 25 of the Double-blind Treatment Phase: cocaine
- Alcohol breath test
- Thyroid-stimulating hormone (TSH)
- Free thyroxine (FT4), only if required for abnormal TSH (refer to Inclusion criteria)

- Calculation of creatinine clearance
- Glycated hemoglobin (HbA1c) test
- A serum follicle stimulating hormone (FSH) level test, only if required for documentation that a female subject is not of childbearing potential (refer to Inclusion Criteria No. 8)

Single, 12-Lead ECG

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

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

A subject must be discontinued from at any time point after baseline (Day 1, predose) if:

- QTcF change from baseline is ≥60 msec AND QTcF >480 msec, or
- QTCF >500 msec.

Vital Signs (temperature, pulse/heart rate, respiratory rate, blood pressure)

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

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

For further details regarding blood pressure, please see Guidance on Blood Pressure Monitoring on Intranasal Dosing Days (Section 6.4).

Tympanic temperature is recommended.

An automated device will be used for measurement of respiratory rate.

Pulse Oximetry

Pulse oximetry will be used to measure arterial oxygen saturation. On each dosing day, the device will be attached to the finger, toe, or ear before the first nasal spray and then, after the first spray it will be monitored and documented. Any arterial oxygen saturation (SpO_2) <93% should be confirmed by an additional measurement on another part of the body.

On intranasal treatment session days, pulse oximetry will be recorded every 15 minutes from predose to t=1.5 hours postdose. If oxygen saturation levels are <93% at any time during the 1.5-hour postdose interval, pulse oximetry will be recorded every 5 minutes until levels return to ≥93% or until the subject is referred for appropriate medical care, if clinically indicated.

Physical Examination, Height, Body Weight

Physical examinations, body weight, and height will be performed/ measured as per the Time and Events Schedule.

Nasal Examinations

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 will be graded as follows: Absent, mild, moderate, or severe.

C-SSRS

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

The C-SSRS is a low-burden measure of the spectrum of suicidal ideation and behavior that was developed in the National Institute of Mental Health Treatment of Adolescent Suicide Attempters Study to assess severity and track suicidal events through any treatment.[54] It is a clinical interview providing a summary of both suicidal ideation and behavior that can be administered during any evaluation or risk assessment to identify the level and type of suicidality present. The C-SSRS can also be used during treatment to monitor for clinical worsening.

Two versions of the C-SSRS will be used in this study, the Baseline/Screening version, and the Since Last Visit version. The Baseline/Screening version of the C-SSRS will be used in the screening/prospective observational phase. In this version, suicidal ideation will be assessed at 2 time points (“lifetime” and “in the past 6 months”) and suicidal behavior will be assessed at 2 time points (“lifetime” and “in the past year”). All subsequent C-SSRS assessments in this study will use the Since Last Visit version, which will assess suicidal ideation and behavior since the subject’s last visit.

CADSS

The CADSS is an instrument for the measurement of present-state dissociative symptoms,[3] and will be administered to assess treatment-emergent dissociative symptoms.[3]

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). Participant’s responses are coded on a 5-point scale (0=not at all through to 4=extremely). CADSS has excellent inter-rater reliability and internal consistency.

PWC-20

The PWC-20 will be administered to assess potential withdrawal symptoms following cessation of intranasal esketamine treatment. An assessment will be performed on Day 25 to establish a baseline prior to discontinuation of intranasal esketamine treatment. In order to better assess potential withdrawal symptoms from the intranasal medication it is recommended that the oral antidepressant medication be continued for at least the first 2 weeks of the follow up phase unless determined as not clinically appropriate.

The PWC-20 is a 20-item simple and accurate method to assess potential development of discontinuation symptoms after stopping of study drug. The PWC-20 is a reliable and sensitive instrument for the assessment of discontinuation symptoms.[61] Discontinuation symptoms occur early and disappear rather swiftly, depending upon speed of taper, daily medication dose, and drug elimination half-life.

9.6. Other Evaluations

MINI

Subjects will undergo MINI (a brief, structured diagnostic interview) to confirm the diagnosis of MDD and to determine if there are other psychiatric conditions present. It has an administration time of approximately 15 minutes.

MGH-ATRQ

The MGH-ATRQ is used to determine treatment resistance in MDD.[14]

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

Clinical Validation Inventory for Study Admission

Independent psychiatrists/psychologists will perform the Clinical Validation Inventory for Study Admission (C-VISA) in the screening/prospective observational phase for all subjects to confirm diagnosis of depression and eligibility for the study.[70]

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

PAQ

Subjects' adherence to their oral antidepressant treatment regimen during the screening/prospective observational phase will be assessed using the PAQ. It is a brief, 2-item subject-report outcome measure that was developed at the University of Texas Southwestern Medical Center to assess how often the subject has taken, and whether he or she has made any changes to his/her antidepressant treatment regimen in the last 2 weeks. The total score is based on the response selected to Question 1 and is interpreted as 0 to 1 =adherent and 2 or more=nonadherent.

9.7. 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 the double-blind treatment phase of the study if he or she has completed the MADRS assessment at the end of the 4-week double-blind treatment phase (ie, Day 28 MADRS).

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 double-blind treatment phase of the study.

Subjects who enter the follow-up phase will be considered to have completed this phase of the study if he or she has completed the MADRS assessment at Week 8 of the follow-up phase, or when the subject meets criteria for relapse (in remitters and responders), whichever occurs earlier.

10.2. Discontinuation of Study Treatment or Withdrawal from the Study

Discontinuation of Study Treatment

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

A subject's study treatment must be discontinued if:

- The investigator believes that for safety reasons or tolerability reasons (eg, adverse event) it is in the best interest of the subject to discontinue study treatment
- The subject becomes pregnant

If a subject discontinues study treatment for any reason before the end of the double-blind phase (including either treatment with intranasal study drug or oral antidepressant), an early withdrawal visit should be conducted within 1 week of the date of discontinuation, followed by progression to

the 8-week follow-up phase. End-of-treatment assessments should be obtained during the early withdrawal visit, and scheduled assessments should be continued during the follow-up phase.

Withdrawal from the Study

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

- Lost to follow-up
- Withdrawal of consent (Note: See "Withdraw of Consent" section below; this should only be selected as a reason for withdrawal if the subject does not agree to any further study assessments or procedures. If the subject is agreeable to participating in the Early Withdrawal visit and the follow-up phase, another reason for withdrawal should be selected.)
- Violation of protocol procedures (determined on a case-by-case basis)
- Blind is broken (double-blind treatment phase)
- Lack of efficacy
- The investigator or sponsor believes (eg, that for safety or tolerability reasons such as an adverse event) it is in the best interest of the subject to discontinue the study. See also guidance on blood pressure monitoring on intranasal dosing days (Section 6.4).
- At any time point after baseline (Day 1, predose), the subject has a:
  - QTcF change from baseline ≥60 msec AND QTcF >480 msec, or
  - QTcF >500 msec.
- Subject becomes pregnant
- Death

If the subject withdraws from the study before the end of the double-blind treatment phase, an Early Withdrawal visit is to be performed, followed by the follow-up phase.

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

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

Withdrawal of Consent

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

Subjects who wish to withdraw from the study should be asked if they are agreeable to continue to an early withdrawal visit (if withdrawing from the double-blind treatment phase) and the follow-up phase, or to be contacted to collect follow-up information. Subjects who are not agreeable to follow-up contact will be withdrawn from the study as "withdrawal of consent." Subjects who no longer wish to take study drug but agree to provide follow-up information will be withdrawn from the double-blind treatment phase with the reason noted as "Other" and will specify the reason why.

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

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

10.3. Withdrawal from the Use of Samples in Future Research

The subject may withdraw consent for use of samples for research (refer to Section 16.2.5, Long Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

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 Statistical Analysis Plan.

11.1. Subject Information

For all subjects who receive at least 1 dose of study drug, descriptive statistics will be provided.

The primary efficacy and safety analysis sets are defined below:

Full Analysis Set: All randomized subjects who receive at least 1 dose of intranasal study medication and 1 dose of oral antidepressant in the double-blind treatment phase.

Safety Analysis Set: All randomized subjects who receive at least 1 dose of intranasal study medication or 1 dose of oral antidepressant in the double-blind treatment phase.

The efficacy and safety analyses in the double-blind treatment phase will be based on the full analysis set and safety analysis set, respectively. Follow-up analysis set which includes all subjects who enter follow-up phase will be used for both efficacy and safety analyses in the follow-up phase.

Subjects who discontinue treatment will continue to the follow-up phase.

Subjects who discontinue treatment but continue with the study assessments will be included in the full analysis, safety analysis and follow-up analysis sets and analyzed separately.

11.2. Sample Size Determination

Assuming a treatment difference for the double-blind phase of 6.5 points in MADRS total score between esketamine plus oral antidepressant compared with oral antidepressant plus intranasal placebo at the Week 4 endpoint, a standard deviation of 12, a one-sided significance level of 0.025, and a drop-out rate of 25%, approximately 117 subjects will be randomized to each treatment arm to achieve greater than 90% power, and a sample size of 105 Chinese subjects per treatment arm (total n = 210) plus 12 non-Chinese subjects per treatment arm (total of n = 24) will be included. The treatment difference and standard deviation used in this calculation were based on results from Panel A of the ESKETINTRD2003 study[10] and based on clinical judgment.

11.3. Efficacy Analyses

Efficacy analyses will be performed on the full analysis set, which will include all randomized subjects who receive at least 1 dose of intranasal study drug and 1 dose of oral antidepressant medication, in the double-blind treatment phase.

Primary Endpoint

The primary estimand, the main clinical quantity of interest to be estimated in the study, is defined by the following 4 components:

- Population: subjects with treatment-resistant depression;
- Variable: change from Day 1 to end of 4-week double-blind treatment phase;
- Intervention Effect: the effect of the initially randomized treatment together with the oral antidepressant medication that would have been observed had all subjects remained on their treatment throughout the double-blind treatment phase;
- Summary Measure: the difference in variable means.

The primary analysis will be based on the full analysis set and the MADRS total scores collected during the double-blind treatment phase.

For the primary efficacy analysis, change from baseline in MADRS total score at Week 4 in the double-blind treatment phase will be analyzed using a mixed-effects model for repeated measures (MMRM). The model will include baseline MADRS total score as a covariate, and treatment, country, class of antidepressant (Serotonin and Norepinephrine Reuptake Inhibitors [SNRI] or Selective Serotonin Reuptake Inhibitor [SSRI]), day, and day-by-treatment interaction as fixed effects. Comparison of the esketamine plus oral antidepressant arm to the active comparator (oral antidepressant plus intranasal placebo) arm will be performed using the appropriate contrast.

Missing data will be closely monitored and additional sensitivity analysis for the primary efficacy endpoint to assess the robustness of the results to missing data might be performed. The detailed assumptions and methods will be provided in the statistical analysis plan (SAP), if necessary.

Secondary Endpoints

For the analysis of the first of the two key secondary efficacy endpoints, change from baseline in MADRS total score at 24 hours post first dose (Day 2), will be analyzed using the same model described above for the MADRS total score at Week 4 in the double-blind treatment phase.

The second key efficacy endpoint, change from baseline in SDS total score at Week 4 in the double-blind treatment phase, will be analyzed using the same models described above for the MADRS total score.

To strongly control Type I error across the primary and the two key secondary efficacy endpoints, a fixed sequence approach[15,16] will be applied to adjust for multiplicity. The hypotheses will be tested sequentially in the following order:

- Change in MADRS total score at the end of the 4-week double-blind treatment phase
- Change in MADRS total score at 24 hours post first dose
- Change in SDS total score

Further details of this approach will be provided in the SAP.

The proportion of subjects showing onset of clinical response by Day 2 (in the event that no MADRS was collected on Day 2, a MADRS collected on Day 3 could be used) that is maintained for the duration of the double-blind treatment phase (≥50% reduction in MADRS total score by the second day after taking the first dose of double-blind medication that continued through the end of the double-blind phase) in esketamine arm will be compared with the active comparator using a Cochran-Mantel-Haenszel chi-square test adjusting for country and class of antidepressant (SNRI or SSRI). Subjects who discontinued the study prior to the end of the double-blind treatment phase will not be considered to have maintained clinical response.

Response and remission rates will be summarized at each visit.

The proportion of subjects who remain in remission through to the end of the follow-up phase will be presented.

Change from baseline in GAD-7 total scores at the end of the 4-week double-blind treatment phase will be analyzed using an ANCOVA model, with treatment, country and class of antidepressant (SNRI or SSRI) as factors, and the respective baseline score as the covariate.

Ranks of change from baseline in CGI-S scores during the 4-week double-blind treatment phase will be analyzed using the MMRM for repeat measures, as described for the MADRS and SDS total scores. Additional analysis method for CGI-S will be used if necessary and the details will be provided in the SAP.

Dimension scores of EQ-5D-5L descriptive system, health status index, and the overall health status score will be summarized over time.

Additionally, scores of all efficacy endpoints will be summarized for all visits in the double-blind period. Summaries will be provided to show consistency of effect among relevant subgroups (eg, antidepressant class SSRI [escitalopram, sertraline] and SNRI [duloxetine, venlafaxine]).

For subjects who receive esketamine during the double-blind treatment phase, the proportion of subjects who relapse during the follow-up phase will be summarized separately for subjects who are remitters (MADRS ≤12 at the end of the double-blind phase) and for subjects who are responders but not remitters (≥50% reduction in MADRS total score, but MADRS >12 at the end of the double-blind phase). In addition, the time to relapse during the follow-up phase will be estimated by the Kaplan-Meier method separately for subjects who are remitters, and subjects who are responders but not remitters. Descriptive statistics (number of relapses, number of censored subjects, and median, 25^{th,} and 75th percentile of time to relapse, if estimable) will be provided.

11.4. Pharmacokinetic Analyses

Plasma esketamine concentrations will be listed for all Chinese subjects. The plasma concentration-time data of esketamine will be analyzed using population PK modeling. Data may be combined with those of other selected studies to support a relevant structural model. Typical population values of basic PK parameters will be estimated together with the inter-individual variability. Additional pharmacokinetic parameters, such as post hoc estimates of C_{max} and AUC, may be calculated if deemed appropriate. Effects of subject demographics, laboratory parameter values, and other covariates on the PK of esketamine will be explored. The results of the population PK analyses may be reported separately.

11.5. Biomarker and Pharmacogenomic Analyses[α]

Baseline biomarker values and changes from baseline biomarker values to the time points specified in the Time and Events Schedule will be summarized if available number is sufficient for analyses. Exploratory analyses may include comparison of biomarker measures between the treatment groups and correlation with baseline and change from baseline biomarker values in the efficacy and other measures. Additional exploratory analyses may also include relationship of baseline and change from baseline in biomarker measures to clinical response, maintenance/stabilization of response, relapse, and non-response.

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

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

[α] Not applicable to China

11.6. Safety Analyses

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

Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events (TEAEs) are adverse events with onset during the treatment phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported adverse events 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 occurring in the follow-up phase will be summarized separately.

TEAEs of special interest will be examined separately (please refer to Section 3.2.6) AEs of special interest will be further listed in the SAP.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an adverse event, or who experience a severe or a serious adverse event.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and at each scheduled time point in each phase of the study. Changes from baseline results will be presented. Frequency tabulations of the abnormalities will be provided. Listings of subjects with laboratory results outside the reference ranges and markedly abnormal results will also be provided.

ECG

The effects on cardiovascular variables will be evaluated by means of descriptive statistics and frequency tabulations. These tables will include observed values and change 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 QTc interval using the following correction methods: QT corrected according to Bazett's formula (QTcB) and QTcF.[2,32,64] Descriptive statistics of QTc intervals and changes from double-blind baseline will be summarized at each scheduled time point. The percentage of subjects with QTc interval >450 msec, >480 msec, or >500 msec will be summarized, as will the percentage of subjects with QTc interval increases from baseline <30 msec, 30-60 msec, or >60 msec.

All important 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

Descriptive statistics of temperature, pulse/heart rate, respiratory rate, pulse oximetry, and blood pressure (systolic and diastolic) (supine) 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

Changes in findings from the baseline nasal examination (including the upper respiratory tract/throat) will be listed by treatment group. Examinations will provide ratings (absent, mild, moderate, or severe) that are based on a visual inspection of the nostrils, nasal mucosa, and throat for nasal erythema, rhinorrhea, rhinitis, capillary/blood vessel disruption and epistaxis. A shift table for changes from double-blind baseline in ratings for each examination will be presented by treatment group.

C-SSRS

Suicide-related thoughts and behaviors based on the C-SSRS will be summarized by treatment group in incidence and shift tables. Separate endpoints for suicidal ideation and suicidal behavior will be defined and summarized descriptively by treatment group. Missing scores will not be imputed.

CADSS

Descriptive statistics of each score and changes from predose will be summarized at each scheduled time point.

PWC-20

Descriptive statistics of each score and changes and/or percent changes from baseline will be summarized at each scheduled time point.

12. ADVERSE EVENT REPORTING

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

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

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

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

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

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

- Results in death
- Is life-threatening (for example, the subject was at risk of death at the time of the event. “Life threatening” 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 Reference Safety Information Section of the Investigator's Brochure.[34]

For duloxetine, escitalopram, sertraline, and venlafaxine XR, the expectedness of an adverse event will be determined by whether or not it is listed in the SmPC or US prescribing information.[17,18,21,22,65,66,71,72]

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 under Attribution Definitions in Section 12.1.2.

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 and/or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Inadvertent or accidental 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)

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 participants). Serious adverse events, including those spontaneously reported to the investigator, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments. Anticipated events will be recorded and reported as described in Attachment 4.

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 Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

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

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

12.3.2. Serious Adverse Events

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

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax).

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

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

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

- 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.
- For convenience the investigator may choose to hospitalize the subject at times during the treatment period.

The cause of death of a subject in a study, 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 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 by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.

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 on 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 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 on 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)

Intranasal Study Drug

Esketamine will be supplied 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 ethylenediaminetetraacetic acid (EDTA) and 1.5 mg/mL citric acid at a pH of 4.5 in water for injection. It is provided in a nasal spray pump, which delivers 16.14 mg esketamine hydrochloride (14 mg esketamine base) per 100 µL spray. Each individual nasal spray pump (device) contains a total of 28 mg (ie, 2 sprays).

The placebo solution will be supplied 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.

Esketamine and placebo will be manufactured and provided under the responsibility of the sponsor. Please refer to the Investigator's Brochure for a list of excipients.[34]

Oral Antidepressant Medications

Duloxetine

Duloxetine 30 mg will be obtained from commercial stock and provided under the responsibility of the sponsor. Please refer to the package insert/SmPC for the physical description and a list of excipients.[17,18]

Escitalopram

Escitalopram 10 mg will be obtained from commercial stock and provided under the responsibility of the sponsor. Please refer to the package insert/SmPC for the physical description and a list of excipients.[21,22]

Sertraline

Sertraline 50 mg will be obtained from commercial stock and provided under the responsibility of the sponsor. Please refer to the package insert/SmPC for the physical description and a list of excipients.[65,66]

Venlafaxine XR

Venlafaxine 75 mg will be obtained from commercial stock and provided under the responsibility of the sponsor. Please refer to the package insert/SmPC for the physical description and a list of excipients.[71,72]

14.2. Packaging

Intranasal Study Drug

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 200 µL. 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 Antidepressant Medication

Oral antidepressant tablets or capsules will remain in their commercial packaging.

If blisters are supplied, each blister will be packaged into a child-resistant dose pack to constitute a subject kit, labeled with a unique medication kit number. These will be labeled according to applicable regulatory requirements.

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.

Please refer to the pharmacy manual/study site investigational product manual and instructions for use documents for additional guidance on study drug preparation, handling, and storage.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study.

The dispensing of study drug to the subject, and the return of study drug from the subject (if applicable), must be documented on the drug accountability form. Subjects must be instructed to return all original containers, whether empty or containing study drug.

The study drug administered to the subject 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. Unused study drug, and study drug returned by the subject, must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study drug, or used returned study drug for destruction, will be documented on the investigational product destruction 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 investigational product destruction 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.

Whenever a subject brings his or her study drug to the study site for pill count (ie, compliance check), this is not seen as a return of supplies.

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:

- Practice intranasal devices
- Investigator's Brochure for esketamine
- Local prescribing information for oral antidepressant options in double-blind treatment phase
- Investigational Product (IP) Binder, including the IP Procedures Manual
- Laboratory manual and materials
- Clinician-administered and subject-reported outcome assessments:
  - Paper versions, as applicable
  - Electronic devices and associated materials
- IWRS Manual
- ECG equipment and associated materials (eg, manual)
- Instructions for Use documents (subject and healthcare provider versions) for intranasal study medication
- Rater qualifications/requirements for select clinician-administered assessments
- Device to measure respiratory rate
- Procedural documents for C-VISA
- Procedural documents for independent, remote rater interviews
- Guidance on recommended order of study procedures
- MGH-ATRQ Guidance document
- SmPCs of the active comparators: Duloxetine, escitalopram, sertraline, and venlafaxine XR

- Subject diary

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Clinical Study in Treatment-resistant Major Depression

Major depressive disorder is a common, severe, chronic, and often life-threatening illness. It is now the leading cause of disability worldwide. There is a clear need to develop novel and improved therapeutics for treatment-resistant depression.

Several clinical studies with esketamine, including the phase 2a global study ESKETINTRD2003, have shown robust antidepressant effects in patients with MDD, including TRD. Furthermore, these clinical studies have shown that esketamine is safe and well tolerated. Based on comparable pharmacokinetic profiles of intranasal esketamine between healthy Caucasian and Chinese subjects (ESKETINTRD1008)[8], and pharmacokinetic, safety and efficacy data from Caucasian subjects with TRD (ESKETINTRD2003)[10], we expect the selected dose of intranasal esketamine to be both efficacious and tolerated in the Chinese population of subjects with TRD.

Selection of Subjects

The primary aim of the study is to evaluate the efficacy of intranasal esketamine plus an oral antidepressant for the treatment of TRD. Thus, the study cannot be completed in healthy subjects.

Potential subjects will be fully informed of the risks and requirements of the study, and during the study subjects will be given any new information that may affect their decision to continue participation.

For eligibility, subjects must have had non-response to at least 1 prior antidepressant treatment and be currently taking an antidepressant treatment at the start of the screening/prospective observational phase that will be continued as prospective treatment in the screening/prospective observational phase. Only subjects with non-response to their current antidepressant treatment after 4 weeks of prospectively observed treatment (for a total duration of antidepressant treatment of at least 6 weeks by the end of the screening/prospective observational phase), will be eligible to proceed to the double-blind treatment phase, when all subjects will receive a new oral antidepressant in addition to intranasal esketamine or placebo. Subjects will receive 4 weeks of treatment in the double-blind treatment phase. The oral antidepressant initiated during the double-blind treatment phase will be continued for a further 8 weeks during the follow-up phase, to maintain the antidepressant effect.

Subjects will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

Justification for Using Placebo

Intranasal placebo is being used as a double-blind for intranasal esketamine to maintain study blinding. All subjects will also receive a newly initiated oral antidepressant during the double-blind treatment phase. Subjects will not be on placebo alone. Assessment of the potential efficacy of a new compound for the treatment of treatment-resistant major depression requires adequate and well controlled clinical studies. This superiority study will compare intranasal esketamine plus a newly-initiated oral antidepressant to switching to an oral antidepressant as an active comparator.

Recent analyses have shown response to placebo varies considerably, from 10% to 55%. Therefore, there is a concern that randomized, controlled studies that rely on comparison with standard antidepressant treatments alone will generate unreliable results with limited assay sensitivity. However, some have considered it unethical to do placebo-controlled studies in major depression due to the potential risk of irreversible harm.[62] In a meta-analysis of drug studies conducted in MDD, it was reported that adult subjects did not have higher rates of suicide behaviors or attempts in the placebo group compared with those receiving an active antidepressant.[39] These studies showed annual suicide rates of 0.8% on the investigational drug, 0.7% on the active comparator, and 0.4% on placebo. Thus, the risk of irreversible harm was not higher in the placebo arm compared with the active control arms.

Some subjects may decide to not participate in a placebo-controlled study due to the potential for increased distress and dysfunction from prolonged depression.

Therefore, the use of an active-controlled study allows for assessment of efficacy of a new compound to allow for scientifically meaningful results.

Moreover, the duration of the double-blind treatment phase is relatively short (4-week duration). Subjects will visit the study site at least twice a week during the double-blind treatment phase and their symptoms will be carefully monitored during each study visit. Safety evaluations will include evaluation of suicidal ideation/behavior at each clinic visit. At any point in the study, the subject may withdraw consent or be removed from the study by the investigator if there are any clinical concerns.

Intranasal esketamine may not be available for subjects after the study.

Precautions to Ensure Subject Safety in the Study

Subjects may participate in the study only if they have adequate capacity to give consent and after fully understanding the potential risks and giving an informed consent. Determination of capacity will be made by the study investigator. Subjects may discontinue the study at any time. The probability of receiving placebo and the concept of random assignment will be explained to the subject. The duration of the study is short, minimizing the time on intranasal placebo (which is being administered with a newly-initiated oral antidepressant). Potential disadvantages and adverse events of participating in the study and alternative treatment options will be discussed. For subjects who do not meet predefined response criteria during the study, clinical care will be arranged between the study investigator and their physician.

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

Subjects will be carefully monitored during the study and subjects who are unable to tolerate study drug during the double-blind treatment phase will be discontinued from the study. If the investigator judges it to be necessary to immediately stop study drug, he or she has the option to do so. Specific guidance is provided regarding blood pressure monitoring on intranasal dosing days (Section 6.4).

Only subjects who had non-response to their current oral antidepressant treatment, where a clinician would consider changing it in the future due to lack of response, will be enrolled.

Only qualified and trained investigators will participate in the study.

The total blood volume to be collected is considered to be within the normal range allowed for this subject population over this time frame. The approximate blood volume to be collected will be 124.5 mL from each Chinese subject (34 mL for eligibility and safety, 16 mL for PK, 74.5 mL for biomarker) and 108.5 mL from each non-Chinese subject (34 mL for eligibility and safety, and 74.5 mL for biomarker), which will be less than a Red Cross blood donation.

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

16.2.2. Independent Ethics Committee or Institutional Review Board

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

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Sponsor-approved training and informational 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), 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.

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

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

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

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required. The re-approval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data, or study conduct).

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

16.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

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

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

Where local regulations require, a separate ICF may be used for the required DNA component of the study.

16.2.4. Privacy of Personal Data

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

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures

or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

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

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory PK, biomarker, DNA and RNA 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, oral antidepressants, to understand depression, to understand differential drug responders, and to develop tests/assays related to esketamine, oral antidepressants, and depression. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.3, Withdrawal from the Use of Samples in Future Research).

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product, 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 IRB (and IEC 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 (see Contact Information page(s) provided separately). 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 sub-investigators
- 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 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 documentations consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

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

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

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

- Race
- History of smoking (all nicotine use, eg, cigarettes (including e-cigarettes or the equivalent of e-cigarettes)
- Blood pressure and pulse/heart rate
- Height and weight
- Details of physical examination

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
- Antidepressant treatment in the current episode of depression

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 CRF 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 CRF. Data in this system may be considered source documentation.

17.5. Case Report Form Completion

Case report forms are provided for each subject in electronic format. All CRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

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. All data relating to the study must be recorded in eCRFs prepared by the sponsor. Data must be entered into the eCRFs in English. Study site personnel must complete the eCRF as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

The investigator must verify that all data entries in the eCRFs are accurate and correct.

All eCRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or study-site personnel must adjust the eCRF (if applicable) and complete the query.

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 uploading data transfers from external service providers 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 eCRFs 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 eCRFs 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 eCRFs with the hospital or clinic records (source documents); a sample will 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 documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the eCRF are consistent with the original source data. Findings from this review of eCRFs and source documents 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 documentation 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, the site monitor may contact the site by telephone for an update on study progress. It is expected that study-site personnel will be available to provide an update on the progress of the study at the site.

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
- Study is terminated by sponsor due to futility

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 and comparison with the eCRFs. 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 eCRF data from all study sites that participated in the study and will represent uploaded data transferred from external service providers into the sponsor's database. 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 sub-study approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 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. aan het Rot M, Collins KA, Murrough JW, et al. Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. Biol Psychiatry. 2010;67(2):139-145.
2. Bazett HC. An analysis of the time-relationship of electrocardiograms. Heart. 1920;7:353-380.
3. Bremner JD, Krystal JH, Putnam FW, Southwick SM, Marmar C, Charney DS, Mazure CM. Measurement of dissociative states with the Clinician-Administered Dissociative States Scale (CADSS). J Trauma Stress. 1998;11(1):125-136.
4. 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.
5. Clinical Study Report ESKETINTRD1001. An open-label Phase 1 study to evaluate the pharmacokinetics of intranasal esketamine administered with and without a nasal guide on the intranasal device. (21 Aug 2014).
6. Clinical Study Report ESKETINTRD1002. An open-label, single-dose study to assess the pharmacokinetics, safety, and tolerability of intranasally administered esketamine in healthy Japanese and Caucasian subjects. (21 Aug 2014).
7. Clinical Study Report ESKETINTRD1003. An open-label, single-dose study to assess the pharmacokinetics, safety, and tolerability of intranasally administered esketamine in healthy elderly and adult subjects. (30 Dec 2014).
8. Clinical Study Report ESKETINTRD1008. An Open-Label, Single-Dose Study to Assess the Pharmacokinetics, Safety, and Tolerability of Intranasally Administered Esketamine in Healthy Han Chinese, Korean, Japanese, and Caucasian Subjects and the Effects of Rifampin on the Pharmacokinetics of Intranasally Administered Esketamine. (03 January 2017).
9. Clinical Study Report ESKETIVTRD2001. A double-blind, double-randomization, placebo-controlled study of the efficacy of intravenous esketamine in adult subjects with treatment-resistant depression. (01 May 2014).
10. Clinical Study Report ESKETINTRD2003 Phase 2a; 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. Janssen Research & Development, LLC.
11. Clinical Study Report KETIVTRD2002. A double-blind, randomized, placebo-controlled, parallel group, dose frequency study of ketamine in subjects with treatment-resistant depression. (5 Sep 2014).
12. Critchlow DG. A case of ketamine dependence with discontinuation symptoms. Addiction. 2006;101(8):1212-1213.
13. 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(4):575-590.
14. Desseilles M, Witte J, Chang TE, Iovieno N, Dording CM, Ashih H, Nyer M, Freeman MP, Fava M, Mischoulon D. Assessing the adequacy of past antidepressant trials: a clinician's guide to the antidepressant treatment response questionnaire. J Clin Psychiatry. 2011;72(8):1152-1154.
15. Dmitrienko A, Tamhane AC, Wiens BL. General multistage gatekeeping procedures. Biom J. 2008 Oct;50(5):667-77.
16. Dmitrienko A, Tamhane AC. Mixtures of multiple testing procedures for gatekeeping applications in clinical trials. Stat Med. 2011 Jun 15;30(13):1473-1488.
17. Duloxetine (Cymbalta®): US Prescribing Information. Lilly USA, LLC, Indianapolis, Indiana, USA; Dec 2014. Available from: http://pi.lilly.com/us/cymbalta-pi.pdf. Accessed 9 Feb 2015.
18. Duloxetine (Cymbalta®): Summary of Product Characteristics. Eli Lilly Nederland, Houten, The Netherlands; Aug 2014. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000572/WC500036781.pdf.Accessed 6 Mar 2015.
19. Ebert B, Mikkelsen S, Thorkildsen C, Borgbjerg FM. Norketamine, the main metabolite of ketamine, is a non-competitive NMDA receptor antagonist in the rat cortex and spinal cord. Eur J Pharmacol. 1997;333:99-104.

20. Endou M, Hattori Y, Nakaya H, Gotoh Y, Kanno M. Electrophysiologic mechanisms responsible for inotropic responses to ketamine in guinea pig and rat myocardium. Anesthesiology. 1992;76:409-418.

21. Escitalopram (Cipralex®): US Prescribing Information. Lundbeck Canada Inc., Quebec, Canada; 12 Nov 2014. Available from: http://www.lundbeck.com/upload/ca/en/files/pdf/product_pi/Cipralex_November_2013/Cipralex.pdf. Accessed 9 Feb 2015.

22. Escitalopram: Summary of Product Characteristics. Actavis Group PTC ehf., Iceland; Jul 2014. Available from: http://www.medicines.org.uk/emc/medicine/28956 (Accessed 6 Mar 2015).

23. EuroQol Group. About EQ-5D. Available from: http://www.euroqol.org/about-eq-5d.html. Accessed 18 Jun 2014.

24. EuroQol Group. EQ-5D-5L User Guide: basic information on how to use the EQ-5D-5L instrument. Version 2.0; Oct 2013.

25. Fond G, Loundou A, Rabu C et al. Ketamine administration in depressive disorders: a systematic review and meta-analysis. Psychopharmacology (Berl). 2014;231(18):3663-3676.

26. 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.

27. Guy W. ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: U.S. Department of Health, Education, and Welfare; 1976.

28. Haas DA, Harper DG. Ketamine: a review of its pharmacologic properties and use in ambulatory anesthesia. Anesth Prog. 1992;39(3):61-68.

29. 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.

30. He X, Li C, Qian J, Cui H, Wu W. Reliability and Validity of A Generalized Anxiety Disorder Scale in General Hospital Outpatients. Shanghai Archives of Psychiatry, 2010, Vol.22 (4).

31. 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.

32. 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.

33. Hurt PH, Ritchie EC. A case of ketamine dependence. Am J Psychiatry. 1994 May;151(5):779.

34. Investigator's Brochure, JNJ-54135419-AAC (esketamine hydrochloride). Edition 6, December 2018.

35. Jansen KL. Ketamine--can chronic use impair memory? Int J Addict. 1990 Feb;25(2):133-9.

36. Ketalar 10 mg/mL solution for injection/infusion: Summary of Product Characteristics; Aug 2014. Pfizer Healthcare Ireland, Dublin, Ireland. Available from: http://www.medicines.ie/medicine/5913/SPC/Ketalar+10mg+ml+Injection+Infusion/. Accessed 25 Feb 2015.

37. Ketamine HCl Injection: US Prescribing Information; Mar 2012. JHP Pharmaceuticals, LLC. Rochester, Minnesota, USA. Available from: http://www.drugs.com/pro/ketalar.html.Accessed 25 Feb 2015.

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

39. Khan A, Warner HA, Brown WA, Symptom reduction and suicide risk in patients treated with placebo in antidepressant clinical trials: an analysis of the Food and Drug Administration database. Arch Gen Psychiatry. 2000 Apr;57(4):311-317.

40. Khin, NA. Update on FDA Exploratory Analyses of Aggregated Efficacy Data from Depression Trials. Slide presentation at NCDEU; May 28-31, 2013; Hollywood, Florida.

41. Leon AC, Olfson M, Portera L, Farber L, Sheehan DV. Assessing psychiatric impairment in primary care with the Sheehan Disability Scale. Int J Psychiatry Med. 1997;27(2):93-105.

42. Lim DK. Ketamine associated psychedelic effects and dependence. Singapore Med J. 2003;44(1):31-34.

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

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

45. Moore NN, Bostwick JM. Ketamine dependence in anesthesia providers. Psychosomatics. 1999 Jul-Aug;40(4):356-9.

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

47. Morgan CJ, Curran HV; Independent Scientific Committee on Drugs. Ketamine use: a review. Addiction. 2012 Jan;107(1):27-38.

48. Morgan CJ, Muetzelfeldt L, Curran HV. Consequences of chronic ketamine self-administration upon neurocognitive function and psychological wellbeing: a 1-year longitudinal study. Addiction. 2010 Jan;105(1):121-33.

49. 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 Jun 1;95(3):219-29.

50. Narendran R, Frankle WG, Keefe R, et al. Altered prefrontal dopaminergic function in chronic recreational ketamine users. Am J Psychiatry. 2005 Dec;162(12):2352-9.

51. Ostad Haji E, Tadic A, Wagner S, et al. Early improvement and serum concentrations of citalopram to predict antidepressant drug response of patients with major depression. Pharmacopsychiatry. 2013 Nov;46(7):261-6.

52. Pal HR, Berry N, Kumar R, Ray R. Ketamine dependence. Anaesth Intensive Care. 2002 Jun;30(3):382-4.

53. 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.

54. Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry. 2007;164:1035-1043.

55. Protocol 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 (SYNAPSE). (28 Apr 2014).

56. Protocol ESKETINTRD3001. A randomized, double-blind, multicenter, active-controlled study to evaluate the efficacy, safety. And tolerability of fixed doses of intranasal esketamine plus an oral antidepressant in adult subjects with treatment-resistant depression. (June 2016).

57. Protocol ESKETINTRD3002. A randomized, double-blind multicenter, active-controlled study to evaluate the efficacy, safety and tolerability of flexible doses of intranasal esketamine plus an oral antidepressant in adult subjects with treatment-resistant depression.

58. Protocol ESKETRINTRD3003. A randomized, double-blind, multicenter, active-controlled study of intranasal esketamine plus an oral antidepressant for relapse prevention in treatment-resistant depression. (June 2016).

59. Protocol ESKETINTRD3004. An open-label, long-term, safety and efficacy study of intranasal esketamine in treatment-resistant depression. (June 2016).

60. Protocol ESKETINTRD3005. A randomized, double-blind, multicenter, active-controlled study to evaluate the efficacy, safety, and tolerability of intranasal esketamine plus an oral antidepressant in elderly subjects with treatment-resistant depression. (January 2016).

61. Rickels K, Garcia-Espana F, Mandos L, Case GW. Physician Withdrawal Checklist (PWC-20). J Clin Psychopharmacol. 2008;28(4):447–451.

62. Rothman KJ, Michels KB. The continuing unethical use of placebo controls. N Engl J Med. 1994;331(6):394-398.

63. Safety Report (Interim) 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 (SYNAPSE). (6 Feb 2015).

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

65. Sertraline (Zoloft®): US Prescribing Information. Pfizer, Inc., New York, New York, USA; Aug 2014. Available from: http://labeling.pfizer.com/ShowLabeling.aspx?id=517. Accessed 9 Feb 2015.

66. Sertraline: Summary of Product Characteristics. Sandoz Limited, Surrey, United Kingdom; Sep 2012. Available from: http://www.medicines.org.uk/emc/medicine/28749/SPC. Accessed 6 Mar 2015.

67. Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. Int Clin Psychopharmacol. 1996 Jun;11 Suppl 3:89-95. Review.

68. Shram MJ, Sellers EM, Romach MK. Oral ketamine as a positive control in human abuse potential studies. Drug Alcohol Depend. 2011 Apr 1;114(2-3):185-93.

69. Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med. 2006;166(10):1092-1097.

70. Targum SD, Pollack MH, Fava M. Redefining affective disorders: relevance for drug development. CNS Neurosci Ther. 2008;14(1):2-9.

71. Venlafaxine Extended-release: US Prescribing Information. Pfizer, Inc., New York, New York, USA; Aug 2014. Available from: http://labeling.pfizer.com/ShowLabeling.aspx?id=612. Accessed 9 Feb 2015.

72. Venlafaxine: Summary of Product Characteristics. Actavis Group PTC ehf, Iceland; May 2012. Available from: http://www.medicines.org.uk/emc/medicine/24329. Accessed 6 Mar 2015).

73. Vesierra (5 mg/mL solution for injection/infusion): Summary of Product Characteristics, Jun 2014. Pfizer Limited, Kent, United Kingdom. Available from: http://www.drugs.com/uk/vesierra-5-mg-ml-solution-for-injection-leaflet.html. Accessed 25 Feb 2015.

74. Walker ER, McGee RE, Druss BG. Mortality in Mental Disorders and Global Disease Burden Implications: A Systematic Review and Meta-analysis. JAMA Psychiatry. 2015 Feb 11.

75. Wieber J, Gugler R, Hengstmann JH, Dengler HJ. Pharmacokinetics of ketamine in man. Anaesthesist. 1975 Jun;24(6):260-3.

76. 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(1):52-58.

77. Xing Y and Ma A. Study on Reliability and Validity of Chinese Version of EQ-5D-5L. Shanghai Medical and Pharmaceutical Journal. 2013;9.

78. 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.

79. Yang P. Recent Advances in Design and Methodology in Psychiatric Clinical Trials. Slide presentation at Joint Statistical Meetings; Aug 3-8, 2013; Montréal, QC Canada.

80. Zeng Q-Z, He Y-L, Liu H, et al., Reliability and Validity of Chinese version of the Generalized Anxiety Disorder 7-item (GAD-7) Scale in Screening Anxiety Disorders in Outpatients from Traditional Chinese Internal Department. Chinese Mental Health Journal, 2013;27(3):163-168.

81. Zhong B, Wang Y, Chen H, Wang X, et al. Reliability, Validity and Sensitivity of Montgomery Asberg Depression Rating Scale for Patients with Current Major Depression Disorder. Behav Med & Brain Sci, January 2011, Vol. 20 (1).

Attachment 1: Prohibited Concomitant Medications with Intranasal Study Medication (Esketamine or Placebo)

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

Please refer to the local prescribing information of the subject's oral antidepressant treatment for information regarding prohibited concomitant medications.

Except where specifically noted, the prohibited medications listed in the following table are prohibited from 1 week (or 5 half-lives, whichever is longer) prior to the first dose of intranasal study medication until after the last dose of intranasal study medication. Note: If a medication is part of the antidepressant treatment regimen being taken at the time of signing the ICF (ie, start of screening/prospective observational phase), dose adjustment is permitted per clinical judgment, but the oral antidepressant treatment is to remain at or above the minimum therapeutic dose (per the MGH-ATRQ) through the end of Week 4. In such cases the investigator may choose to taper the relevant medication during the up to 3-week taper period based on their clinical judgment.

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

Drug Class	Episodic Use (as needed)	Continuous Use	Comments	Reason for Prohibition
Amantadine	N	N		PD interaction
Anorexiants (eg, phentermine, phendimetrazine)	N	N		Safety
Anticholinesterase inhibitors	N	N		Subject population is excluded
Anticonvulsants	N	N	Subjects with seizures are excluded. Use as adjunctive treatment for major depressive disorder (MDD) is prohibited. – Note: Anticonvulsants used for indications other than seizures may be allowed (eg, valproate for migraine; pregabalin)	Safety and PD interaction
Antidepressants (*other than the specific antidepressant started in the double-blind treatment phase of the study*)	N	N	– Only 1 of the 4 predefined oral antidepressant treatment options are permitted. – If a subject is taking a monoamine oxidase inhibitor (MAOI) during the screening/prospective observational phase, there must be a minimum washout interval of 2 weeks prior to the first dose of intranasal study medication. – Even if used for other indications (eg, trazodone for sleep), the use of any medication listed on the ATRQ is not permitted during the treatment phase.	Safety and PD interaction
Antipsychotics	N	N		PD interaction

Drug Class	Episodic Use (as needed)	Continuous Use	Comments	Reason for Prohibition
Benzodiazepines (at dosages less than or equal to the equivalent of 6 mg/day lorazepam) and non-benzodiazepine sleeping medication (including: zolpidem, zaleplon, eszopiclone, and ramelteon)	Y	Y	Prohibited within 12 hours prior to the start of each intranasal treatment session	Safety and PD interaction
Benztropine	Y	N	Prohibited if use is continuous.	Safety and PD interaction.
Chloral hydrate, melatonin, valerian	N	N		Safety and PD interaction
Clonidine	Y	N	Use of blood pressure control is allowed	Safety and PD interaction
Corticosteroids (systemic)	Y	N	Inhaled, intranasal, topical, and ophthalmic steroids are not prohibited. Intermittent IM/IV/oral corticosteroids are permitted per sponsor approval (chronic use prohibited).	PD interaction
Cough/cold preparations/nasal solutions containing vasoconstrictors, decongestants	Y	Y	Intranasally-administered decongestants (vasoconstrictors) should not be used from 1 hour prior to each intranasal study medication administration. Pseudoephedrine- containing oral products should not be used within 12 hours prior to an intranasal treatment session.	Safety and PD interaction
CYP3A4 inducers - Potent	N	N	Subjects may not take a known potent inducer of hepatic CYP3A activity within 2 weeks of the first administration of intranasal study medication until at least 24 hours after the last intranasal dose of study medication. Examples (not all-inclusive): Efavirenz, nevirapine, barbiturates, carbamazepine, glucocorticoids, modafinil, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort	PK
Dextromethorphan	N	N		PD interaction
Diphenhydramine	Y	N	Prohibited within 12 hours prior to the start of each intranasal treatment session	Safety
Ketanserin	N	N		Safety
Lithium	N	N		PD interaction
Memantine	N	N		PD interaction
Methyldopa	N	N		Safety and PD Interaction

Drug Class	Episodic Use (as needed)	Continuous Use	Comments	Reason for Prohibition
Metyrosine	N	N		Safety and PD interaction
Non-vitamin K antagonist oral anticoagulation agents (eg, dabigatran, rivaroxaban, apixaban	N	N		Safety
Opioids	N	N		PD interaction
Psychostimulants (eg, amphetamines, methylphenidate)	N	Y	Prescribed psychostimulants taken for indications other than MDD can be continued but must not be taken within 12 hours prior to the intranasal treatment session or for 2 hours after the intranasal treatment session.	Cardiovascular safety
ADHD medications (eg, atomoxetine, guanfacine)	N	Y	Can be continued but must not be taken within 12 hours prior to the intranasal treatment session or for 2 hours after the intranasal treatment session.	Safety
Reserpine	N	N		PD interaction
Scopolamine	N	N		PD interaction
Thyroid hormone supplement for treatment of thyroid condition only (not for depression)	N	Y		Safety
Thyroxine/ triiodothyronine (T3), thyroid hormone prescribed for depression	N	N		PD interaction
Warfarin	N	N		Primary condition where used is excluded
Abbreviations: N, Prohibited; PD, pharmacodynamics; PK, pharmacokinetics; Y, Permitted, with restrictions (please refer to the column labeled “Comments” for additional guidance).				

Attachment 2: New York Heart Association Classification of Cardiac Disease

New York Heart Association Classification of Cardiac Disease

Category	Description
Functional Capacity	
Class I	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.
Objective Assessment	
A	No objective evidence of cardiovascular disease.
B	Objective evidence of minimal cardiovascular disease.
C	Objective evidence of moderately severe cardiovascular disease.
D	Objective evidence of severe cardiovascular disease.

Source: Criteria Committee of the New York Heart Association. Functional capacity and objective assessment. In: Dolgin M, ed. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels, 9th ed. Boston, MA: Little, Brown & Co; 1994, 253-255.

Attachment 3: Oral Antidepressant Titration Schedule for Double-Blind Treatment Phase

The titration schedule for the 4 oral antidepressants to be used in the current study is provided below. Adjustments to the titration schedule may be required in other countries in order to conform to local prescribing information.

Global titration schedule

	Titration Schedule			
Oral Antidepressant (Active Comparator)	**Week 1 (Starting Day 1)**	**Week 2 (Starting Day 8)**	**Week 3 (Starting Day 15)**	**Week 4 (Starting Day 22)**
Duloxetine	60 mg[a]	60 mg	60 mg	60 mg
Escitalopram	10 mg	20 mg	20 mg	20 mg
Sertraline	50 mg	100 mg	150 mg	200 mg
Venlafaxine XR	75 mg	150 mg	225 mg	225 mg

[a] Subjects should be initiated with 60 mg/day. Subjects that have in the past shown increased sensitivity towards serotonin reuptake inhibitors (SSRI) /norepinephrine reuptake inhibitors (SNRI) can, at the discretion of the treating physician, be started on a 30 mg dose and up-titrated into the therapeutic range of 60 mg by the start of Week 2

Attachment 4: Anticipated Events

Anticipated Event

An anticipated event is an adverse event (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease related) or background regimen. For the purposes of this study the following events will be considered anticipated events.[17,18,21,22,34,65,66,71,72]

For esketamine and major depressive disorder (MDD) (including treatment-resistant depression [TRD]; based on DSM-5):

- Suicidal thinking, ideation, and behavior
- Sleep changes, difficulty sleeping, reduced sleep, abnormal sleep, tiredness, fatigue, and reduced energy
- Difficulty in sexual desire, performance or satisfaction
- Reduced appetite and weight changes (loss or increase)
- Activation or hypomania/ mania
- Irritability, anger, and impulsive behavior
- Agitation, tension, panic attacks, and phobia

For esketamine, regarding events related to concomitant therapy with oral antidepressants (from the product's reference safety information/US prescribing information):

- Duloxetine
  - Most commonly observed adverse reactions from pooled studies of all indications (incidence of at least 5% and at least twice the incidence in placebo subjects) were nausea, dry mouth, somnolence, fatigue, constipation, decreased appetite, and hyperhidrosis (sweating). Duloxetine treatment worsens glycemic control in some subjects with diabetes.
  - Increased the risk compared to placebo of suicidal thinking and behavior; serotonin syndrome; hepatotoxicity; hepatic failure; orthostatic hypotension, syncope; abnormal bleeding; severe skin reactions, including erythema multiforme and Stevens-Johnson Syndrome (SJS); activation of mania or hypomania; hyponatremia.
- Venlafaxine XR
  - According to the US prescribing information, adverse events in short-term studies occurring in at least 5% of subjects receiving venlafaxine XR and at a rate twice the incidence in placebo subjects: abnormal ejaculation, gastrointestinal complaints (nausea, dry mouth, and anorexia), central nervous system complaints (dizziness, somnolence, and abnormal dreams), and sweating. Sustained hypertension is noted within Warnings and Precautions section.
  - Increased the risk compared to placebo of suicidal thinking and behavior, treatment-emergent insomnia and nervousness, activation of mania/hypomania, hyponatremia, mydriasis, abnormal bleeding, sustained hypertension, and serotonin syndrome.
- Escitalopram
  - Most commonly observed adverse reactions (incidence of approximately 5% or greater and approximately twice the incidence in placebo subjects) were insomnia, ejaculation disorder (primarily ejaculatory delay), nausea, sweating increased, fatigue, and somnolence.
  - Increased the risk compared to placebo of suicidal thinking and behavior, serotonin syndrome, activation of mania/hypomania, hyponatremia and abnormal bleeding

- Sertraline
  - Most common treatment-emergent AEs associated with sertraline (incidence of at least 5% for sertraline or at least twice the incidence in placebo subjects) were ejaculation failure, dry mouth, increased sweating, somnolence, tremor, dizziness, fatigue, pain, malaise, abdominal pain, anorexia, constipation, diarrhea/loose stools, dyspepsia, nausea, agitation, insomnia, and decreased libido, and serotonin syndrome.
  - Increased the risk compared to placebo of suicidal thinking and behavior, activation/mania; bleeding events related to SSRI use (have ranged from ecchymosis, hematomas, epistaxis, and petechiae to life-threatening hemorrhages), hyponatremia (appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion [SIADH]); serotonin syndrome

Reporting of Anticipated Events

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

Anticipated Event Review Committee (ARC)

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

Statistical Analysis

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

INVESTIGATOR AGREEMENT

JNJ-54135419 (esketamine)
Clinical Protocol ESKETINTRD3006 Amendment 2

INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Dong Jing Fu, MD, PhD

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.

Confidential – FOIA Exemptions Apply in U.S. 142
Status: Approved, Date: 21 January 2021

Janssen Research & Development *

Clinical Protocol

COVID-19 Appendix

Protocol Title

A Randomized, Double-blind, Multicenter Active-controlled Study to Evaluate the Efficacy, Pharmacokinetics, Safety and Tolerability of Flexible Doses of Intranasal esketamine Plus an Oral Antidepressant in Adult Subjects with Treatment-resistant Depression

Protocol ESKETINTRD3006; Phase 3

JNJ-54135419 (esketamine)

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

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

Status: Approved
Date: 22 July 2020
Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-RIM-111573, 1.0

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL

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

COVID-19 APPENDIX

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by 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 guidance from the China Forums of Clinical Research Capacity Building and Human Research Participants Protection (CCHRPP) and any disaster/emergency response/good clinical practice (GCP) notification, that the clinical site may have already enforced in line with the Central Drug Evaluation (CDE) guidance on Drug Clinical Trial Management under COVID-19 Pandemic Situation, the sponsor is providing temporary options for study-related subject management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of subjects and site staff. The safety of the subjects and relevant study site personnel should be considered as priority. If, at any time, a subject's safety is considered by the investigator to be at risk, study treatment may be discontinued after discussion with the sponsor, and study follow-up will be conducted according to GUIDANCE SPECIFIC TO THIS PROTOCOL.

Obtaining oral/verbal consent for ongoing subjects: Re-consenting of subjects will be performed as applicable for the measures taken (including remote consenting by phone) and according to local guidance for informed consent applicable during the COVID-19 pandemic.

Every effort should be made to adhere to protocol-specified assessments for subjects on study treatment. Modifications to protocol-required assessments may be permitted after consultation between the participant and investigator, and with the agreement of the sponsor. Missed assessments/visits will be captured in the clinical trial management system (CTMS) for protocol deviations.

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. 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 subjects on study treatment while site capabilities are compromised by COVID-19-related restrictions. As restrictions are lifted and the acute phase of the COVID-19 pandemic resolves, sites should revert to original protocol conduct as soon as feasible.

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

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

Screening / Prospective Observational Phase

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

- Screening of new subjects should be delayed until the rate of COVID-19 infection is reduced and under control.
- Due to uncertainty around the ability to conduct on site clinical visits, subjects that are currently in screening should be screen failed as per Exclusion Criterium 25 (see Section 4.2) and clinical standard of care for the treatment of depression should be arranged by the study investigator and/or the subject's treating physician.
- The sponsor will evaluate and approve / reject requests to rescreen an individual subject on a case-by-case basis after the COVID-19 infection is under control.

Double-blind Treatment Phase

Due to the wide spread of site locations, the risk level of COVID-19 viral infection and restrictions might be different at each site. The decision to continue with on-site intranasal dosing or to miss intranasal dosing and to conduct a remote phone call visit should be made by the investigator taking into consideration the subject's disease status and the potential impact of the COVID-19 viral infection, and after consultation with the sponsor.

If it is feasible for the subject to be assessed and dosed at the study site, and the subject is willing to do so, the original protocol requirements and procedures should be followed. To reduce time spent by the subject on site during the dosing day and limit direct contact with multiple site staff members, clinician rating scales (Clinical Global Impression – Severity [CGI-S], Columbia Suicide Severity Rating Scale [C-SSRS] and Physician Withdrawal Checklist; 20-item [PWC-20]) can be completed remotely (via phone). Site staff are advised to wear the necessary personal protective equipment when seeing the subject, to ensure that the subject is protected when on site, and to obtain subject information regarding recent travel or contact history of COVID-19 suspected cases.

If it is not feasible for the subject to be assessed and dosed at the study site, the following recommendations should be followed:

- The decision to miss the intranasal dosing temporally or to proceed directly to early withdrawal from the double-blind treatment phase and entry to the follow-up phase should be at the discretion of investigator and after consultation with the sponsor. The subject should be contacted for assessments that can be conducted remotely by telephone as specified in the Time and Events schedule of the protocol.

- The subject should continue to take oral antidepressant (AD) as per protocol.

- Rating Scales: Every effort should be made to complete the Montgomery-Åsberg Depression Rating Scale (MADRS) assessment remotely as outlined in the protocol (ie, via telephone by an independent rater), and within the scheduled timeframe (see Time and Events Schedule). If this cannot occur, the sponsor medical monitor or delegate should be contacted for directions. Data obtained from the clinician completed rating scale assessments and patient report outcome (PRO) that is outlined in the Remote Site Assisted Administration Form should be collected remotely per the electronic Clinical Outcome Assessments (eCOA) COVID-19 site administration assistance process.

- Safety Assessments: information on adverse events and concomitant therapies should be obtained and documented at each remote visit as per the visit schedule. If it is determined by the investigator that it necessary to have laboratory assessments (such as hematology, chemistry, urine drug screen, urinalysis, urine/serum pregnancy test) and echocardiographic (ECG) assessments, then these assessments could be done in a nearby hospital/clinic or at a local laboratory instead of at the central laboratory as stipulated in the protocol. Assessments that were not conducted will be regarded as missing data. Testing should be resumed as soon as the conditions permits.

If a subject cannot be contacted for a remote visit, follow procedures in Section 10.2 of the protocol.

Follow-up Phase

- Further clinical standard of care for the treatment of depression will be arranged by the investigator. Medication changes are permitted per protocol (see Section 9.1.4). The decision to continue with oral AD treatment, and the choice of oral AD will be at the discretion of the investigator taking into consideration the subject's disease status and the potential impact of the COVID-19 virus infection.
- Rating scales/safety assessments can be completed remotely by telephone. Detailed guidance is specified in the prior section “Double-blind Treatment Phase”
- It is recommended that close contact be maintained with study subjects and remote contact arranged consistent with the subject’s regularly scheduled visit interval.

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

Exposure to COVID-19

- If a subject develops COVID-19 infection during the screening phase, the subject should be screen failed. After the acute phase of the COVID-19 pandemic, any potential subject who has had COVID-19 virus and has fully recovered may be considered for screening/re-screening following a discussion with the Sponsor's study responsible physician.
- If a subject develops confirmed COVID-19 infection during the double-blind treatment phase, the principal investigator should contact the sponsor's medical monitor to discuss the best course of action based on a risk/benefit assessment.
- If a subject develops confirmed COVID-19 infection during the follow-up phase, the principal investigator should contact the sponsor's medical monitor. If feasible, the subject, should complete assessments remotely until recovered.
- The subject's COVID-19 infection should be reported to the sponsor following the usual Adverse Event/Serious Adverse Event reporting requirements.

Data Collection and Documentation

Discontinuations of study treatment and withdrawal from the study due to COVID-19 related adverse events (AEs) / serious adverse events (SAEs) should be documented as discontinuation due to AE. If a subject has died due to COVID-19, "death" should be selected as the reason for treatment discontinuation. Discontinuations for other COVID-19 reasons (eg, site closure) should be documented with the prefix "COVID-19-related" in the eCRF.

All relevant communications and discussions applicable to the decision-making processes and actions taken in association with the situation related to COVID-19 should be documented in the eCRF, including (but not limited to the following examples):

- Site rater will verify that the correct subject is being interviewed and document in the source medical notes of this verification.
- For screen failures for a reason related to COVID-19, document the reason under "a violation for Exclusion Criterion 25" on the Inclusion/Exclusion Criteria form, and also add the following comment on the Comments form: "Subject is screen failure due to COVID-19 outbreak."
- For early withdrawal for a reason related to COVID-19 (other than AE), document the reason under "Other" using the following format: "COVID-19 related [and additional details as appropriate]" in the Disposition form.
- Document remote safety assessment for ongoing subject, review of adverse events and concomitant medications and safety-related scale outcomes. Data obtained from the clinician completed rating scale assessments and patient report outcome (PRO) that is outlined in the Remote Site Assisted Administration Form should be collected remotely per the e(COA) COVID-19 site administration assistance process.
- Document treatment status and any changes in standard of care/oral antidepressant treatment choices.
- Document all attempts made by the site personnel to contact the subject, in the event that the site personnel have not been able to reach the subject.

- For missed doses of study drug, the dosing form should be inactivated and “COVID-19 related [and additional details as appropriate]" entered on the Comments form.
- Missed / out of window assessments should be documented with “COVID-19-related [and additional details as appropriate]” in the comment section of the eCRF. Assessments that cannot be performed during the current situation and/or because the subject(s) want to avoid any potential risk to COVID-19 exposure, will be regarded as "missing data" and will need to be recorded as a related protocol deviation in the source documents. Testing should be resumed as soon as the conditions permits.

All COVID-19-related deviations from the main study protocol will be documented in CTMS according to COVID-19 Data Management Guidance.

Oral/verbal consent for ongoing subjects

Due to changes in this specific guidance in response to the global COVID-19 pandemic, it may influence subject’s willingness to continue participating in the study. Below is general guidance for capturing enough evidence for an oral/verbal consent. Country specific guidance should be followed for alternating consenting methods.

The following should be collected and documented in the relevant subject record that is retained at the investigational study site

1. Who consented: Name of the subject.
2. When they consented: The time and date when the consent conversation took place
3. What they were told at the time: What changes or new aspect of the study the subject agreed to (eg., some of scheduled study visits may be conducted by telephone instead of going into the study doctor’s office)
4. How they consented: The consent result, the method used (eg., telephone)
5. Who captured the oral/verbal consent: Name and signature of the Investigator or staff member who captured the subject's consent.
6. Impartial witness, if applicable: Who was present as impartial witness and how the impartial witness was selected.
7. Oral/verbal re consenting will be followed by written consent upon the subject's return to the site.

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. The acceptability of alternate consenting methods will vary by country based upon local/country guidance, laws, and regulations (which take precedence over the above Janssen guidance).

Statistical Analysis

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

INVESTIGATOR AGREEMENT

COVID-19 Appendix
JNJ-54135419 (esketamine) Clinical Protocol ESKETINTRD3006

INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Vanina Popova, MD

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.

CONFIDENTIAL – FOIA Exemptions Apply in U.S. 7

Status: Approved, Date: 22 July 2020