

Janssen Research & Development ***Clinical Protocol**

An Open-label, Long-term, Safety and Efficacy Study of Intranasal Esketamine in Treatment-resistant Depression

Safety and Sustenance of Esketamine Treatment Response With Repeated Doses at Intervals Determined by Symptom Severity (SUSTAIN-2)

**Protocol ESKETINTRD3004; Phase 3
AMENDMENT 4****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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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	Issue Date
Original Protocol	21 April 2015
Amendment 1	11 June 2015
Amendment 2	17 February 2016
Amendment 3	6 June 2016
Amendment 4	6 July 2016

Amendments below are listed beginning with the most recent amendment.

Amendment 4 (6 July 2016)

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

The overall reason for the amendment: To remove the exclusion criteria for subjects aged ≥ 65 years with first degree AV block. Data from Phase 1 studies (ESKETINTRD1003 and 1012) and preliminary data from the current study showed no effect on the PR interval in subjects aged ≥ 65 years.

Applicable Section(s)	Description of Change(s)
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Rationale: Based on analyses of available data that showed no impact of intranasal esketamine on PR interval, evidence of 1st degree AV block was removed as an exclusion criterion for subjects aged ≥ 65 years.

4.2.1. Direct-Entry Subjects	<p>The following text was deleted from Exclusion Criterion 11.2:</p> <ul style="list-style-type: none"> - Evidence of 1st degree AV block (in subjects ≥ 65 years only): <ul style="list-style-type: none"> - During Screening: If the PR interval on the initial ECG is > 200 msec but < 240 msec, the average PR interval of 2 ECGs recorded 4 minutes apart on the same day must not be > 200 msec. - On Day 1 (predose): If the PR interval is > 200 msec but < 240 msec based on the site-evaluated ECG; the average PR interval of 2 ECGs, recorded 4 minutes apart on the same day, must not be > 200 msec.
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Amendment 3 (6 June 2016)

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

The overall reason for the amendment: To modify entry criteria with respect to PR interval based on Phase 1 and Phase 2 data, to add the information about the long-term safety study 54135419TRD3008; to implement changes and align language being applied across all Phase 3 studies in the esketamine development program; to correct errors and make minor clarifications in the text of the inclusion and exclusion criteria.

Applicable Section(s)	Description of Change(s)
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Rationale: Based on analyses from phase 1 and 2 studies that showed no impact of esketamine on PR interval, 1st degree AV block (PR interval > 200 msec) was removed as an exclusion criterion for subjects < 65 years; however, it is maintained as an exclusion criterion for subjects ≥ 65 years old, as the number of elderly subjects exposed to intranasal esketamine was limited so far.

Applicable Section(s)	Description of Change(s)
4.2.1 Direct Entry Subjects	Revised Exclusion Criterion 11.1 so that 1 st degree AV block only applies for subjects ≥ 65 years. Qualified the conditions for retesting during screening (for the initial ECG) and on Day 1 (predose ECG) such that if the PR interval is > 200 msec but < 240 msec, the average PR interval of 2 ECGs, recorded 4 minutes apart on the same day, must not be > 200 msec. Clarified that if QTcF is prolonged on the initial ECG, the average QTcF was to be calculated from the total of three ECGs.
Rationale: To add information about the open-label safety extension study 54135419TRD3008 that may be available for eligible subjects participating in this study.	
Synopsis, Overview of Study Design, Follow-up Phase; 3.1.1. Study Phases; 9.1.5. Follow-up Phase 10.1. Criteria for Completion	Added the following statement: An open label safety extension study, 54135419TRD3008, may be available (pending country and site approval) for eligible subjects participating in the ESKETINTRD3004 study. Please refer to the 54135419TRD3008 protocol for full details, when available.
Rationale: Corrections to two of the inclusion criteria for direct entry subjects that were inadvertently combined.	
4.1.1. Direct Entry Subjects	The sentence below was moved from Inclusion Criterion 4 to Inclusion Criterion 3.2 (it was inadvertently included in Inclusion Criterion 4 in Amendment 2): “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.”
Rationale: In Amendment 2, inclusion of subjects who have thyroid-stimulating hormone (TSH) outside the normal ranges was permitted; however, the text indicating that a subject must have a normal TSH at screening was not removed from Amendment 2. This has been corrected in Amendment 3.	
4.1.1. Direct Entry Subjects	The following sentence was removed from Inclusion Criteria 6.2: “For subjects without a pre-existing history of hypothyroidism, a normal thyroid-stimulating hormone [TSH] is required at screening.” The second bullet of this criterion was revised to read as follows (new text in bold font; strikethrough text deleted): “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 within the normal range, such cases should be abnormal and considered to be clinically significant (after discussion ed directly with the medical monitor) before the subject is enrolled. If the FT4 value is out of range, the subject is not eligible. ” In the last bullet of this criterion the phrase “and have thyroid stimulating hormone [TSH] within normal range at screening” was deleted.

Applicable Section(s)	Description of Change(s)
	<p>Rationale: Inclusion criterion no. 14 was revised to specify the same requirements for contraception for female partners of male study subjects as specified for female subjects, and to add additional text regarding highly effective methods of birth control for female partners of male study subjects (this text was implemented in prior amendments for the other Phase 3 protocols in the esketamine development program; however it was not included in Amendment 2 of the ESKETINTRD3004 protocol).</p>
4.1.3. Both Types of Subjects (Direct-entry and Transferred-entry Subjects)	<p>The text of inclusion criterion no. 14 has been changed as follows (bold text added; strikethrough text deleted):</p> <p>During the study (ie, from Day 1 of the open-label induction phase), and for a minimum of 1 spermatogenesis cycle (defined as approximately 90 days) after receiving the last dose of study drug, in addition to the user independent highly effective method of contraception, a man who is sexually active with a woman of childbearing potential</p> <ul style="list-style-type: none"> - 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). who is sexually active with a woman of childbearing potential must agree to use a double barrier method of contraception (eg, diaphragm or cervical/vault caps plus condom with spermicidal foam/gel/film/cream/suppository). - who is sexually active with a woman who is pregnant must use a condom if his partner is pregnant. - must agree not to donate sperm. <p>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.</p>
	<p>Rationale: Clarification of exclusion criterion for direct entry subjects with non-response to previous treatment, for consistency with other esketamine Phase 3 protocols.</p>
Synopsis, Subject Population, Direct-entry subjects; 4.2.1. Direct Entry Subjects	<p>Exclusion Criterion 1 for direct-entry subjects was revised to indicate that a subject could be excluded if their depressive symptoms have previously not responded to either of the following (the word “or” was added):</p> <p>esketamine or ketamine in the current major depressive episode per clinical judgment, or</p> <p><u>All</u> of the 4 oral antidepressant treatment options available in the respective country for the open-label induction phase (ie, duloxetine, escitalopram, sertraline, and venlafaxine XR) in the current major depressive episode (based on MGH-ATRQ).</p>
	<p>Rationale: Revision to exclusion criterion for direct entry subjects due to errors in the text of the criterion.</p>
4.2.1 Direct Entry Subjects	<p>Deleted the following note from Exclusion Criterion 8.1, which is a duplication in the text of the criterion:</p> <p>“Note: subjects who had unstable angina or myocardial infarction with revascularization done >12 months prior to screening and are symptom-free, can be included.”</p> <p>Deleted the word “regimen” from the second paragraph of Exclusion Criteria 9.1. Sentence now reads “A potential subject may have his/her current antihypertensive medication(s) adjusted during the screening phase and be re-evaluated to assess their blood pressure control.”</p>

Applicable Section(s)	Description of Change(s)
Rationale: Clarification to inclusion criterion for direct entry subjects for consistency with updated protocol template text.	
4.1.1 Direct Entry Subjects	Revised Inclusion Criterion 8.1 to add the leading statement “Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.”
Rationale: To clarify that subjects taking prescribed psychostimulants at the start of the screening phase may continue to take this medication during the study, except on intranasal treatment session days, to allow subjects to safely use these medications at other permitted times during study participation.	
4.2.1. Direct-entry Subjects	Modified Exclusion Criterion 14.1 to add that subjects who have a positive test result at screening due to prescribed psychostimulants taken for an indication other than MDD (e.g. amphetamine, methylphenidate etc.) are permitted to take this medication during the study (in accordance with Attachment 1). Deleted amphetamines from the text of the second bullet so that this bullet only applies to opiates or barbiturates.
Rationale: Clarification made regarding the usage of antidepressant treatments for indications other than depression during the screening phase and for the use of corticosteroids, psychostimulants, and ADHD medications.	
Attachment 1	<p>The phrase “or placebo” was deleted from the title of Attachment 1, as there is no placebo in this study.</p> <p>Added the following statement to the text preceding the table (to align the text in Attachment 1 with the protocol section 9.1.2).: “Of note, other than for MAOIs (see table below), for all antidepressants being taken at the start of or during the screening phase, no washout or drug-free period is required after discontinuing the antidepressant treatment; however, if clinically indicated, the antidepressant treatment can be tapered and discontinued during the screening phase.”</p> <p>For corticosteroids, changed “oral” to “systemic”; allowed episodic use (previously prohibited); added that intermittent IM/IV corticosteroids are permitted (chronic use prohibited).</p> <p>For pseudoephedrine, clarified that is an orally administered agent (not intranasal).</p> <p>For psychostimulants and ADHD medications, continuous use is allowed (previously prohibited); added that these prescribed medications 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. Qualified that this applies to prescribed psychostimulants taken for indications other than MDD.</p>
Rationale: To revise a visit window during the open label induction phase to allow more flexibility for conducting the visit.	
Time and Events Schedule, Screening and Open-label Induction Phase	For Visit 2.9 during the induction phase, the visit window was revised to ± 1 day (rather than -1 day).
Rationale: Clarification to text regarding measurement of pulse oximetry, to align with other Phase 3 protocols.	
9.2.1. Safety Evaluations, Pulse Oximetry	The following statement was added: Any arterial oxygen saturation (SpO ₂) <93% should be confirmed by an additional measurement on another part of the body.

Applicable Section(s)	Description of Change(s)
Rationale: Removal of requirement for reporting treatment emergent changes in (or worsening from baseline) nasal examinations as adverse events, as reporting for such instances should be at the discretion of the Investigator.	
9.2.1. Safety Evaluations, Nasal Examinations	Deleted the following text: Any treatment emergent change or worsening from the baseline examination will be recorded as an adverse event.
Rationale: Clarification of adverse event reporting procedures in the instance of pregnancy. In addition, clarification that all SAEs must be reported using the SAE Form.	
12.3.1. Adverse Events	Text revised as follows (bold text added; strikeout text removed): 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, within 30 days after the last dose of study drug, 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.
Rationale: Removal of MDMA from urine drug screen results that will lead to discontinuation as prescribed psychostimulants are now permitted.	
4.3. Prohibitions and Restrictions	MDMA was deleted from the list of drugs that will lead to discontinuation if detected in the urine drug screen during the study.
Rationale: Minor changes were made throughout the protocol for compliance with updated protocol template text, and to correct for an omission in the previous amendment, regarding the template convention for indicating modified exclusion criterion.	
Cover page	Updated Sponsor Statement to remove Janssen Infectious Diseases BVBA.
4.2.1. Direct-Entry Subjects	Corrected Exclusion Criterion 2 to show that it was first modified in amendment 1 (not amendment 2), and inserted a line (numbered as 2.1) to show that it was modified again in amendment 2, in order to agree with the template numbering convention (this line was inadvertently left out of Amendment 2). The content of this criterion was not modified in this amendment, thus this exclusion criterion remains numbered as 2.2 (as it was in Amendment 2).
17.5 Case Report Form Completion	Deleted text stating "All data relating to the study must be recorded in CRF."
References	Removed edition number and date from reference 41.
Investigator Agreement Page	Removed the "LAST PAGE" designation.

Amendment 2 (17 February 2016)

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

The overall reason for the amendment: The overall reason for this amendment is to update and/or clarify protocol content based on ongoing feedback received during the study initiation activities. In addition, key protocol entry criteria for direct entry subjects have been added for transferred entry subjects, in order to confirm that subject's, who completed ESKETINTRD3005, continue to meet the criteria at entry to the ESKETINTRD3004 study.

Applicable Section(s)	Description of Change(s)
Rationale: A stated-choice preference survey was added as an exploratory measure to analyze subject's willingness to accept tradeoffs between treatment-related benefits and harm.	
Synopsis, Objectives and Hypothesis; Synopsis, Medical Resource Utilization; Synopsis, Statistical Methods; Time & Events Schedule; 2.1. Objectives; 3.2.8. Patient Stated-choice Preference Survey; 9.6. Other Evaluations; 11.7 Patient Stated-choice Preference Survey	<p data-bbox="545 327 1442 390"><u>Addition of Sections 3.2.8., and 11.7. for Patient Stated-choice Preference Survey, and inclusion of additional text to section 9.6. Other Evaluations.</u></p> <p data-bbox="545 401 1442 548">‘The Patient Stated-choice Preference Survey (stated-choice conjoint analysis) will be used as an exploratory tool to assess the manner and degree to which the study subjects value or weigh the clinical outcome associated with esketamine treatment, thus allowing assessment of the maximum acceptable treatment-related risk subjects would accept for various degrees of benefit.’</p> <p data-bbox="545 558 1442 590"><u>Exploratory Objectives:</u> the following text was added:</p> <ul data-bbox="545 600 1442 716" style="list-style-type: none"> • “To assess subject tradeoff preferences for key benefit and harm outcomes associated with TRD treatment, using a stated-choice conjoint analysis survey. Reporting of these survey results may be conducted separately from this study”. <p data-bbox="545 726 1442 758"><u>Medical Resource Utilization, Other Evaluations:</u> the following text was added;</p> <ul data-bbox="545 768 1442 863" style="list-style-type: none"> • “Patient stated-choice preference survey to assess subject tradeoff preferences for key benefit and harm outcomes associated with TRD treatment, using a stated-choice conjoint analysis survey”. <p data-bbox="545 873 1442 905"><u>Statistical Methods:</u> the following text added;</p> <p data-bbox="545 915 1442 1094">“Patient stated-choice preference Summary statistics and a regression model will be used to estimate a distribution of preferences weights for each level of each benefit and harm in the preference survey (described in a SAP). Maximum acceptable risk for harms will be calculated for varying degrees of benefit. Analyses and reporting of these survey results may be conducted separately from this study”.</p> <p data-bbox="545 1104 1442 1199"><u>Time and Events Schedule:</u> Open-label Induction Phase (Direct-entry Subjects and Transferred-entry Non-responder Subjects Only) Patient Stated-choice Preference Survey to be completed during visit 2.9.</p> <p data-bbox="545 1251 1442 1283">Addition of following legends:</p> <p data-bbox="545 1293 1442 1440">o) Patient Stated-choice Preference Survey to be completed only by English-speaking subjects at United States, United Kingdom and Australia sites. The survey will not be conducted in any other countries, regardless of whether the subjects in those other countries speak English. The survey is conducted only once per subject.</p> <p data-bbox="545 1451 1442 1598">p) The survey should be completed during or shortly after Visit 2.9, or if the subject has completed this visit prior to when the survey becomes available, trial sites should have the subject complete the survey at the earliest possible opportunity or at early withdrawal. The survey should be administered predose (if/when performed on intranasal dosing days).</p> <p data-bbox="545 1608 1442 1703"><u>Time & Events Schedule:</u> Optimization/Maintenance Phase (Responder Subjects from the Open-label Induction Phase and Transferred-entry Responder Subjects from ESKETINTRD3005)</p> <p data-bbox="545 1713 1442 1776">Patient Stated-choice Preference Survey’ to be completed during visit 3.5. or during Early Withdrawal/End of Optimization/Maintenance Phase</p> <p data-bbox="545 1787 1442 1818">Addition of following legends:</p> <p data-bbox="545 1829 1442 1913">o) Patient Stated-choice Preference Survey to be completed only by English-speaking subjects in United States, United Kingdom and Australia sites. The survey will not be conducted in any other countries, regardless of whether the</p>

Applicable Section(s)	Description of Change(s)
	<p>subjects in those other countries speak English. The survey is conducted only once per subject.</p> <p>p) NOTE for transferred-entry responder subjects from ESKETINTRD3005 study who enter directly to the optimization/maintenance phase, the survey should be completed during or shortly after Visit 3.5, or if the subject completed this visit prior to when the survey becomes available, the subject should complete the survey at the earliest possible opportunity or at early withdrawal. The survey should be administered pre-dose (if/when performed on intranasal dosing days). Subjects who completed the Patient Stated-choice Preference survey while enrolled in ESKETINTRD3005 should not be issued the survey.</p>
	<p>Rationale: Clarification of the definition of MDD and obsessive compulsive disorder, under criteria for subject exclusion.</p>
Synopsis, Study Population; 4.2. Exclusion Criteria, 4.2.1. Direct-entry Subjects	<p>The text of the current exclusion criteria no.2. was modified:</p> <ul style="list-style-type: none"> - Subjects with MDD with “psychotic features” will be excluded - “Only” subjects with “current” obsessive compulsive disorder will be excluded.
	<p>Rationale: Subjects with previously diagnosed cognitive impairment may be more vulnerable to any potential effects of esketamine on the cognitive function. Generally diseases pre-specified in this exclusion criterion are typically observed in the elderly population, however one cannot exclude the possibility that they will occur in a subject < 65 years old.</p>
4.2. Exclusion Criteria, 4.2.1. Direct-entry Subjects;	<p>The text of the current exclusion no. 7 was modified.</p> <p>The initial sentence: “Subject aged ≥ 65 years” will be deleted and replaced by “Subject who:”</p> <ul style="list-style-type: none"> - Has a Mini Mental State Examination (MMSE) <25 - Has neurodegenerative disorder (eg, Alzheimer’s disease, vascular dementia, Parkinson’s disease), or evidence of mild cognitive impairment (MCI).
Synopsis, Subject population, Direct-entry subjects;	<p>Deletion of the following text: “≥ 65 years” as this criteria no longer applies to the following statement ‘In addition, subjects will be excluded if they have a neurodegenerative disorder’</p>
9.6. Other Evaluations, MMSE	<p>Deletion of the following sentence: “This assessment is only completed at screening in subject’s ≥ 65 years”.</p>
4.2. Exclusion Criteria, 4.2.1. Direct-entry Subjects	<p>The text of exclusion criteria no.8. was modified, such that the following cardiovascular conditions will now be excluded:</p> <ul style="list-style-type: none"> • 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 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’. - “Note: subjects who had unstable angina or myocardial infarction with revascularization done >12 months prior to screening and are symptom-free, can be included.”
4.2. Exclusion Criteria, 4.2.1. Direct-entry Subjects	<p>The text of the current exclusion criteria no. 9 was modified as follows:</p> <p>On Day 1 of the open-label induction phase;</p> <p>For subjects <65 years: a supine systolic blood pressure (SBP) >140 mmHg or a diastolic blood pressure (DBP) >90 mmHg is exclusionary.</p> <p>For subjects ≥ 65 years: a SBP >150 mmHg or a DBP >90 mmHg is exclusionary.</p> <p><u>Correction:</u> “<” 65 years, and not ‘\leq’ 65 years.</p>

Applicable Section(s)	Description of Change(s)
	The text will now state: antihypertensive “medication(s)” rather than “therapy”.
Rationale: Clarification of definition of clinically significant ECG abnormalities as defined by QT interval corrected according to Fridericia’s formula (QTcF).	
4.2. Exclusion Criteria, 4.2.1. Direct-entry Subjects	<p>The text of the current exclusion criteria no.11 was modified as follows:</p> <ul style="list-style-type: none"> • The first subbullet, was separated into 2 separate bullets, and the following bold text was added: <ul style="list-style-type: none"> - During screening, a QT interval corrected according to Fridericia’s formula (QTcF): ≥ 450 msec; if the QTcF is prolonged on the initial ECG, the average QTcF of three ECG’s, recorded 4 minutes apart, must not be ≥ 450 msec. - On Day 1 (predose), a QT interval corrected according to Fridericia’s formula (QTcF): ≥ 450 msec based on the site-evaluated ECG; if the QTcF is prolonged on the initial ECG, the average QTcF of three ECG’s, recorded 4 minutes apart, must not be ≥ 450 msec. • In the second subbullet, the following bold text was added: <ul style="list-style-type: none"> - Evidence of 2nd or 3rd degree AV block, or 1st degree AV block with PR interval > 200 msec “[may repeat the ECG once, and use average of both readings, if the initial PR interval is < 240 msec]”. - The word “complete” was added to LBBB and RBBB.
Rationale: The use of concomitant medications that prolong the QT interval/corrected QT (QTc) interval is permitted.	
4.2. Exclusion criteria	<p>The current exclusion criteria no. 12 has been modified:</p> <p>The following text has been deleted, as:</p> <p>The “use of concomitant medications that prolong the QT interval/corrected QT (QTc) interval” no longer excludes a subject from study enrollment.</p>
Rationale: Inclusion of a repeat screening test for abnormal ALT and AST values during the screening phase.	
4.2. Exclusion criteria	<p>The current exclusion criteria no. 13 has been modified:</p> <p>Where the subject has a history of, or symptoms and signs suggestive of liver cirrhosis OR alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values $\geq 2x$ the upper limit (of normal), the following is applicable:</p> <p>“Repeat of screening test for abnormal ALT and AST is permitted once during the screening period, provided per investigator discretion and provided that there is an alternative explanation for the out of range value.”</p>
Rationale: Clarification that a positive test for cannabinoids on Day 1 (predose) of the open-label induction phase is exclusionary, but not at screening.	
4.2. Exclusion Criteria, 4.2.1. Direct-entry Subjects	<p>The text of the current exclusion criteria no. 14 was modified:</p> <p>Clarification that “a positive test for cannabinoids at the start of the screening phase is not exclusionary, however, a positive test result for cannabinoids on Day 1 (predose) of the open label induction phase is exclusionary”.</p>
Rationale: The term “secondary diabetes” was removed from the exclusion criterion because, as stated in the criterion, any uncontrolled diabetes mellitus is exclusionary.	
4.2. Exclusion Criteria, 4.2.1. Direct-entry Subjects	<p>The text of the current exclusion criteria no. 16 was modified to delete the terms “secondary diabetes”.</p>

Applicable Section(s)	Description of Change(s)
	Rationale: Provide clarification that investigator's clinical judgment based on the assessment will be used to exclude subjects on the basis of any anatomical or medical condition that may impede delivery or absorption of intranasal study drug.
4.2. Exclusion Criteria, 4.2.1. Direct-entry Subjects	The text of exclusion criteria no. 18 was modified to indicate that the 'investigator's clinically judgment based on the assessment' will be used to determine eligibility. Text that is redundant (ie, examples of structural or functional abnormalities) has been deleted.
	Rationale: Exclusion criteria no. 19 is no longer relevant.
4.2. Exclusion Criteria, 4.2.1. Direct-entry Subjects	The text of exclusion criteria no. 19 has been deleted.
	Rationale: Clarification that a subject is excluded if currently enrolled in an investigational study, which is interventional, and clarification that the limit for participation in 2 or more MDD or other psychiatric condition clinical interventional studies in the previous 1 year is based on studies with different investigational medications..
4.2. Exclusion Criteria, 4.2.1. Direct-entry Subjects	The text of exclusion criteria no. 24 has been modified to include: <ul style="list-style-type: none"> - Subject who has participated in 2 or more MDD or other psychiatric condition clinical interventional studies "(with different investigational medication)" in the previous 1 year) - Subject is currently enrolled in an investigational "interventional" study.
	Rationale: Correction to exclusion criteria, which now specifies a time interval of 6 weeks after last dose of intranasal study drug
4.2. Exclusion Criteria, 4.2.1. Direct-entry Subjects	The text of exclusion criteria no. 25 was modified: 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.
	Rationale: Subjects with severe renal impairment (creatinine clearance < 30 ml/min) are being excluded (exclusion criteria no. 32), as a safety precaution, since the effect of impaired renal clearance on the PK of intranasal esketamine is not fully known and subjects may be more vulnerable to blood pressure increases.
4.2. Exclusion Criteria, 4.2.1. Direct-entry Subjects; 4.2.2. Transferred-entry Subjects	Added exclusion criteria no. 32 for all direct-entry subjects: Severe renal impairment (creatinine clearance < 30 ml/min). In order to distinguish between direct-entry and transferred entry subjects, the exclusion criteria have not been numbered sequentially; <ul style="list-style-type: none"> - Direct-entry subjects (section 4.2.1.): criterion no. 32 follows criterion no. 29. - Transferred entry subjects (section 4.2.2.): criteria no.'s 30 and 31 remain the same. - Transferred entry subjects (section 4.2.2.): criteria no. 32 added A NOTE has been added clarifying that: <ul style="list-style-type: none"> - The following criterion (ie, no. 32) is intentionally not numbered sequentially.
	Rationale: Clarification to inclusion criterion regarding nonresponse to oral antidepressant treatments in current episode of depression was added.
Synopsis, Subject Population; 4.1. Inclusion Criteria; 3.1.1. Study Phases; 9.1.2. Screening Phase	The text of the current inclusion criteria no. 3 was modified: <ul style="list-style-type: none"> • Nonresponse to ≥ 2 oral antidepressant treatments in the current episode of depression as assessed using the MGH-ATRQ. • Non-response is confirmed by documented records (eg,

Applicable Section(s)	Description of Change(s)
	<p>medical/pharmacy/prescription records or a letter from a treating physician).</p> <ul style="list-style-type: none"> - For specific tricyclic antidepressants which are 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.
	<p>Rationale: Inclusion of an additional lab test which measures levels of free thyroxine, in the event that TSH values are out of range.</p>
4.1. Inclusion Criteria, 4.1.1. Direct-entry Subjects	<p>The text of the inclusion criteria no. 6 was modified to include an additional lab test for assessing levels of free thyroxine:</p> <ul style="list-style-type: none"> - For any subject (regardless of thyroid history), if the TSH value is out of range, a free thyroxine (FT4) will be conducted. If the FT4 value is within the normal range, such cases should be discussed directly with the medical monitor before the subject is enrolled. If the FT4 value is out of range, the subject is not eligible.
	<p>Rationale: Clarification of the criteria for assessing pregnancy in women of childbearing potential.</p>
4.1. Inclusion Criteria, 4.1.1. Direct-entry Subjects	<p>The text of the current inclusion criteria no.9 now states that:</p> <ul style="list-style-type: none"> • A woman of childbearing potential must have a “highly sensitive” negative serum (β-human chorionic gonadotropin [β-hCG]) at the start of the screening phase. • A negative urine pregnancy test “must be obtained before the first dose of study drug” on Day 1 of the open-label induction phase prior to the first intranasal treatment session.
	<p>Rationale: Inclusion criteria for methods of birth control were updated per new Sponsor protected template.</p>
4.1. Inclusion Criteria, 4.1.1. Direct-entry Subjects; 4.1.3. Both Types of Subjects (Direct-entry and Transferred-entry Subjects)	<p>4.1.1. Inclusion Criteria Direct Entry Subjects no. 10 has been moved from section 4.1.1. Direct-entry subjects to section 4.1.3. Both types of subjects (Direct-entry and Transferred-entry subjects) and modified per 3001 protocol amendment.</p> <p>This is now Inclusion Criteria no. 14</p> <p>The text of the current inclusion criteria no. 10 was modified and moved to no.14: During the study (ie, from Day 1 of the open-label induction phase) and for a minimum of 1 spermatogenesis cycle (defined as approximately 90 days) after receiving the last dose of intranasal study medication, in addition to the user independent highly effective method of contraception, a man</p> <ul style="list-style-type: none"> • who is sexually active with a woman of childbearing potential must agree to use a double-barrier method of contraception (eg, diaphragm or cervical/vault caps plus condom with spermicidal foam/gel/film/cream/suppository). • who is sexually active with a woman who is pregnant must use a condom • must agree not to donate sperm.
4.1. Inclusion Criteria, 4.1.1. Direct-entry Subjects	<p>The text of the current inclusion criteria no. 8 was also modified:</p> <p>A woman must be either:</p> <ol style="list-style-type: none"> a. Not of childbearing potential defined as: <ul style="list-style-type: none"> o postmenopausal <p><i>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</i></p>

Applicable Section(s)	Description of Change(s)
	<p><i>of 12 months of amenorrhea, a single FSH measurement is insufficient.</i></p> <ul style="list-style-type: none"> ○ permanently sterile <p>Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.</p> <p>b. Of childbearing potential and</p> <ul style="list-style-type: none"> ○ practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly). <p>Examples of highly effective contraceptives include</p> <p>-user-independent methods:</p> <p>implantable progestogen-only hormone contraception associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); vasectomized partner; sexual abstinence (<i>sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study 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.</i>)</p> <p>-user-dependent methods:</p> <p>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</p> <p><i>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.</i></p> <p><i>Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method.</i></p> <ul style="list-style-type: none"> ○ agrees to use a highly effective method throughout the study and for at least 6 weeks after the last dose of study drug. <p>Note: If the childbearing potential changes after start of the study or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active) a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.</p>
Rationale:	Confirmation that the subject remains in a stable medical condition while being transferred from the ESKETINTRD3005 to the ESKETINTRD3004 study.
4.1. Inclusion Criteria, 4.1.2. Transferred-entry Subjects (From Study ESKETINTRD3005)	<p>The text of inclusion criteria no. 11 was modified to include additional information:</p> <p>The study specific eligibility criteria referred to are now in Sections “4.1.2”, 4.1.3 and 4.2.2. Additional text:</p> <p>“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 at entry into the study. If there are any abnormalities that are not specified in the inclusion and exclusion criteria, their clinical significance must be</p>

Applicable Section(s)	Description of Change(s)
	<p>determined by the investigator and recorded in the subject's source documents and initialed by the investigator.</p> <p>Subject must be medically stable on the basis of clinical laboratory tests performed at screening. If the results of the serum chemistry panel, hematology, or urinalysis are outside the normal reference ranges, the subject may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for the population under study. This determination must be recorded in the subject's source documents and initialed by the investigator.”</p>
Rationale: Clarification of guidelines for intranasal esketamine dose titration during the open-label induction and optimization/maintenance phase	
Synopsis, Dosage and Administration;	<u>Open-label induction phase</u> (all subjects):
6.1.1. Open-label Induction phase;	The following text has been deleted: “No up titration in dose is permitted during the open-label induction phase if there was a prior down titration due to elevated blood pressure”.
6.1.2. Optimization/Maintenance phase (Table 7)	<u>Optimization/Maintenance phase</u> (transferred-entry responder subjects only):
	The following text has been deleted: “An up titration is not allowed if a subject has had a prior down titration from a higher dose due to elevated blood pressure”
Rationale: Allow option for subjects to start at a 30 mg dose of duloxetine in the oral antidepressant titration schedule.	
1.2.2.1. Duloxetine; Attachment 3	<p>Deletion of text in Section 1.2.2.1. stating: ‘although not in the US prescribing information, an initial starting dose of 30 mg/day has also been evaluated’.</p> <p>The following text has been added, as the US prescribing information does indicated that:</p> <p>”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”.</p> <p>“In the current study, subjects should be initiated with 60 mg/day. Subjects who have in the past shown increased sensitivity towards SSRI/SNRI’s, 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 open-label induction phase.</p> <p>“In Taiwan and South Korea (only), all subjects (ie, including those <65 years of age) should receive an initial dose of 30 mg during Week 1 of the screening phase (see Attachment 3)”.</p> <p><u>Attachment 3, Legend (a) added:</u></p> <p>^aDuloxetine: Subjects should be initiated with 60 mg/day. Subjects that have in the past shown increased sensitivity towards serotonin reuptake inhibitors (SSRI) and 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.</p>
Rationale: Update to align with new protocol template text regarding data being collected for medical resource utilization	
9.5. Medical Resource Utilization	<ul style="list-style-type: none"> Deleted text that specified “including surgeries and other selected procedures; “number and character of diagnostic and therapeutic tests and procedures”, and “outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications)”.
Rationale: A predose ECG at visit 3.2 was necessary as it represents a baseline for the optimization/maintenance phase; a post dose ECG is a safety evaluation	
Time & Events Schedule,	Time & Events Schedule for the optimization/maintenance phase;

Applicable Section(s)	Description of Change(s)
Optimization/Maintenance Phase	A 12-lead ECG reading has been added to visit 3.2 in Time & Events Schedule.
Rationale: Addition of an extra PWC-20 assessment for potential withdrawal symptoms following cessation of intranasal esketamine treatment, during Week 1 of the Follow-up Phase.	
Time & Events Schedule, Follow-up Phase	Time & Events Schedule for the Follow-up phase; Addition of PWC-20 assessment in Week 1 of the Follow-up Phase.
Rationale: Clarify that in the event that an intranasal treatment session is postponed/delayed (within a visit window) due to a predose vital sign assessment (eg, blood pressure), on the actual day of intranasal treatment session, specific assessments (including predose) must be performed/repeated, as specified in the T&E Schedule.	
9.2.1. Safety Evaluations; Time & Events Schedule	Where a decision has been made to postpone/delay the intranasal treatment session within the visit window, all time points (including predose) of the following assessments listed in Time & Events Schedule (open-label induction phase footnote ‘m’, optimization/maintenance phase footnote ‘n’) must be repeated on the actual intranasal treatment session day: vital signs (ie, blood pressure, pulse, respiratory rate and temperature), 12-lead ECG, C-SSRS (since last visit), MOAA/S, pulse oximetry, BPRS+, and CADSS, and CGADR. Footnote ‘m’ of the open-label induction phase, and footnote ‘n’ of the optimization/maintenance phase, indicate what needs to be performed/repeated for a postponed (within the visit window) intranasal dosing visit.
Rationale: Footnote corrected to specify at which clinic visit a predose and/or postdose 12-lead ECG will be performed.	
Time & Events Schedule, Open-label Induction Phase only	The footnote ‘f’ was corrected to indicate that: Twelve-lead ECG will be performed at t = 1 h postdose “only (ie, no predose ECG required)” at Visits 2.3, 2.5, and 2.8.
Rationale: Clarify arterial oxygen saturation level that requires further monitoring.	
9.2.1. Safety Evaluations	The symbol “<” was added to this sentence to clarify that additional assessments are required when oxygen saturation levels are < 93%: The text now states that: “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.” The following text on adverse event reporting was deleted: “Any arterial oxygen saturation (SpO ₂) <93% and lasting for more than 2 minutes, and confirmed by an additional manual measurement on another part of the body, will be reported as an adverse event”
Rationale: Clarification of the description for the HVLt-R recall test.	
9.2.1.. Safety Evaluations	Changes added to the description of the HVLt-R recall test: <ul style="list-style-type: none"> • Administration includes a delayed recall (20 minute) trial and a 24-word recognition list. • The test administrator reads instructions and word lists aloud, and records words recalled/recognized by the subjects. • Scores include learning, delayed recall, and recognition. • Additional text added stating that “All subjects will complete a practice session for the computerized cognitive battery during the screening phase. There is no practice session for the HVLt-R.”

Applicable Section(s)	Description of Change(s)
Rationale: Clarification of guidance on blood pressure monitoring on intranasal treatment session days.	
6.1. Intranasal Study Drug, Guidance on Blood Pressure Monitoring on Intranasal Treatment Session Days (Subjects < 65 years of age)	<p>Clarification that guidance on blood pressure monitoring;</p> <p>Subjects <65 years:</p> <p><u>Predose blood pressure monitoring:</u></p> <ul style="list-style-type: none"> • If subsequent to fulfilling the inclusion and exclusion criteria on Day 1 “(ie, applicable for all other treatment session days after Day 1)”, a subject’s “predose systolic blood pressure (SBP) >140 mmHg and/or diastolic blood pressure (DBP) >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”, predose SBP is >140 mmHg and/or DBP is >90 mmHg, then dosing should be postponed. • -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. <p><u>Postdose blood pressure monitoring:</u></p> <ul style="list-style-type: none"> • 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 cardiologist, “other specialist” or primary care physician, for a follow-up assessment. <ul style="list-style-type: none"> – 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 predose blood pressure, at the next scheduled visit is within the acceptable range (see bullet point above). • If at any postdose time point on the dosing day the SBP is ≥200 mmHg and/or the DBP is ≥120 mmHg, the subject “must” discontinue from further dosing and be referred “to a” cardiologist, “other specialist or primary care physician for a” follow-up assessment. <p>Addition of the following criteria for discharge based on post-dose blood pressure assessments:</p> <p>During the open-label induction 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:</p> <ul style="list-style-type: none"> • the blood pressure is <160 mmHg SBP and <100 mmHg DBP, or • “in the investigator’s clinical judgment, the subject is clinically stable and can be discharged from the study site”, or • the subject is referred for appropriate medical care, if clinically indicated. • “If the blood pressure remains ≥ 180 mmHg SBP and/or ≥110 mmHg DBP, 2 hours after dosing, the subject should be referred for immediate medical treatment”.
6.1. Intranasal Study Drug, Guidance on Blood Pressure Monitoring on Intranasal Treatment Session Days (Subjects ≥ 65 years of age)	<p>Clarification that guidance on blood pressure monitoring;</p> <p>Subjects ≥65 years:</p> <p><u>Predose blood pressure monitoring:</u></p> <ul style="list-style-type: none"> • If subsequent to fulfilling the inclusion and exclusion criteria on Day 1 “(ie, applicable for all other treatment session days after Day 1)”, a subjects “predose systolic blood pressure (SBP) >150 mmHg and/or diastolic blood pressure (DBP) >90 mmHg”, it is recommended to repeat the blood pressure measurement after subject rests in sitting or recumbent position.

Applicable Section(s)	Description of Change(s)
	<ul style="list-style-type: none"> • If “after rest and repeated measurements”, predose SBP is >150 mmHg and/or DBP is >90 mmHg, then dosing should be postponed. • -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.
	<p><u>Postdose blood pressure monitoring:</u></p> <ul style="list-style-type: none"> • If at any postdose time point on the dosing day, the SBP is ≥ 180 mmHg but <190 mmHg and/or the DBP is ≥ 100 mmHg but <110 mmHg, further intranasal dosing should be interrupted and cardiologist, “other specialist” or primary care physician for a follow-up assessment. <ul style="list-style-type: none"> - 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 predose blood pressure, at the next scheduled visit is within the acceptable range (see bullet point above). • If at any postdose time point on the dosing day the SBP is ≥ 190 mmHg and/or the DBP is ≥ 110 mmHg, the subject “must” discontinue from further dosing and be referred “to a” cardiologist, “other specialist or primary care physician for a” follow-up assessment. <p>Addition of the following criteria for discharge based on post-dose blood pressure assessments:</p> <p>During the open-label induction 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:</p> <ul style="list-style-type: none"> • the blood pressure is <160 mmHg SBP and <100 mmHg DBP, or • “in the investigator’s clinical judgment, the subject is clinically stable and can be discharged from the study site”, or • the subject is referred for appropriate medical care, if clinically indicated. • “If the blood pressure remains ≥ 180 mmHg SBP and/or / ≥ 110 mmHg DBP, 2 hours after dosing, the subject should be referred for immediate medical treatment”.

Rationale: Provide further clarification on how the current oral antidepressant treatment regimen should remain unchanged for the duration of the screening phase.

Synopsis, Overview of Study Design; 3.1.1. Study Phases;	<p>Eligible subjects who are entering the open-label induction phase will discontinue all of their current oral antidepressant medication(s), being used for depression treatment, including adjunctive/augmentation therapies, prior to the start of the induction phase.</p> <ul style="list-style-type: none"> - 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 (e.g., zolpidem, zaleplon) during the screening phase can continue these medications. - No dose increases beyond the equivalent of 6 mg/day of lorazepam, or new benzodiazepine or non-benzodiazepine sleep medications are permitted, with the exception of the use of permitted benzodiazepine as rescue medication (where required).
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Applicable Section(s)	Description of Change(s)
	Rationale: Clarification that both direct entry and transferred entry subjects will receive the same dose of oral antidepressant on proceeding to the optimization/maintenance phase.
3.1.1. Study Phases, Optimization/Maintenance Phase	New text added to section: Responder subjects who are eligible to proceed to the optimization/maintenance phase, will continue receiving the same oral antidepressant medication(s) as taken in the last week of the induction phase of ESKETINTRD3004 study. "Both for direct entry and transferred entry subjects, the dose of the oral antidepressant the subject is on at the end of the induction phase is continued into the subsequent study phase."
	Rationale: Update list of substances that can be ingested or that are restricted prior to intranasal study medication based on the recent drug-interaction study results.
4.3. Prohibitions and Restrictions	Removal of the following restriction: 'Subjects should not ingest grapefruit juice, Seville oranges, or quinine for 24 hours before an intranasal dose of study medication is to be administered. 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) during the screening phase can continue these medications during the study. No dose increases beyond the equivalent of 6 mg/day of lorazepam, or new benzodiazepine medications are permitted during the study, with the exception of the use of permitted benzodiazepine rescue medication. Benzodiazepines and non-benzodiazepine sleeping medication (eg, zolpidem, zaleplon, eszopiclone, and ramelteon) are prohibited within 12 hours prior to the start of each intranasal treatment session or cognition testing.
	Rationale: Clarifications for the use of prestudy and concomitant therapies.
8. Prestudy and Concomitant Therapy; 4.3. Prohibitions and Restrictions	Clarification of the following: Concomitant Therapy Antidepressant treatments which are not listed on the MGH-ATRQ, but were used, or are currently being used, as antidepressant treatments in the current depressive episode must be recorded under 'Concomitant Therapy' eCRF. Concomitant therapies must be recorded from signing of the informed consent and continuing up the last visit. If a subject routinely takes his/her oral antihypertensive medications in the morning on dosing days, the morning dose should be taken prior to intranasal dosing. Prohibitions and Restrictions Subjects receiving psychotherapy (including cognitive behavioral therapy; CBT) can continue receiving psychotherapy. New psychotherapy is allowed during this study. Any change in existing therapy or new therapy must be documented on the concomitant therapies form.
	Rationale: Changes to Attachment 1, including the table listing of Prohibited Concomitant Medications:
Attachment 1	<ul style="list-style-type: none"> - Deletion of row referring to CYP3A4 inhibitors as prohibited concomitant medication. - Additional example of anorexiant (eg, phendimetrazine) that are prohibited as concomitant medication for reasons of safety. - An additional example of anticonvulsants (eg, pregabalin) that are permitted as concomitant medication when used for indications other than seizures was added. - Methylphenidate, modafinil, and armodafinil, were added as additional examples of prohibited psychostimulants.

Applicable Section(s)	Description of Change(s)
	<ul style="list-style-type: none"> - A new row was added for prohibited non-stimulant ADHD medications (eg, atomoxetine, guanfacine). - Addition of new text to comments on the use of antidepressants in this study, stating that "Even if used primarily for sleep, trazodone use is not permitted during the treatment phase". - Deletion of text in comments on the use of Non-benzodiazepine sleeping medication. - Clarification that benzodiazepine medication should be taken at dosages equal to or less than the equivalent of 6 mg/day of lorazepam. - Addition of new text to comments on the use of cough/cold preparations/nasal solutions containing vasoconstrictors, decongestants "pseudoephedrine – containing products should not be used within 12 hours prior to an intranasal treatment session". This is for reasons of safety and due to potential PD interactions. - Added row for non-vitamin K antagonist oral anticoagulant agents (eg, dabigatran, rivaroxaban, apixaban). - Deletion of text in comments on the use of thyroid hormone supplements.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification of criteria for withdrawal of consent	
10.2. Withdrawal from the Study	<p>For clarification the following additions to the text were made:</p> <p>Withdrawal of consent: 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.</p> <p>If the subject withdraws from the study before the end of the open-label induction phase or optimization/maintenance phase, an Early Withdrawal visit is to be performed.</p> <p>If the 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 site personnel should attempt to obtain both primary and secondary telephone contact numbers (eg, home, work, and mobile numbers), as well as other contact information (eg, email addresses) from subjects. In addition the study site should emphasize the importance of follow-up information to the subject before initiation of the open-label induction phase. The measures taken to follow-up must be documented.</p> <p>Subjects who withdraw will not be replaced.</p> <p>Addition of the following text:</p> <p><u>Withdrawal of Consent</u> 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 (e.g. due to an adverse event or lack of efficacy). Subjects who wish to withdraw from the study should be asked if they are agreeable to 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 study, with the reason noted as “Other” and will specify the reason why.</p> <p>For a subject who “withdraws consent”, it is recommended that the subject withdraw consent in writing; if the subject refuses or is physically unavailable, the study site should document and sign the reason for the subject’s failure to withdraw consent in writing and maintain it with the subjects source records.</p> <ul style="list-style-type: none"> – The investigator will be responsible for making all required notifications to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC).
Rationale: Clarification of procedures that need to be followed with respect sample collection and handling, on withdrawal of a subject from the study.	
10.2. Withdrawal from the Study	<p>Addition of new text specifying that:</p> <ul style="list-style-type: none"> • When a subject withdraws before completing the study, the reason for withdrawal must be documented in the CRF and in the source document. • Study drug assigned to the withdrawn subject may not be assigned to another subject. • Subjects who withdraw will not be replaced. • If a subject withdraws before the end of the open-label induction phase, assessments must be obtained.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification on administration of oral antidepressant	
Synopsis, Overview of Study Design; 1.2. Oral Antidepressants: Study Medication; 3.1.1. Study Phases; 3.2.4. Treatment Groups and Dose Selection; 9.1.4. Optimization/Maintenance phase	Addition of the following criteria, applicable to both direct-entry and transferred-entry non-responder subjects: <u>Induction phase:</u> Subjects “should” continue to take the same oral antidepressant throughout the course of the study. <u>Maintenance/Optimization phase:</u> Subjects “should” continue to take the same oral antidepressant during the study, “unless poorly tolerated, in which case the oral antidepressant may be discontinued after review with sponsor”.
Rationale: Inclusion of tests for measuring free thyroxine (FT4) and for determining rates of creatinine clearance	
9.2.1.. Safety Evaluations	Inclusion of the following tests at time points specified in the Time & Events Schedule: <ul style="list-style-type: none"> • Free thyroxine (FT4), if applicable • Calculation of creatinine clearance
Rationale: Clarification on the use of oral antidepressant in the morning on the intranasal esketamine dosing days.	
6.2 Oral Antidepressants	The following sentence has been added: “If the oral antidepressant is taken in the morning on a dosing day, intranasal dosing may proceed provided acceptable blood pressure based on the pre-dose blood pressure guidance.
Rationale: Provide further clarification to site staff requirements for intranasal treatment sessions.	
Synopsis, Dosage and administration; 6.1. Intranasal Study Drug	On all intranasal treatment session days, a site staff member with training in cardiopulmonary resuscitation (eg, Basic Life Support course or equivalent courses) that is up to date per local regulations must be present with the subject during the intranasal treatment sessions and the postdose observational period. 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 study drug.
Rationale: Clarification on the oral antidepressant used by the transferred- entry subjects	
3.1.1. Study Phases, Figure 1	A legend was added to the study diagram in Figure 1 (study diagram),: Footnote “a” was added to replace the asterisk denoting the footnote. Footnote “b” was added, which contains the following text: “At entry to the ESKETINTRD3004, transferred-entry subjects will continue to receive the same oral AD initiated in the ESKETINTRD3005 study. The new oral AD is for direct entry subjects only.”
Rationale: Alert site staff to ECG readings that would raise safety concerns and necessitate subject withdrawal and study discontinuation	
9.2.1. Safety Evaluations; 10.2. Withdrawal from the Study	The following text was added: -The subject must be discontinued at any time point after baseline (Day 1, predose), if: <ul style="list-style-type: none"> • QTcF change from baseline is ≥ 60 msec and QTcF > 480 msec, or • QTcF > 500 msec.

Applicable Section(s)	Description of Change(s)
Rationale: Correction to the Volume of Blood collected from each Subject for Study Evaluations.	
9.1.1. Overview, Table 9	<p>Total Volume of Blood to be collected is now 139 mL.</p> <p>This reflects the following changes:</p> <ul style="list-style-type: none"> - Volume of Blood sample for Biomarker: Protein is now 10 mL - Volume of Blood sample for Biomarker: DNA is now 6 mL - Screening Phase: Row added to blood volume table to include: A single 3.5 mL sample per subject for analysis of blood levels of free thyroxine (FT4), if required. Addition of footnote 'e' "for any subject (regardless of thyroid history), if the TSH value is out of range, a free thyroxine (FT4) will be conducted." - Open-label Induction Phase: The two rows for 'Biomarker: protein visits' have been merged to a single row, that will now state: "Biomarker: protein (at Visits 2.1, 2.3, and 2.9). The volume of sample collected at each visit is 10 mL, and the number of samples per subject is now 3. - Optimization/Maintenance Phase (only): Hematology. The number of blood samples per subject has been changed to 7 samples. The total volume of blood taken for hematology is now 14 mL. - Optimization/Maintenance Phase (only): Serum Chemistry. The number of blood samples per subject has been changed to 7 samples. The total volume of blood taken for serum chemistry is now 17.5 mL. - Delete footnote 'c' Blood volume listed under protein biomarkers represents the combined volume of several different collection tubes. - The Note in the legend now states: 'Note: "10 mL" of blood for protein biomarkers represents the volume of several tubes combined'
Rationale: Clarification of the language regarding subjects who develop treatment emergent ulcerative cystitis to indicate the discontinuation of such subjects is mandatory.	
3.2.5. Safety Evaluations; 9.2.1. Safety Evaluations	<p>Updated/added the text in these sections describing the BPIC-SS and instructions for discontinuing due to ulcerative cystitis, to read as follows; "If a subject is diagnosed with ulcerative cystitis, the subjects must be discontinued from the study and followed up with appropriate medical care."</p>
Rationale: Update Source Documentation in line with changes to the Template	
17.4. Source Documentation	<p>The following text (bold) was added:</p> <p>At a minimum, source documentation "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 to confirm data collected in the eCRF.</p> <p><u>Deletion of following:</u></p> <p>Data recorded directly into the eCRF as source data:</p> <ul style="list-style-type: none"> - Race - Blood pressure and pulse/heart rate - Height and weight - Details of physical examination

Applicable Section(s)	Description of Change(s)
Rationale: Update the process for completion of the Case Report Form (CRF) in line with new changes to template	
17.5. Case Report Form Completion	<p>The following updates were included:</p> <ul style="list-style-type: none"> - All data relating to the study must be recorded in CRF. - All CRF entries, correction, 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. - All subject measurements (eg, clinician reported questionnaires) will be completed by the same individual who made the initial baseline determination whenever possible. - If correction to an eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways: <ul style="list-style-type: none"> - (i) Investigator and Study site personnel can make correction in the eDC tool at their own initiative or in response to an auto query (generated by the eDC tool) - (ii) Sponsor or sponsor delegate can generate a query for resolution by the study-site personnel.
Rationale: Update list of study-specific materials and removal of sentence referring to an additional document outlining required equipment for supportive ventilation. This sentence was added to this protocol in error, and is now being removed in order to be consistent with the other phase 3 protocols, as no additional document was provided.	
15. Study-Specific Materials	<ul style="list-style-type: none"> - ‘Guidance document for the use of the MGH-ATRQ’ has been added. - Removal of the statement: ‘Guidance on required equipment for supportive ventilation and resuscitation will be provided in a separate document.’ - ‘Web-based Patient Stated-choice Preference Survey’ has been added
Rationale: Minor errors and clarification were noted.	
Throughout the protocol	Grammatical, formatting, or spelling changes were made.
12.3.1. All Adverse Events	Removal of the statement: ‘Any other information that is required to do an emergency breaking of the blind’
Time & Events Schedule, Open-label Induction Phase	Dispensing of oral antidepressant for a subject who has discontinued treatment, has been added to visit 2.9.
4.3 Prohibitions and Restrictions	<p>Clarification of the abbreviations used:</p> <p>Electroconvulsive therapy (ECT), deep brain stimulation (DBS), transcranial magnetic stimulation (TMS) and vagal nerve stimulation (VNS) are prohibited from study entry through the end of the last treatment phase.</p>
10.3 Withdrawal from the Use of Samples in Future Research	This paragraph has been designated as a distinct section 10.3. Withdrawal from the use of Samples in Future Research

Amendment 1 (11 June 2015)

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

The overall reason for the amendment: The overall reason for the amendment is to allow for the use of a 28 mg dose throughout the study, based on pharmacokinetic data from study ESKETINTRD1012 in elderly subjects.

Applicable Section(s)	Description of Change(s)
Rationale: Based on pharmacokinetic data from study ESKETINTRD1012 a change was made to allow for the use of a 28 mg dose of esketamine throughout the study which could potentially improve safety and tolerability	
1.1.2.1. Pharmacokinetics and Product Metabolism; 1.1.2.3. Safety and Tolerability	Description of preliminary pharmacokinetic results for study ESKETINTRD1012 was added in addition to a safety overview from the study.
1.1.2.2. Pharmacodynamics and Efficacy; 3.2.4 Treatment Groups and Dose Selection	Justification statement for including the 28 mg dose beyond Day 1, based on PK data from ESKETINTRD1012, was added.
Synopsis Dosage and Administration; 6.1.1. Open-label Induction Phase; 6.1.2. Optimization/Maintenance Phase	For direct-entry and transferred-entry non-responder subjects ≥ 65 years, the dose titration of intranasal esketamine was revised to allow for use of a 28 mg dose throughout the induction phase and optimization/maintenance phase. For transferred entry responder subjects, the dose titration of intranasal esketamine was revised to allow for the use of a 28 mg dose throughout the optimization/maintenance phase. Added guidance that dose changes are determined by the investigator based on efficacy and tolerability and in accordance with blood pressure guidelines.
Synopsis Overview of Study Design; 1.2. Oral Antidepressants: Study Medication' 3.1. Overview of Study Design; 3.1.1. Study Phases; 3.2.4 Treatment Groups and Dose Selection	Addition of 28 mg dose which can be continued throughout the study for subjects ≥ 65 years of age.
Rationale: More conservative blood pressure parameters related to patient dosing were incorporated to improve subject safety	
Synopsis Dosage and Administration; 6.1 Intranasal Study Drug; 6.1.1 Open-label Induction Phase	Added that prior to intranasal dosing, subjects ≥ 65 years of age must have a pre-dose blood pressure $\leq 150/90$ mm Hg and prior to dose escalation, subjects ≥ 65 years of age must have had a post-dose blood pressure, on the prior intranasal dosing day, of <180 mmHg systolic and <100 mm Hg diastolic.
6.1 Intranasal Study Drug	A separate guidance for monitoring blood pressure on intranasal treatment session days was created for subjects ≥ 65 years of age: if on the dosing day, the post-dose SBP is ≥ 180 mm Hg but ≤ 190 mm Hg and/or the DBP is ≥ 100 mm Hg but <110 mm Hg, further intranasal dosing should be interrupted. If post dose the SBP is ≥ 190 mm Hg and/or the DBP is ≥ 110 mm Hg, the subject should discontinue from further dosing.

Applicable Section(s)	Description of Change(s)
T&E Schedule Screening and Open-label Induction Phase; T&E Schedule Optimization/Maintenance Phase	Added guidance in footnote that if dosing is postponed (but occurs within visit window) due to blood pressure elevation, predose procedures and all procedures at postdose time points (if applicable) must be repeated on the actual dosing day (a footnote was added for each assessment that is to be repeated).
Synopsis Dosage and Administration; 6.1.1 Open-label Induction Phase; 6.1.2. Optimization/Maintenance Phase	Added that no up-titration is permitted during the open-label induction phase if there was a prior down titration due to elevated blood pressure.
Rationale: Correction/clarification made to the planned number of enrolled subjects	
Synopsis, Overview of Study Design; Synopsis, Statistical Methods; 3.1. Overview of Study Design; 11.2 Sample Size Determination	Text previously stated that 750 subjects would be enrolled into the study. Correction was made to state that 750 <u>direct-entry</u> subjects would be enrolled, plus transferred entry subjects from study ESKETINTRD3005. Clarification added to meet the regulatory requirement of having 100 subjects 65 years or older, the number will be made up of direct entry subjects plus transferred entry subjects from study ESKETINTRD3005.
Rationale: Exclusion criteria expanded to include additional DSM-5 diagnostic codes for intellectual disability and autism spectrum disorder	
Synopsis Subject Population; 4.2.1. Exclusion Criteria Direct-entry Subjects	Exclusion criteria #2 for direct-entry subjects was expanded to include additional DSM-5 diagnostic codes for intellectual disability as well as autism spectrum disorder.
Rationale: Updated to clarify that those without a history of thyroid disease are required to have a normal Thyroid Stimulating Hormone (TSH) level at Screening.	
4.1.1 Inclusion Criteria Direct-entry Subjects	Added to inclusion criteria #6 for Direct-entry subjects the requirement for a normal TSH at screening, even for subjects without an existing history of hyperthyroidism. Also added that if the TSH is below the normal range, free thyroxine (fT ₄) levels will be measured and if fT ₄ is within the normal range the subject can be enrolled.
Rationale: Correction to the number of missing consecutive MADRS assessments that will lead to a subject being discontinued from the study	
Synopsis Dosage and Administration; 6.1.2. Optimization/Maintenance Phase; 10.2 Criteria for Withdrawal from the Study	Subjects who miss 4 or more consecutive MADRS assessments (changed from >4) in the optimization/maintenance phase will be discontinued from the study.
Rationale: Correction to dispensing of oral antidepressants during the open-label induction phase	
T&E Schedule Open-label Induction Phase	Removed dispensing of oral antidepressants on study Day 28.
Rationale: Correction to SDS assessments during the open-label induction phase	
T&E Schedule Open-label Induction Phase	Added SDS assessment on study Day 15.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification on recommendation for continuation of oral antidepressants during the follow-up phase	
Synopsis Overview of Study Design; Synopsis Dosage and Administration; 3.1.1. Study Phases; 6.1.3 Follow-up Phase; 6.2.3. Follow-up Phase; 9.1.5. Follow-up Phase	The decision to continue the oral antidepressant in the follow-up phase remains at the discretion of the investigator. Language was added that continuation of oral antidepressant is strongly recommended to “facilitate maintenance of clinical benefit”. Guidance now states that it is “strongly” recommended to continue the oral antidepressant for “the duration” of the follow-up phase (changed from “at least the first 2 weeks”).
Rationale: Correction to exclusion criteria for subjects with pulmonary insufficiency	
4.2.1. Direct-entry Subjects	Exclusion criterion #6 was deleted as this criterion statement “current or past history of significant pulmonary insufficiency/condition” was duplicated in Exclusion criteria #10.
Rationale: Correction to exclusion criteria for subjects who had major surgery	
4.2.1 Direct-entry subjects	The following statement was removed from Exclusion criterion #27 “Note: Subjects with planned surgical procedures to be conducted under local anesthesia may participate”.
Rationale: Clarification on use of intranasal decongestants	
6.1 Intranasal Study Drug	Clarification added that subjects should wait for at least 1 hour after using an intranasal decongestant or corticosteroid before administering esketamine.
Rationale: Correction to description of MMSE	
9.6. Other Evaluations	The description of the MMSE was incorrect. The statement “attention (total score, 5), calculation (total score, 5)” was changed to “attention and calculation (total score, 5)”.
Rationale: Correction made to description of oral antidepressant packaging	
14.2. Packaging	Reference to blister packaging was removed.
Rationale: Clarification that SIGMA is the structured interview guide of the MADRS	
9.3.1.1 Montgomery-Asberg Depression Rating Scale (MADRS)	The following sentence was added to describe the MADRS “The structured interview guide for the MADRS (SIGMA) will be used for each administration”.
Rationale: Clarify that menstrual cycle tracking is only applicable to women with a menstrual cycle	
T&E Schedule Open-label Induction Phase, Optimization/Maintenance Phase, Follow-up Phase; 9.6 Other Evaluations	Added statement “with a menstrual cycle” to definition of applicable women.
Rationale: Blood volume table updated to include tricyclic antidepressant blood level testing	
9.1.1. Overview	Row added to blood volume table for tricyclic antidepressant blood level. Applicable to subjects taking specific tricyclic antidepressants at a dose below the MGH-ATRQ minimum therapeutic dose – a blood level that is within the therapeutic range is acceptable to establish the adequacy of antidepressant treatment.

Applicable Section(s)	Description of Change(s)
Rationale: Correction for use of new form for documenting return to the sponsor of unused study drug, or used returned study drug for destruction.	
Section 14.5. Drug Accountability	Drug return form replaced with Investigational product destruction form.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

An Open-label, Long-term, Safety and Efficacy Study of Intranasal Esketamine in Treatment-resistant Depression

Study Acronym: SUSTAIN-2

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.

Ketamine and esketamine (S-ketamine, the S enantiomer of ketamine) are approved and widely used for the induction and maintenance of anesthesia via intramuscular (IM) or intravenous (IV) administration. The desired analgesic-anesthetic effects of ketamine and esketamine are attributed to the blockade of ionotropic N-methyl-D-aspartate (NMDA) glutamate receptors. 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 will investigate the long-term (up to 52 weeks) safety and efficacy of intranasal esketamine plus an oral antidepressant in subjects with TRD.

OBJECTIVES AND HYPOTHESIS

Primary Objective

The primary objective of this study is to assess the long-term safety and tolerability of intranasal esketamine plus a newly initiated oral antidepressant in subjects with TRD, with special attention to the following:

- Potential effects on cognitive function
- Potential treatment-emergent symptoms of cystitis and/or lower urinary tract symptoms
- Potential withdrawal and/or rebound symptoms following cessation of intranasal esketamine treatment

Secondary Objectives

To assess the effect of intranasal esketamine plus a newly initiated oral antidepressant in subjects with TRD on

- Safety and tolerability with special attention to the following:
 - Treatment-emergent adverse events (TEAEs), including TEAEs of special interest
 - Local nasal tolerability
 - Effects on heart rate, blood pressure, respiratory rate and blood oxygen saturation

- Effects on alertness and sedation
- Potential psychosis-like effects
- Dissociative symptoms
- Potential effects on suicidal ideation/behavior.
- Long-term efficacy, including effects on:
 - Depressive symptoms (clinician and self-reported), overall severity of depressive illness, functional impairment and associated disability, anxiety symptoms, and health-related quality of life and health status
 - Response rate over time, defined as:
 - percentage of subjects with $\geq 50\%$ reduction from baseline (induction phase) in the Montgomery-Asberg Depression Rating Scale (MADRS) total score,
 - percentage of subjects with $\geq 50\%$ reduction from baseline (induction phase) in the Patient Health Questionnaire, 9-item (PHQ-9) total score
 - Remission rate over time, defined as:
 - percentage of subjects with MADRS total score ≤ 12 ,
 - percentage of subjects with PHQ-9 total score ≤ 5

Exploratory Objectives

- To assess the potential relationship of biomarkers with response/non-response to intranasal esketamine plus an oral antidepressant in subjects with TRD
- To assess medical resource utilization
- To assess subject tradeoff preferences for key benefit and harm outcomes associated with TRD treatment, using a stated-choice conjoint analysis survey. Reporting of these survey results may be conducted separately from this study.

Hypothesis

There is no formal hypothesis for this safety study.

OVERVIEW OF STUDY DESIGN

This is an open-label, multicenter, long-term study to evaluate the safety and efficacy of intranasal esketamine plus a newly initiated oral antidepressant in subjects with TRD. Subjects will enter the study either directly (referred to as 'direct-entry subjects') or after completing the double-blind induction phase of ESKETINTRD3005, a short-term efficacy study in elderly subjects with TRD (referred to as 'transferred-entry subjects'). Approximately 750 direct entry subjects will be enrolled in this study, plus transferred-entry subjects from study ESKETINTRD3005. At total of at least 100 subjects 65 years or older (who are either direct entry subjects or transferred entry subjects from the ESKETINTRD3005 study) will be enrolled.

ESKETINTRD3005 is a randomized, double-blind, active-controlled, 4-week study in male and female elderly subjects (≥ 65 years) with TRD to assess the efficacy, safety, and tolerability of flexibly dosed intranasal esketamine (28 mg, 56 mg or 84 mg) plus a newly initiated oral antidepressant, compared with a newly initiated oral antidepressant (active comparator) plus intranasal placebo.

Transferred-entry subjects who are non-responders (defined as <50% reduction in the MADRS total score from baseline [Day 1] at the end of the 4-week double-blind induction phase of ESKETINTRD3005 study) will be referred to as ‘transferred-entry non-responder subjects’ in the subsequent sections of the protocol. Transferred-entry subjects who are responders (defined as $\geq 50\%$ reduction in the MADRS total score from baseline [Day 1]) at the end of the 4-week double-blind induction phase of ESKETINTRD3005 study) will be referred to as ‘transferred-entry responder subjects’ in the subsequent sections of the protocol.

An Independent Data Monitoring Committee (IDMC) will be commissioned for this study to review safety data periodically.

This study (ESKETINTRD3004) has 4 phases:

- Up to 4-week screening phase (direct-entry subjects only)
- A 4-week open-label induction phase (direct-entry subjects and transferred-entry non-responder subjects)
- A 48-week open-label optimization/maintenance phase (all responder subjects from the open-label induction phase of the current study, and transferred-entry responder subjects).
- A 4-week follow-up phase (for all subjects treated with intranasal esketamine)

The maximum duration of the subject’s participation in ESKETINTRD3004 study will be 60 weeks for direct-entry subjects; 56 weeks for transferred-entry non-responder subjects, and 52 weeks for transferred-entry responder subjects. The end of the study will occur when at least 300 subjects have received treatment with intranasal esketamine for 6 months and at least 100 subjects for 12 months (Note: the total number of subjects will be based on subjects from this study and subjects from other intranasal esketamine Phase 3 studies).

A description of the study phases is provided below.

Screening Phase

After giving informed consent, direct-entry subjects with TRD who are ≥ 18 years of age (or older if the minimum legal age of consent in the country in which the study is taking place is >18 years), will be screened to determine eligibility for study participation. Transferred-entry subjects from ESKETINTRD3005 study will not participate in this 4-week screening phase.

Direct-entry subjects will be eligible for screening regardless of whether or not they are currently taking oral antidepressant treatments. At screening, subjects must have had a nonresponse to ≥ 2 different oral antidepressant treatments in the current episode of depression, as assessed by the Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire (MGH-ATRQ), and confirmed by documented records (eg, medical/pharmacy/prescription records or a letter from treating physician etc.), in their current episode of depression.

Eligible subjects taking antidepressant medication(s) at the start of the screening phase must discontinue all of their current oral antidepressant medication(s), being used for depression treatment, including adjunctive/augmentation therapies, prior to the start of the induction phase. 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) during the screening phase can continue these medications. No dose increases beyond the equivalent of 6 mg/day of lorazepam, or new benzodiazepine medications are permitted. If clinically indicated, the antidepressant treatments may either be tapered and discontinued during the screening phase, or, discontinued and switched directly to 1 of the 4 new oral antidepressant medication(s) on Day 1 of the open-label induction phase, per clinical judgment.

Subjects not currently taking oral antidepressant medication(s) at screening will start 1 of the 4 new oral antidepressant medication (duloxetine, escitalopram, sertraline, or venlafaxine extended release [XR]) on Day 1 of the open-label induction phase.

Subjects meeting the inclusion/exclusion criteria are eligible to proceed to the open-label induction phase.

Open-label Induction Phase (4 weeks)

Direct-entry subjects and transferred-entry non-responder subjects will participate in this phase.

Direct-entry subjects: Intranasal esketamine treatment will be self-administered at scheduled treatment sessions in the clinic/study site, twice weekly for 4 weeks. Subjects who are <65 years old will start intranasal esketamine with an initial dose of 56 mg on Day 1, with the dose adjusted based on efficacy and tolerability in the subsequent visits of the induction phase (flexible dose: 56 mg or 84 mg). Subjects who are ≥65 years old will start intranasal esketamine with an initial dose of 28 mg on Day 1, with the dose adjusted based on efficacy and tolerability (28, 56 or 84 mg) in the subsequent visits of the induction phase. In addition, all direct-entry subjects will initiate a new, open-label oral antidepressant on Day 1, which should be taken daily during the study.

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 nonresponse to in the current depressive episode, has not been previously intolerant to (lifetime), and is available in the participating country.

Transferred-entry non-responder subjects from ESKETINTRD3005 study (all will be ≥65 years old) will join this study at the start of the open-label induction phase. These subjects will start intranasal esketamine with an initial dose of 28 mg on Day 1, with the dose adjusted based on efficacy and tolerability (28, 56 or 84 mg) in the subsequent visits of the induction phase. These subjects should continue taking the same oral antidepressant (at the same dose) during the study, as taken in the last week of the double-blind induction phase of ESKETINTRD3005 study.

Transferred-entry subjects' may participate in this study only if it is clinically appropriate in the opinion of the investigator.

For transferred-entry non-responder subjects, results of all assessments performed on Day 28 of the induction phase of that study (Visit 2.9 of ESKETINTRD3005 study) will not be repeated as part of Visit 2.1 of the current study. For these subjects, the Day 28 visit of the ESKETINTRD3005 study will coincide with Day 1 (Visit 2.1) for the current study. There is no gap allowed between studies.

Optimization/Maintenance Phase:

Responder subjects at the end of the induction phase (≥50% reduction in MADRS from baseline [Day 1] to end of induction phase) of the ESKETINTRD3004 study, will be eligible to proceed to the optimization/maintenance phase; and continue receiving open-label intranasal esketamine treatment (at the same dose; 28 mg, 56 mg, or 84 mg) and should continue to take the same oral antidepressant (at the same dose) as taken in the last week of the induction phase of ESKETINTRD3004 study, unless poorly tolerated, in which case the oral antidepressant may be discontinued after review with sponsor.

Non-responders at the end of the induction phase of the current study will complete an early withdrawal visit and proceed to the follow-up phase.

Eligible transferred-entry responder subjects from the ESKETINTRD3005 study (all will be ≥65 years old) will join the current study starting from the optimization/maintenance phase. Transferred-entry subjects may participate in this study only if, it is clinically appropriate in the opinion of the investigator. These subjects will start intranasal esketamine with an initial dose of 28 mg (Week 5; Study Day 32) and have their dose adjusted over the following 3 weeks of the optimization/maintenance phase as described

below under the section Dosage and Administration. Subjects should continue to take the same oral antidepressant (at the same dose) during the study, as taken in the last week of the double-blind induction phase of ESKETINTRD3005 study, unless poorly tolerated, in which case the oral antidepressant may be discontinued after review with sponsor.

For transferred-entry responder subjects', results of all assessments performed on Day 28 of the induction phase (Visit 2.9 of ESKETINTRD3005 study) will not be repeated as part of Visit 3.1 of the current study. The Day 28 visit of the ESKETINTRD3005 study will coincide with Day 28 (Visit 3.1) for the current study. There is no gap allowed between studies.

For all subjects, the intranasal treatment session frequency will be reduced from that in the induction phase (twice weekly) to weekly for the first 4 weeks of optimization/maintenance phase (ie, Week 5 to Week 8). After the first 4 weeks, the frequency of intranasal treatment sessions will be adjusted to either once weekly or once every other week based on the severity of depressive symptoms, as assessed by the MADRS total score. A maximum of 3 changes in intranasal treatment session frequency from weekly to every other week is permitted during the optimization/maintenance phase.

Follow-up Phase:

This phase will include all subjects who have received at least 1 dose of intranasal study medication in this study. Follow-up visits will be performed at 1, 2 and 4 weeks after the last dose of intranasal study drug.

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. There will be no intranasal esketamine administered during this phase. Subject will be provided with an additional 4 week supply of the oral antidepressant medication, to ensure that there is no interruption of oral antidepressant therapy during the transition to further clinical/standard of care.

The decision to continue the oral antidepressant in this phase will be at the discretion of the investigator. However, in order to better assess potential withdrawal symptoms from intranasal study drug and facilitate maintenance of clinical benefit, the oral antidepressant medication should be continued for the duration of the follow-up phase unless determined as not clinically appropriate.

An open label safety extension study, 54135419TRD3008, may be available (pending country and site approval) for eligible subjects participating in the ESKETINTRD3004 study. Please refer to the 54135419TRD3008 protocol for full details, when available.

SUBJECT POPULATION

Direct-entry subjects

The study population will include men and women, ≥ 18 years of age (or older if the minimum legal age of consent in the country in which the study is taking place is >18 years), who meet the Diagnostic and Statistical Manual of Mental Disorders (5th Edition; DSM-5) diagnostic criteria for single-episode MDD (if a single episode MDD, the duration of episode must be ≥ 2 years), or recurrent MDD without psychotic features, based upon clinical assessment, and confirmed by the Mini-International Neuropsychiatric Interview (MINI). At screening, the subject must have a MADRS total score of ≥ 22 , which corresponds to at least moderate depression.

Direct-entry subjects will be eligible for screening regardless of whether or not they are currently taking oral antidepressant medications. At screening, direct-entry subjects must have had non-response to ≥ 2 oral antidepressant treatments in the current episode of depression, as assessed using the Massachusetts General Hospital – Antidepressant Treatment Response Questionnaire (MGH-ATRQ) and documented records (eg, medical/pharmacy/prescription records or a letter from treating physician, etc.).

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 all of the oral antidepressant treatment options available in the respective country for the open-label induction phase (ie, duloxetine, escitalopram, sertraline, and venlafaxine XR) in the current major depressive episode (based on MGH-ATRQ). Subjects will also be excluded if they have a current or prior DSM-5 diagnosis of a psychotic disorder or MDD with psychosis, bipolar or related disorders (confirmed by the MINI), obsessive compulsive disorder (current only), intellectual disability (DSM-5 diagnostic codes 317, 318.0, 318.1, 318.2, 315.8, and 319), autism spectrum disorder, borderline personality disorder, antisocial personality disorder, histrionic personality disorder, or narcissistic personality disorder; if they have homicidal ideation/intent or suicidal ideation with some intent to act within 6 months prior to the start of the screening phase per the investigator's clinical judgment and/or based on the Columbia Suicide Severity Rating Scale (C-SSRS); or if they have a history of moderate or severe substance or alcohol use disorder according to DSM-5 criteria. In addition, subjects will be excluded if they have neurodegenerative disorder (eg, Alzheimer's Disease, vascular dementia, Parkinson's disease) or evidence of mild cognitive impairment (MCI), or a Mini Mental State Examination (MMSE) score <25.

Transferred-entry Subjects

All transferred-entry subjects (elderly subjects ≥ 65 years old) who have completed the double-blind induction phase of the ESKETINTRD3005 study will be eligible for this study.

- Non-responder subjects will join the study at the start of the open-label induction phase
- Responder subjects will join the study from the start of the optimization/maintenance phase.

DOSAGE AND ADMINISTRATION

Intranasal Study Medication

Open-label Induction Phase:

This phase is only for direct-entry subjects and transferred-entry non-responder subjects. All subjects will self-administer intranasal esketamine twice a week for 4 weeks at the study site.

For direct-entry subjects <65 years, the dose titration of intranasal esketamine will be done as follows:

Open-Label Induction Phase Dose Titration of Intranasal Esketamine for Direct-entry Subjects <65 Years

Day	Dose	Dose Titration Guidance
Day 1	56 mg	
Day 4	56 or 84 mg	The dose may be increased to 84 mg or remain at 56 mg, as determined by the investigator based on efficacy and tolerability.
Day 8	56 or 84 mg	The dose may be increased to 84 mg (if Day 4 dose was 56 mg), remain the same as Day 4, or be reduced to 56 mg (if Day 4 dose was 84 mg), as determined by the investigator based on efficacy and tolerability.
Day 11	56 or 84 mg	The dose may be increased to 84 mg (if Day 8 dose was 56 mg), remain the same as on Day 8, or be reduced to 56 mg (if Day 8 dose was 84 mg), as determined by the investigator based on efficacy and tolerability.
Day 15	56 or 84 mg	A dose reduction from 84 mg to 56 mg is permitted, if required for tolerability. If the dose is 56 mg on Day 11, no dose increase is permitted on Day 15.
Day 18, 22, 25	56 mg or 84 mg	No dose increase from 56 mg is permitted beyond Day 15. If needed for tolerability, one additional dose down-titration from 84 mg to 56 mg is permitted from Day 15 until Day 25.

For direct-entry and transferred-entry non-responder subjects ≥ 65 years, titration of intranasal esketamine will be done as follows:

Open-Label Induction Phase Dose Titration of Intranasal Esketamine for Direct-entry and Transferred-entry Non-responder Subjects ≥ 65 Years

Day	Dose	Dose Titration Guidance*
Day 1	28 mg	
Day 4	28 or 56 mg	The dose may remain at 28 mg or be increased to 56 mg, as determined by the investigator based on efficacy and tolerability
Day 8, 11, 15	28, 56 or 84 mg	The dose may be maintained, or increased or reduced by 28 mg from the previous dosing session, as determined by the investigator based on efficacy and tolerability. No dose increase is permitted beyond Day 15.
Days 18, 22 and 25	28, 56 or 84 mg	No dose increase is permitted beyond Day 15. If needed for tolerability, a dose reduction by 28 mg from the previous dose is permitted on Days 18, 22, and 25.

*Dose changes are determined by the investigator based on efficacy and tolerability and in accordance with blood pressure guidelines.

From Day 8 to Day 15, inclusive, for those who have had a prior down titration from a higher dose, a dose increase by 28 mg is allowed based on clinical judgment.

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. 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 study drug.

- Prior to the first intranasal dose on Day 1 of the open-label induction phase, direct-entry subjects will practice spraying (into the air, not intranasal) a demonstration intranasal device that is filled with a placebo solution.
- All subjects will self-administer the intranasal study drug at treatment sessions at the study site. Intranasal treatment sessions should not take place on consecutive days.
- After Day 1 all dosing decisions are to be determined by the investigator based on efficacy and tolerability.
- Instructions for intranasal dosing for subjects ≥ 65 years of age (only):
 - Prior to intranasal dosing, subjects must have a blood pressure $\leq 150/90$ mm Hg
 - Prior to any dose escalation, subjects ≥ 65 years of age must have had a post-dose blood pressure, on the prior intranasal dosing day, of <180 mmHg systolic and <100 mm Hg diastolic blood pressure.

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.

Optimization/maintenance Phase

Subjects who meet the response criteria at the end of the 4-week induction phase will participate in the optimization/maintenance phase. Subjects will receive weekly treatment sessions of intranasal esketamine

for the first 4 weeks of optimization/maintenance phase at the same dose from the open-label induction phase.

Those entering the optimization/maintenance phase following the open-label induction phase may have the dose adjusted during this phase for tolerability.

Eligible transferred-entry responder subjects from ESKETINTRD3005 will join the study at this phase. The first intranasal treatment session for these subjects will begin on Study Day 32 of the optimization/maintenance phase. For the first 4 weeks of optimization/maintenance phase, these subjects will receive weekly treatment sessions with open-label intranasal esketamine as described in the table below.

Optimization/Maintenance Phase Dose Titration of Intranasal Esketamine for Transferred-entry Responder Subjects

Week	Dose	Dose Titration Guidance
Week 5	28 mg	
Week 6	28 or 56 mg	The dose may remain at 28mg or be increased to 56mg as determined by the investigator based on efficacy and tolerability
Week 7, 8	28, 56 or 84 mg	The dose maybe maintained, increased or reduced by 28mg from the previous dosing session No dose increase is permitted after Week 8 For those who have had a prior down titration from a higher dose, a dose increase by 28 mg is allowed based on clinical judgment.
Week 9 through end of phase	28, 56 or 84 mg	No dose increase is permitted after Week 8. If needed for tolerability, a dose reduction by 28mg from the previous dose is permitted from week 9 through the end of the phase.

Instructions for intranasal dosing for subjects ≥ 65 years:

- After week 5 all dosing decisions are to be determined by the investigator based on efficacy and tolerability.
- Prior to intranasal dosing, subjects must have a blood pressure $\leq 150/90$ mm Hg
- Prior to any dose escalation, subjects ≥ 65 years must have had a post-dose blood pressure, on the prior intranasal dosing day, of <180 mmHg systolic and <100 mmHg diastolic.

Intranasal Treatment Session Frequency

As described above, for all subjects, the frequency of intranasal treatment sessions will be reduced from the twice-weekly frequency used in the induction phase to weekly for the first 4 weeks of the optimization/maintenance phase (Week 5 to Week 8).

During the optimization/maintenance phase, the MADRS will be performed weekly for all subjects either at the clinic visit (prior to intranasal treatment session) or remotely during a telephone contact visit (if no intranasal treatment session planned that week).

After the first 4 weeks of this phase (ie, starting from Week 8), the intranasal treatment session frequency will be adjusted (if applicable) at fixed, 4-week intervals (starting at Week 8, and subsequently at Weeks 12, 16, 20, 24, 28, 32, 36, 40, 44, 48), based on the guidance below.

Week 8:

- If the MADRS total score is ≤ 12 :
 - The esketamine treatment session frequency will be changed to every other week (ie, the next intranasal treatment session after Week 8 will be at Week 10)
- If the MADRS total score is > 12 :
 - There will be no change in esketamine treatment session frequency
- If the MADRS assessment at Week 8 is missed, the last MADRS total score available prior to Week 8 will be used to determine if a change in treatment session frequency is indicated at Week 8. In this case:
 - If the MADRS total score is ≤ 12 , the subject will reduce the frequency to receive intranasal treatment sessions every other week for the next 4 weeks (ie, next treatment sessions will be at Weeks 10 and 12)
 - If the MADRS total score is > 12 , the subject will continue to receive weekly intranasal treatment sessions and no further change to the treatment session frequency is permitted for the next 4 weeks

From Week 12 onwards and at subsequent visits every 4 weeks:

- If the MADRS total score is ≤ 12 :
 - If esketamine treatment session frequency is weekly, the frequency will be changed to every other week. (eg, If this is Week 12, the next intranasal treatment session after Week 12 will be at Week 14)
 - If esketamine treatment session frequency is every other week, there will be no change in frequency
- If the MADRS total score is > 12 :
 - If esketamine treatment session frequency is weekly, there will be no change in frequency
 - If esketamine treatment session frequency is every other week, the frequency will be changed to weekly
- If the MADRS is missed at that week, the last MADRS total score available prior to that week will be used to determine if a change in treatment session frequency is indicated at that week.
 - If the MADRS total score is ≤ 12 :
 - If esketamine treatment session frequency is weekly, the frequency will be changed to every other week. (eg, If this is Week 12, the next intranasal treatment session after Week 12 will be at Week 14)
 - If esketamine treatment session frequency is every other week, there will be no change in frequency
 - If the MADRS total score is > 12 :
 - If esketamine treatment session frequency is weekly, there will be no change in frequency
 - If esketamine treatment session frequency is every other week, the frequency will be changed to weekly

A maximum of 3 changes in intranasal treatment session frequency from weekly to every other week is permitted during the optimization/maintenance phase. After this time, if a given subject is unable to

sustain improvement on every other week treatment sessions, they will remain on a weekly frequency for the remainder of the study.

If a subject misses >4 consecutive intranasal treatment sessions and/or ≥ 4 consecutive MADRS assessments in the optimization/maintenance phase, the subject will be discontinued from the study, complete an early withdrawal visit, and will proceed to the follow-up phase.

Oral Antidepressants

Study-site personnel will instruct subjects on how to store and take the oral antidepressant treatment supplied during this study for at-home use.

On intranasal treatment sessions days, it is recommended that oral antidepressant treatment not be taken until at least 3 hours after the intranasal treatment session.

Screening Phase for direct-entry subjects

Subjects will be eligible for screening regardless of whether or not they are currently taking oral antidepressant medication(s).

Subjects taking oral antidepressant medication(s) at screening phase will discontinue their current antidepressant medication(s) prior to the start of the induction phase. If clinically indicated, the antidepressant medication(s) can be either tapered and discontinued during the screening period, or discontinued and switched directly to the new oral antidepressant on Day 1 of the open-label induction phase, per clinical judgment.

Subjects currently not taking any oral antidepressant medication(s) at screening will start 1 of 4 oral antidepressant medications on Day 1 of the induction phase.

Open-label induction and optimization/maintenance phases

Direct-entry subjects: Starting on Study Day 1 of the open-label induction phase, a new, open-label oral antidepressant will be initiated, and will be continued during the induction and optimization/maintenance phases of this study. 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, and will be 1 that the subject has not previously had a nonresponse to in the current episode (based on MGH-ATRQ), has not been previously intolerant to (lifetime), and that is available in the participating country.

Dosing of the new antidepressant will begin on Day 1 and will follow the local prescribing information for the respective product, with a forced titration to the maximally tolerated dose. A protocol-specified titration schedule is provided. As subjects may not be able to tolerate the higher doses of the oral antidepressant during the induction phase, a down titration of the dose is permitted based on clinician's judgment.

Transferred-entry subjects (responder and non-responder subjects): These subjects will continue taking the same oral antidepressant medication(s) (duloxetine, escitalopram, sertraline, or venlafaxine XR), which they started on Day 1 of the double-blind induction phase of ESKETINTRD3005 study, at the same dose, during their participation in the optimization/maintenance phase of this ESKETINTRD3004 study.

Study-site personnel will instruct subjects on how to store and take the oral antidepressant treatment supplied during this study for at home use. A subject diary will be provided to capture oral antidepressant study medication use.

On intranasal dosing days, it is recommended the oral antidepressant medication not be taken until at least 3 hours after the intranasal treatment session.

Follow-up 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.

No intranasal esketamine will be administered during this phase.

All subjects will be provided with an additional 4-week supply of the oral antidepressant medication, at the last clinic visit prior to entering the follow-up phase, to ensure there is no interruption of antidepressant therapy during the transition to further clinical/standard of care.

The decision to continue the oral antidepressant in this phase will be at the discretion of the investigator, however, in order to better assess potential withdrawal symptoms from intranasal study drug and facilitate maintenance of clinical benefit, it is strongly recommended that the oral antidepressant be continued for the duration of the follow-up phase unless determined as not clinically appropriate.

SAFETY AND TOLERABILITY EVALUATIONS

Safety evaluations will include:

- Monitoring of TEAEs, including TEAEs of special interest
- Clinical laboratory tests, including hematology, serum chemistry, and urinalysis
- Physical examination and body weight measurements
- Serum and urine pregnancy testing (for women of childbearing potential)
- Urine drug screen
- Alcohol breath test

Safety evaluations to assess short-term effects following intranasal esketamine dosing will include:

- 12-lead electrocardiogram
- Vital signs
- Pulse oximetry
- Clinician Administered Dissociative States Scale (CADSS), to assess treatment-emergent dissociative symptoms
- Four-item positive symptom subscale of the Brief Psychiatric Rating Scale (BPRS+), to assess treatment-emergent psychotic symptoms
- Modified Observer's Assessment of Alertness/Sedation (MOAA/S), to measure treatment-emergent sedation
- Clinical Global Assessment of Discharge Readiness (CGADR), to document the subject's current clinical status based on the clinician's assessment of the readiness to be discharged from the study site

Safety evaluations will also include assessment of any long-term adverse events, with special attention to:

- Nasal examination and nasal symptom questionnaire to assess local nasal tolerability
- Columbia Suicide Severity Rating Scale (C-SSRS), to assess suicidal ideation and behavior
- Bladder Pain/ Interstitial Cystitis Symptom Score (BPIC-SS), to monitor for symptoms of cystitis, bladder pain, and interstitial cystitis

- Physician Withdrawal Checklist (PWC-20) to assess potential withdrawal symptoms following cessation of intranasal esketamine treatment
- Computerized cognitive battery and Hopkins Verbal Learning Test-Revised (HVLTR), to assess the effect of intranasal esketamine on cognition

EFFICACY EVALUATIONS/ENDPOINTS

Efficacy endpoints include the following: mean total score over time, individual scores over time, as well as change from baseline in the total score and individual scores for the following rating scales:

- Depressive symptoms, using the MADRS and self-reported PHQ-9
- Overall severity of illness, using the Clinical Global Impression Severity (CGI-S)
- Symptoms of anxiety, using the Generalized Anxiety Disorder, 7-items (GAD-7) scale
- Health-related quality of life and health status, using the European Quality of Life (EuroQol) Group, 5 Dimension, 5-Level (EQ-5D-5L) questionnaire
- Functioning and associated disability, using the Sheehan Disability Scale (SDS)

Long-term efficacy will also be assessed by:

- Response rate over time, defined as:
 - percentage of subjects with $\geq 50\%$ reduction from baseline (induction phase) in the MADRS total score
 - percentage of subjects with $\geq 50\%$ reduction from baseline (induction phase) in the PHQ-9 total score
- Remission rate over time, defined as:
 - percentage of subjects with MADRS total score ≤ 12
 - percentage of subjects with PHQ-9 total score ≤ 5

BIOMARKER AND PHARMACOGENOMIC (DNA) EVALUATIONS

Assessment of biomarkers and their potential relationship to maintenance/stabilization of response and non-response 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 DNA and biomarkers (protein) may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

MEDICAL RESOURCE UTILIZATION

Medical resource utilization data, associated with medical encounters, will be collected using the Healthcare Resource Use Questionnaire (HRUQ) during the optimization/maintenance phase and follow-up phase. The HRUQ includes information regarding utilization of healthcare services (including the timing and type of services), enabling changes in level and quantity of services to be considered as a variable in economic models.

Other Evaluations

Patient stated-choice preference survey to assess subject tradeoff preferences for key benefit and harm outcomes associated with TRD treatment, using a stated-choice conjoint analysis survey.

STATISTICAL METHODS

Analysis Sets

The following analysis sets will be used to summarize efficacy and safety data:

Full Analysis Set for open-label induction phase: will be defined as all subjects who receive at least one dose of intranasal esketamine or 1 dose of oral antidepressant during this phase.

Full Analysis Set for optimization/maintenance phase: will be defined as all subjects who receive at least one dose of intranasal esketamine or 1 dose of oral antidepressant during this phase.

Sample Size Determination

No formal sample size calculation was performed for the study. The projected sample size of 750 direct entry subjects plus transferred entry subjects is considered adequate to obtain at least 300 subjects who have received treatment with esketamine for 6 months and at least 100 subjects for 12 months (Note: the total number of subjects will be based on subjects from this study and subjects from other intranasal esketamine Phase 3 studies). The number of transferred entry subjects is based on predictions related to discontinuation rate and efficacy, and therefore may vary.

The sample size will include at least 100 older subjects (who are either direct entry subjects or transferred entry subjects from the ESKETINTRD3005 study) aged ≥ 65 years.

Safety Analysis

Safety data for the open label induction phase, the optimization/maintenance phase and follow-up phase will be analyzed separately for each phase as well as for the entire treatment period (induction and optimization/maintenance phase).

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized. Subjects who die, who discontinue treatment due to an adverse event, or who experience a severe or a serious adverse event will be summarized separately.

TEAEs of special interest will be examined separately grouped in the following categories: drug abuse, dependence and withdrawal (standardized MedDRA queries [SMQ]), increased blood pressure, increased heart rate, dizziness/vertigo; impaired cognition; anxiety and lower urinary tract symptoms SMQ including cystitis.

Body weight, systolic and diastolic blood pressure, pulse/heart rate, respiratory rate, 12-lead electrocardiogram (ECG), pulse oximetry, and clinical laboratory test results, and changes from baseline will be tabulated over time, using descriptive statistics. Any treatment-emergent abnormalities will be listed.

Changes in findings from the baseline nasal examination (including the upper respiratory tract/throat) will be listed. A shift table for changes in rating for each examination (visual inspection of the nostrils, nasal mucosa, and throat for nasal erythema, rhinorrhea, rhinitis, capillary/blood vessel disruption, crust formation on the nose, and epistaxis) will be presented. Scoring from the nasal symptom questionnaire will be summarized descriptively.

Cognitive status from the computerized test battery and HVLT-R, bladder symptom/cystitis data from the BPIC-SS, and withdrawal symptoms from the PWC-20 will be provided as descriptive statistics of scores and their changes (and/or percent changes) from predose or baseline, as appropriate per assessment.

Dissociative data from the CADSS, psychosis-like effect data from the BPRS+, sedation data from the MOAA/S, and data from the CGADR including changes from baseline, will be summarized at each

scheduled time point. Suicidal ideation and behaviors based on the C-SSRS will be summarized in incidence and shift tables.

Efficacy Analysis

Depression symptoms assessed by MADRS as well as PHQ-9, global change in severity (CGI-S), social, occupational and family functioning related disability (SDS), anxiety (GAD-7), and health status (EQ-5D-5L), will be summarized descriptively at each scheduled visit for each phase, using both last observation carried forward and observed case data. The proportions of subjects who responded and remitted based on the MADRS total score as well as PHQ-9 total score will be provided over time for each phase.

Biomarker and Pharmacogenomic Analysis

Baseline biomarker values and changes from baseline biomarker values to the time points specified in the Time and Events Schedule will be summarized. Exploratory analyses may include correlation of biomarker values at baseline and change from baseline in biomarker values with the efficacy parameters 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 and non-response.

Pharmacogenomic analyses may include candidate gene analyses or genome-wide association analyses in relation to treatment response, maintenance/stabilization of response, non-response and MDD/TRD.

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

Medical Resource Utilization Analysis

Medical resource utilization data (including HRUQ results) will be analyzed descriptively.

Patient stated-choice preference

Summary statistics and a regression model will be used to estimate a distribution of preferences weights for each level of each benefit and harm in the preference survey (described in a SAP). Maximum acceptable risk for harms will be calculated for varying degrees of benefit. Analyses and reporting of these survey results may be conducted separately from this study.

TIME AND EVENTS SCHEDULE (Screening [Direct-entry Subjects Only] and Open-label Induction Phase [Direct-entry and Transferred-entry Non-responder Subjects from ESKETINTRD3005 Study Only])

Phase	Screening	Open-label Induction Phase								
	(Direct-entry Subjects Only)	(Direct-entry Subjects and Transferred-entry Non-responder Subjects Only)								
Visit number	1	2.1 ^b	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9 ^a
Week	Within 4 weeks of Day 1	1	2		3			4		
Study day		1 (baseline)	4	8	11	15	18	22	25	28
Clinic visit window (in days)	-	-	±1	±1	±1	±1	±1	±1	±1	±1
Study Procedures										
Screening/Administrative										
Informed consent (ICF)- direct entry subjects	X									
ICF- transferred-entry non-responder subjects		X ^c								
Medical history, psychiatric history, demographics, and employment status	X									
MINI	X									
MMSE	X									
MGH-ATRQ ⁿ	X									
Height	X									
Inclusion/exclusion criteria-direct-entry subjects	X	X ^c								
Inclusion/exclusion criteria-transferred-entry subjects		X ^c								
Patient Stated-choice Preference Survey ^o										X ^p
Prestudy therapy	X									
Preplanned surgery/procedures- direct entry subjects	X									
Preplanned surgery/procedures-transferred-entry non-responder subjects		X ^c								
STOP-Bang Questionnaire (including assessment of BMI and neck circumference)	X									
Study Drug										
Dispensing of oral antidepressant		X								X
Practice session for use of intranasal device (Direct entry subjects only)		X ^c								
Intranasal esketamine ^m		X	X	X	X	X	X	X	X	
Drug accountability (intranasal study medication)		X	X	X	X	X	X	X	X	

Phase	Screening	Open-label Induction Phase								
	(Direct-entry Subjects Only)	(Direct-entry Subjects and Transferred-entry Non-responder Subjects Only)								
Visit number	1	2.1 ^b	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9 ^a
Week	Within 4 weeks of Day 1	1	2		3		4			
Study day		1 (baseline)	4	8	11	15	18	22	25	28
Clinic visit window (in days)	-	-	±1	±1	±1	±1	±1	±1	±1	±1
Drug accountability (oral antidepressant study medication)										X
Dispense subject diary for oral antidepressant		X								
Review subject diary and update (if applicable)			X	X	X	X	X	X	X	X
Oral antidepressant compliance check				X		X		X		X
Collect/return of subject diary										X
Safety Assessments (Site-completed)										
Physical examination	X	X ^{b, c}								X
Nasal examination ^c	X	X ^b								X
Vital signs ^c : blood pressure, pulse, respiratory rate, temperature ^m	X	X	X	X	X	X	X	X	X	
Vital signs ^c (postdose): blood pressure, pulse, respiratory rate ^m	.	X	X	X	X	X	X	X	X	
Weight	X	X ^b								X
12-lead ECG ^{l, m}	X	X		X		X			X	
C-SSRS: Baseline/Screening version	X									
C-SSRS: Since last visit version ^{c, m}		X ^b	X	X	X	X	X	X	X	X
MOAA/S and pulse oximetry ^{g, m}	X	X	X	X	X	X	X	X	X	
BPRS ^{+, h, m}		X	X	X	X	X	X	X	X	
CADSS ^{h, m}		X	X	X	X	X	X	X	X	
CGADR ^{l, m}		X	X	X	X	X	X	X	X	
PWC-20 ^l									X	
Safety Assessments (Subject-completed)										
Nasal symptom questionnaire ^k		X	X		X		X		X	
BPIC-SS ^c		X ^b				X				X
Efficacy Assessments (Clinician)										
MADRS (7-day recall)	X	X ^b		X		X		X		X
CGI-S ^c	X	X ^b	X	X	X	X		X		X
Subject-completed Assessments										
PHQ-9 ^d	X	X ^b				X				X
SDS ^d	X	X ^b				X				X
GAD-7 ^d	X	X ^b								X

Phase	Screening	Open-label Induction Phase								
	(Direct-entry Subjects Only)	(Direct-entry Subjects and Transferred-entry Non-responder Subjects Only)								
Visit number	1	2.1 ^b	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9 ^a
Week	Within 4 weeks of Day 1	1	2	3	4					
Study day		1 (baseline)	4	8	11	15	18	22	25	28
Clinic visit window (in days)	-	-	±1	±1	±1	±1	±1	±1	±1	±1
EQ-5D-5L ^d	X	X ^b				X				X
Cognition Testing										
Practice sessions (only for direct-entry subjects)	X									
Computerized test battery and HVLT-R		X ^b								X
Clinical Laboratory Assessments										
TSH, HbA1c	X									
Lipid panel (fasting)	X									
Hematology, chemistry ^c	X	X ^b								X
Urine drug screen ^c	X	X				X			X	
Alcohol breath test	X	X								
Urinalysis ^c	X	X ^b				X				X
Serum pregnancy test (only for females of child bearing potential)	X									
Urine pregnancy test ^c (only for females of child bearing potential)		X ^b				X				X
Biomarkers										
Blood sample collection (protein) ^{c,1}	X	X ^b		X						X
Blood sample collection (DNA) ¹	X									X
Ongoing Subject Review										
Menstrual cycle tracking (Start date of last menstrual period prior to study visit; only for female subjects <65 years with menstrual cycle)	X	X ^b							X	
Concomitant Therapy										Ongoing
Adverse Events										Ongoing

Footnotes:

Abbreviations: BMI=Body mass index; BPIC-SS=Bladder Pain/Interstitial Cystitis Symptom Score; BPRS+=Four-item Positive Symptom Subscale of the Brief Psychiatric Rating Scale; C= clinic visit; CADSS=Clinician Administered Dissociative States Scale; CGADR=Clinical Global Assessment of Discharge Readiness; CGI-S =Clinical Global Impression – Severity; C-SSRS=Columbia Suicide Severity Rating Scale; ECG=electrocardiogram; EQ-5D-5L=EuroQoL-5D, 5-level; GAD-7=7-item Generalized Anxiety Disorder scale; HbA1C=glycosylated hemoglobin; HVLT-R=Hopkins Verbal Learning Test-Revised; ICF=informed consent form; MADRS=Montgomery-Asberg Depression Rating Scale; MGH-ATRQ=Massachusetts General Hospital Antidepressant Treatment History Questionnaire; MINI=Mini International Neuropsychiatric Interview; MMSE= Mini Mental State Examination; MOAA/S=Modified Observer's Assessment of Alertness/Sedation; PHQ-9=Patient Health Questionnaire – 9; PWC-20= 20-item Physician Withdrawal Checklist; SDS=Sheehan Disability Scale; STOP-Bang=Snoring, Tired, Observed Apnea, High Blood Pressure, Body mass index, Age, Neck Size, Gender (a questionnaire); 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.

- a) If a subject withdraws before the end of the open-label induction phase (ie, Visit 2.9, Day 28) for reasons other than withdrawal of consent, an early withdrawal visit (refer to Time and Events Schedule: Optimization/Maintenance Phase) should be conducted, 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.
- b) For transferred-entry non-responder subjects. Visit 2.9 (Day 28) of 3005 study coincides with Visit 2.1 (Day 1) of 3004 study, and assessments of Visit 2.9 (Day 28) of 3005 study do not need to be repeated on Visit 2.1 (Day 1) of 3004 study.
- c) Predose (if/when performed on intranasal dosing days).
- d) Subject-reported outcome assessments should be administered before all other study related procedures during a clinic visit.
- e) Postdose vital signs will be performed at 40 minutes, 1 hour, and 1.5 hours postdose. Please refer to Section 6.1 for guidance on blood pressure monitoring on intranasal dosing days.
- f) Twelve-lead ECG will be performed predose and 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 2.3, 2.5 and 2.8. A time window of ± 15 minutes will be permitted.
- g) The MOAA/S will not be performed at Visit 1 (pulse oximetry only). The MOAA/S will be performed every 15 minutes from predose to t=+1.5 hours postdose (please refer to Section 9.2.1 for further guidance on MOAA/S assessments). Pulse oximetry will be performed every 15 minutes from predose to t=1.5 hours postdose (please refer to Section 9.2.1 for further guidance on timing of pulse oximetry assessments).
- h) The BPRS+ and CADSS to be performed predose and at 40 minutes and 1.5 hours postdose.
- i) CGADR to be performed at 1 hour and 1.5 hours postdose; if the response is not “Yes” at 1.5 hours postdose, the assessment will be repeated every 15 minutes until a “Yes” response is achieved or until the subject is referred for appropriate medical care if clinically indicated. A subject should not be discharged before study visit procedures are complete.
- j) PWC-20 to be performed pre-dose in all subjects.
- k) Nasal symptom questionnaire will be performed predose and at 1 hour postdose.
- l) It is preferred that subjects adhere to a low fat diet on the day of sample collection
- m) If intranasal dosing is postponed (but occurs within the visit window) due to blood pressure elevation, predose procedures and procedures at all postdose time points (if applicable) must be repeated on the actual intranasal dosing day.
- n) For specific tricyclic antidepressants which are 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.
- o) Patient Stated-choice Preference Survey to be completed only by English-speaking subjects at United States, United Kingdom and Australia sites. The survey will not be conducted in any other countries, regardless of whether the subjects in those other countries speak English. The survey is conducted only once per subject.
- p) The survey should be completed during or shortly after Visit 2.9, or if the subject has completed this visit prior to when the survey becomes available, trial sites should have the subject complete the survey at the earliest possible opportunity or at early withdrawal. The survey should be administered predose (if/when performed on intranasal dosing days).

TIME AND EVENTS SCHEDULE (Optimization/Maintenance Phase [Responder Subjects from the Open-label Induction Phase and Transferred-entry Responder Subjects from ESKETINTRD3005 Study])

Phase	Optimization/Maintenance Phase ^c (Responder Subjects from the Open-label Induction Phase and Transferred-entry Responder Subjects from ESKETINTRD3005)											
	Visit Number ^a	3.1 ^b	3.2	3.3	3.4	3.5	3.6 to 3.X					EW or End of O/M Phase ^c
							Study procedure frequency from Week 9 through end of phase					
Week	4	5	6	7	8	Every week	Every 2 Weeks	Every 4 Weeks	Every 8 Weeks	Every 12 Weeks		
Study Day	28	32	39	46	53	Every 7 days	Every 14 days	Every 28 days	Every 56 days	Every 84 days		
Clinic (C) or Telephone Contact (T)	C	C	C	C	C	C/T	C	C	C	C	C	
Study Procedures												
Screening/Administrative												
Informed consent (for transferred-entry responder subjects only)	X											
Inclusion/exclusion criteria (transferred-entry responder subjects only)	X											
Preplanned surgery/procedures-transferred-entry responder subjects	X ^e											
Study Drug												
Intranasal esketamine treatment ⁿ		X	X	X	X	X ^d	X ^d					
Adjustment of intranasal treatment session frequency (if applicable)					X			X				
Dispensing oral antidepressant (open-label) ^e	X				X			X ^d			X	
Dispense subject diary for oral antidepressant	X											
Oral antidepressant compliance check ^e , including review of subject diary		X		X			X ^d				X	
Collect/return of subject diary											X	
Drug accountability for intranasal study medication		X	X	X	X	X ^d						
Drug accountability for oral antidepressant ^e					X			X ^{d,e}			X	
Efficacy Assessments (Clinician)												
MADRS (7-day recall) ^e		X	X	X	X	X					X	
CGI-S ^e		X	X	X	X	X ^d					X	
Subject-Completed Assessments												
PHQ-9 ^f		X		X				X			X	
SDS ^f					X			X			X	
GAD-7 ^f					X			X			X	

Phase	Optimization/Maintenance Phase ^c										EW or End of O/M Phase ^c
	(Responder Subjects from the Open-label Induction Phase and Transferred-entry Responder Subjects from ESKETINTRD3005)										
	Visit Number ^a	3.1 ^b	3.2	3.3	3.4	3.5	3.6 to 3.X				
Study procedure frequency from Week 9 through end of phase											
Week	4	5	6	7	8	Every week	Every 2 Weeks	Every 4 Weeks	Every 8 Weeks	Every 12 Weeks	
Study Day	28	32	39	46	53	Every 7 days	Every 14 days	Every 28 days	Every 56 days	Every 84 days	
Clinic (C) or Telephone Contact (T)	C	C	C	C	C	C/T	C	C	C	C	
Study Procedures											
EQ-5D-5L ^l		X		X			X				X
Patient Stated-choice Preference Survey ^o					X ^p						X ^p
Safety Assessments (Clinician)											
Physical examination, nasal examination, weight					X			X ^{d, e}			X
Vital signs (predose): blood pressure, pulse, respiratory rate, and temperature ⁿ		X	X	X	X	X ^d					X
Vital signs (postdose) ^g : blood pressure, pulse, and respiratory rate only ⁿ		X	X	X	X	X ^d					
12-lead electrocardiogram ^{h, n}		X	X		X			X ^d			X
C-SSRS (since last visit version) ^{e, n}		X	X	X	X	X ^d					X
MOAA/S ^{i, n}		X	X	X	X	X ^d					
Pulse oximetry ^{i, n}		X	X	X	X	X ^d					
BPRS+ and CADSS ^{j, n}		X	X	X	X	X ^d					
CGADR ^{k, n}		X	X	X	X	X ^d					
PWC-20 (performed [pre-dose if applicable] at last clinic visit of this phase)											X
Safety Assessments (Subject)											
Nasal symptom questionnaire ^l		X			X			X ^d			
BPIC-SS ^e					X			X ^d			X
Cognitive Testing											
Computerized cognitive battery and HVLt-R ^e										X ^d	X
Clinical Laboratory Tests											
Hematology and chemistry ^e					X				X ^d		X
Urinalysis ^e					X				X ^d		X
Urine drug screen ^e					X				X ^d		
Alcohol breath test ^e					X				X ^d		
Urine pregnancy test ^e (only for females of child bearing potential)					X				X ^d		
Serum pregnancy test(only for females of child bearing potential)											X

Phase	Optimization/Maintenance Phase ^c (Responder Subjects from the Open-label Induction Phase and Transferred-entry Responder Subjects from ESKETINTRD3005)											
	Visit Number ^a	3.1 ^b	3.2	3.3	3.4	3.5	3.6 to 3.X					EW or End of O/M Phase ^c
							Study procedure frequency from Week 9 through end of phase					
Week	4	5	6	7	8	Every week	Every 2 Weeks	Every 4 Weeks	Every 8 Weeks	Every 12 Weeks		
Study Day	28	32	39	46	53	Every 7 days	Every 14 days	Every 28 days	Every 56 days	Every 84 days		
Clinic (C) or Telephone Contact (T)	C	C	C	C	C	C/T	C	C	C	C	C	
Study Procedures												
Medical Resource Utilization												
HRUQ ^e			X		X		X ^d				X	
Biomarker												
Blood sample collection (protein) ^{e,m}					X						X	
Ongoing Subject Review												
Menstrual cycle tracking (start date of last menstrual period prior to study visit; only for females of child bearing potential with a menstrual cycle)					X			X ^d				
Concomitant therapy	<i>Ongoing</i>											
Adverse events	<i>Ongoing</i>											

Footnotes:

Abbreviations: BPIC-SS = Bladder Pain/Interstitial Cystitis Symptom Score; BPRS+ = Four-item Positive Symptom Subscale of the Brief Psychiatric Rating Scale; CADSS = Clinician-Administered Dissociative States Scale; CGADR = Clinical Global Assessment of Discharge Readiness; CGI-S = Clinical Global Impression - Severity; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EQ-5D-5L = European Quality of Life (EuroQol) Group, 5-Dimension, 5-Level; EW = Early Withdrawal; GAD-7 = Generalized Anxiety Disorder, 7-item; HbA1C= Glycated hemoglobin; HRUQ=Healthcare Resource Use Questionnaire; HVLT-R = Hopkins Verbal Learning Test - Revised; MADRS = Montgomery-Asberg Depression Rating Scale; MOAA/S = Modified Observer's Assessment of Alertness/Sedation; PHQ-9 = Patient Health Questionnaire, 9-item; PWC-20 = Physician Withdrawal Checklist, 20-item; 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.

- a) Visits (clinic or telephone contacts) will be conducted weekly during the optimization/maintenance phase. Clinic visits (visit window: ±3 days) will be conducted for all intranasal treatment sessions (weekly from week 5 to 8; weekly or every other week from week 9 to the end of phase); Telephone contact visits (visit window +/- 3 days) for MADRS assessment will occur on the weeks without a clinic visit. Due to the variable clinic visit frequency, following Visit 3.5, visit numbers will continue sequentially (eg, 3.6, 3.7, etc) until the subject completes the phase. The frequency of study procedures from Week 9 to the end of the phase is provided within the respective column (ie, every week, 2 weeks, 4 weeks, 8 weeks, and 12 weeks).
- b) Results for all assessments performed on Day 28 of the open-label induction phase of ESKETINTRD3004 (direct and transferred-entry non-responder subjects) or Day 28 of the ESKETINTRD3005 (transferred-entry responder subjects) will not be repeated as part of Visit 3.1. For transferred-entry responder subjects, the Day 28 visit of the double-blind induction phase in ESKETINTRD3005 must coincide exactly with Day 28 (Visit 3.1) for this study. There is no gap allowed between studies. All transferred-entry responder subjects must meet all of the transferred-entry subject-specific inclusion criteria and none of the exclusion criteria in order to be enrolled.

- c) If a subject withdraws before the end of the induction or optimization/maintenance phase for reasons other than withdrawal of consent, or has completed the induction phase but is not eligible to continue to the optimization/maintenance phase, an early withdrawal visit should be conducted followed by the follow-up phase (Refer to Time and Events Schedule: Follow-up Phase). If the early withdrawal visit is conducted on the same day as a scheduled visit, duplicate assessments are not required. Subjects who are currently in the optimization/maintenance phase at the time the study is completed, as well as subjects who completed this phase, will conduct an End of Optimization/Maintenance phase visit followed by the follow-up phase.
- d) Performed only at clinic visits for intranasal treatment sessions (omit if telephone contact visit). If necessary, the study procedure can be performed ± 1 week to the subject's clinic visit schedule (based on the frequency of intranasal treatment sessions).
- e) Predose (if/when performed on intranasal dosing days).
- f) Subject-reported outcome assessments should be administered before all other study-related procedures during a clinic visit.
- g) Postdose vital signs will be performed at $t = +40$ minutes, 1 hour, and 1.5 hours postdose. Please refer to Section 6.1 for guidance for blood pressure monitoring on intranasal dosing days.
- h) At clinic visit 3.2 the 12-lead electrocardiogram will be performed predose and at 1 hour postdose. At the remaining clinic visits for intranasal treatment sessions with 12-lead electrocardiogram scheduled, it will be performed at 1 hour postdose. A time window of ± 15 minutes is permitted.
- i) The MOAA/S will be performed every 15 minutes from predose to $t = 1.5$ hours postdose (please refer to Section 9.2.1 for further guidance on MOAA/S assessments). Pulse oximetry will be performed every 15 minutes from predose to $t = 1.5$ hours postdose (please refer to Section 9.2.1 for further guidance on timing of pulse oximetry assessments).
- j) The BPRS+ and CADSS to be performed predose and at 40 minutes and 1.5 hours postdose.
- k) CGADR to be performed at 1 hour and 1.5 hour postdose; if the response is not "Yes" at 1.5 hour postdose, the assessment will be repeated every 15 minutes until a "Yes" response is achieved or until the subject is referred for appropriate medical care if clinically indicated. A subject should not be discharged before study visit procedures are complete.
- l) Nasal symptom questionnaire will be performed predose and at 1 hour postdose.
- m) It is preferred that subjects adhere to a low fat diet on the day of sample collection.
- n) If intranasal dosing is postponed (but occurs within visit window) due to blood pressure elevation, predose procedures and procedures at all postdose time points (if applicable) must be repeated on the actual intranasal dosing day.
- o) Patient Stated-choice Preference Survey to be completed only by English-speaking subjects in United States, United Kingdom and Australia sites. The survey will not be conducted in any other countries, regardless of whether the subjects in those other countries speak English. The survey is conducted only once per subject.
- p) NOTE for transferred-entry responder subjects from ESKETINTRD3005 study who enter directly to the optimization/maintenance phase, the survey should be completed during or shortly after Visit 3.5, or if the subject completed this visit prior to when the survey becomes available, the subject should complete the survey at the earliest possible opportunity or at early withdrawal. The survey should be administered predose (if/when performed on intranasal dosing days). Subjects who completed the Patient Stated-choice Preference Survey while enrolled in ESKETINTRD3005 should not be issued the survey.

TIME AND EVENTS SCHEDULE (Follow-up Phase)

Phase	Follow-up Phase ^a		
	4.1	4.2	4.3
Visit Number	1	2	4
Weeks After Last Intranasal Dose	1	2	4
Clinic (C) Visit or Telephone Contact (T)	T	C	C
Study Procedures			
Study Drug			
Drug accountability (oral antidepressant study medication)			X
Oral Antidepressant Compliance			
Oral antidepressant compliance check		X	X
Safety Assessments (Clinician-Completed)			
Physical examination			X
Nasal examination			X
Vital signs: blood pressure, pulse, respiratory rate, temperature		X	X
12-lead electrocardiogram			X
C-SSRS: Since last visit version		X	X
PWC-20	X	X	X
Safety Assessments (Subject-Completed)			
BPIC-SS ^b		X	X
Efficacy Assessments (Clinician-Completed)			
MADRS	X	X	X
CGI-S		X	X
Efficacy Assessments (Subject-Completed)			
PHQ-9 ^b		X	X
SDS ^b			X
GAD-7 ^b			X
EQ-5D-5L ^b		X	X
Cognition testing			
Computerized test battery and HVLT-R			X
Medical Resource Utilization			
HRUQ		X	X
Clinical Laboratory Assessments			
Hematology and chemistry			X
Urinalysis		X	X
Serum pregnancy test(only for females of child bearing potential)			X
Biomarker			
Blood sample collection (protein) ^b			X
Ongoing Assessments			
Menstrual cycle tracking (start date of last menstrual period prior to study visit; only for female subjects <65 years with a menstrual cycle)			X
Concomitant therapy		<i>Ongoing</i>	
Adverse events		<i>Ongoing</i>	

Footnotes:

Key: BPIC-SS = Bladder Pain/Interstitial Cystitis Symptom Score; CGI-S = Clinical Global Impression - Severity; C-SSRS = Columbia Suicide Severity Rating Scale;
EQ-5D-5L = European Quality of Life (EuroQol) Group, 5-Dimension, 5-Level; GAD-7 = Generalized Anxiety Disorder, 7-item; HRUQ = Healthcare Resource Utilization Questionnaire;
HHLT-R = Hopkins Verbal Learning Test - Revised; MADRS = Montgomery-Asberg Depression Rating Scale; PHQ9= Patient Health Questionnaire9, SDS = Sheehan Disability Scale;
PWC-20 = Physician Withdrawal Checklist, 20-item.

- a) Visit window will be ± 3 days.
- b) Subject-reported outcome assessments should be administered before all other study-related procedures during a clinic visit.

ABBREVIATIONS

AHI	apnea-hypopnea index
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ASA	American Society of Anesthesiologists
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BDNF	brain-derived neurotrophic factor
BMI	body mass index
BPIC-SS	Bladder Pain/Interstitial Cystitis Symptom Score
BPRS	(the full 18-item) Brief Psychiatric Rating Scale
BPRS+	(the 4-item) Brief Psychiatric Rating Scale, positive-symptom subscale
β-hCG	β-human chorionic gonadotropin
CADSS	Clinician-Administered Dissociative States Scale
CGADR	Clinical Global Assessment of Discharge Readiness
CGI-S	Clinical Global Impression - Severity
C _{max}	maximum plasma concentration
CPR	cardiopulmonary resuscitation
CRF	case report form
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	cytochrome P450, with any appended letters (2B6, 3A4, etc) indicating subtypes
DBS	Deep brain stimulation
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) Group, 5-Dimension, 5-Level (questionnaire)
EQ-VAS	EuroQol group: Visual Analogue Scale
EU	European Union
FSH	follicle stimulating hormone
FT4	Free thyroxine
GAD-7	Generalized Anxiety Disorder, 7-item (scale)
GCP	Good Clinical Practice
HCL	hydrochloride
HDL	high-density lipoprotein
HDRS	Hamilton Depression Rating Scale
HIV	human immunodeficiency virus
HPA	hypothalamic pituitary adrenal
HRUQ	Healthcare Resource Use Questionnaire
HVLT-R	Hopkins Verbal Learning Test - Revised
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IDS-C ₃₀	Inventory of Depressive Symptomatology - Clinician-rated, 30 item
IEC	Independent Ethics Committee
IM	intramuscular
IRB	Institutional Review Board
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine system
IV	intravenous
IWRS	interactive web response system
JRD	Janssen Research & Development
LDL	low-density lipoprotein
LSD	lysergic acid diethylamide
LBBB	left bundle branch block

MADRS	Montgomery-Asberg Depression Rating Scale
MAOI	monoamine oxidase inhibitor
MCI	mild cognitive impairment
MDMA	3, 4-methylenedioxy-methamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview
MMRM	mixed-effects model for repeated measures
MMSE	Mini Mental State Examination
MOAI	monoamine oxidase inhibitor
MOAA/S	Modified Observer's Assessment of Alertness/Sedation
MDD	major depressive disorder
MGH-ATRQ	Massachusetts General Hospital - Antidepressant Treatment Response Questionnaire
MGH-FRLHQ	Massachusetts General Hospital - Female Reproductive Lifecycle and Hormones Questionnaire
NMDA	N-methyl-D-aspartate
NYHA	New York Heart Association
OSA	obstructive sleep apnea
PACs	premature atrial contractions
PCP	primary care physician
PCP	phencyclidine
PHQ-9	Patient Health Questionnaire, 9-item
PK	pharmacokinetics
PQC	product quality complaint
PTSD	posttraumatic stress disorder
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
RBBB	right bundle branch block
SAP	statistical analysis plan
SD	standard deviation
SDS	Sheehan Disability Scale
SE	standard error
SmPC	Summary of Product Characteristics
SMQ	standardized MedDRA queries
SNRI	serotonin-norepinephrine reuptake inhibitor
SpO ₂	saturation of peripheral blood oxygen
SSRI	selective serotonin reuptake inhibitors
STOP-Bang	<u>S</u> norring, <u>T</u> iredness, <u>O</u> bserved Apnea, <u>H</u> igh Blood <u>P</u> ressure, <u>B</u> ody Mass Index, <u>A</u> ge, <u>N</u> eck Size, <u>G</u> ender (questionnaire)
SUSAR	suspected unexpected serious adverse reaction
TEAEs	treatment-emergent adverse events
TMS	transcranial magnetic stimulation
T _{max}	time to reach the maximum plasma concentration
TRD	treatment-resistant depression
TSH	thyroid stimulating hormone
USPI	United States Prescribing Information
US	United States
VNS	Vagal nerve stimulation
XR	extended-release

1. INTRODUCTION

Major depressive disorder (MDD) is a serious, recurrent, and disabling psychiatric illness⁹¹. It is the second leading cause of years lost to disability worldwide and is associated with excess mortality, and the estimated median years of potential life lost is 10 years.^{92,97} About 30% of patients fail to achieve remission despite treatment with multiple antidepressant medications, and are considered to have treatment-resistant depression (TRD).^{31,74} In patients who respond to antidepressants, the time to onset of effect is typically 4 to 7 weeks, during which time patients continue to suffer from their symptoms and continue to be at risk of self-harm, as well as being impacted by the associated harm to their personal and professional lives.^{74,79} Therefore, 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.^{21,24}

Ketamine and esketamine (S-ketamine, the S enantiomer of ketamine) are approved and widely used for the induction and maintenance of anesthesia via intramuscular (IM) or intravenous (IV) administration.⁴⁴ The desired analgesic-anesthetic effects of ketamine and esketamine are attributed to the blockade of ionotropic N-methyl-D-aspartate (NMDA) glutamate receptors.^{52,67,99}

Monoamines (serotonin, norepinephrine, and/or dopamine) are only modulatory transmitters; therefore, conventional monoaminergic antidepressants would not be expected to robustly affect synaptic transmission, activity-dependent release of brain-derived neurotrophic factor (BDNF), or synaptogenesis.²⁴ In contrast, the mechanism of action of ketamine and esketamine is distinct from conventional antidepressants and both ketamine and esketamine profoundly affects fast excitatory glutamate transmission, increases BDNF release, and stimulates synaptogenesis.²⁴

Most literature reports of the antidepressant effects of ketamine describe studies using IV administration of the racemate, with a few exceptions.⁴⁷ Janssen Research & Development (JRD) is developing intranasal esketamine as an antidepressant therapy as, in contrast to the racemate, it has higher NMDA receptor affinity over arketamine (R-ketamine), thereby requiring a lower volume which can be administered via the intranasal route.^{51,63,68}

For the most comprehensive nonclinical and clinical information regarding esketamine (JNJ-54135419), please refer to the latest edition of the Investigator's Brochure.⁴¹

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. Summary of Nonclinical Findings

Safety Pharmacology

The following text is quoted from the United States (US) prescribing information for anesthetic Ketalar[®] (ketamine hydrochloride injection)⁴⁴ 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, unanesthetized 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.⁴¹

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 to 72 mg/day. Heart rate was slightly increased.

Further details can be found in the Investigator's Brochure.⁴¹

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.⁴¹

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 as IM induction followed by IV maintenance duration was 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.⁴¹

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.⁴¹

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.⁴¹

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 and 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.²⁶ 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:⁴⁴

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.⁴¹ 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.⁴¹

1.1.2. Clinical Studies

1.1.2.1. Pharmacokinetics and Product Metabolism

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.⁹⁶ Like ketamine, norketamine is a noncompetitive antagonist at the NMDA receptor.^{25,38} Norketamine has a half-life in plasma of approximately 5 hours.³⁶ The major human hepatic CYPs that catalyze ketamine N-demethylation in vitro are CYP2B6 and CYP3A4.^{37,69,98} The CYP enzymes responsible for the formation of norketamine metabolites include CYP2A6 and CYP2B6.⁶⁹ Published results of a clinical PK study indicate that esketamine does not invert to the R-enantiomer.³³

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.⁶ Less than 3% of an administered dose was excreted in urine as parent drug.⁹⁴

A summary of the pharmacokinetics (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 ESKTIVTRD2001.¹⁴ 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.¹⁴ 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, ESKETINTRD1012, and the double-blind phase of Panel A of the ESKETIVTRD2003 that inform dose selection for the Phase 3 program are described below. 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.¹¹ 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 of C_{max} (T_{max}) 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 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 363 ng*h/mL, respectively). The semi-reclined position of the head and the instruction to subjects to sniff 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.¹² On average, plasma esketamine C_{max} and AUC values were up to 48% higher in Japanese subjects compared with Caucasian subjects.

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).¹³ Subjects received a single intranasal treatment of esketamine 28 mg. Median time to reach the maximum plasma concentration (T_{max}) of esketamine was approximately 30 minutes for both age groups. The geometric means of C_{max} and AUC from time 0 to infinite

time, AUC_{∞} , for esketamine were approximately 21% and 17% higher, respectively, in the elderly compared with younger adult subjects.

Study ESKETINTRD1012 evaluated the pharmacokinetics and safety of a single intranasal 84-mg dose, which was self-administered by 8 healthy subjects who were ≥ 75 years of age and 8 healthy younger adults (18 to 55 years of age).¹⁰ Preliminary data showed the median time to reach the maximum plasma concentration (T_{max}) of esketamine was 0.53 hours and 0.83 hours, in healthy elderly subjects ≥ 75 years of age and younger adults, respectively. The means of the C_{max} and area under the plasma concentration-time curve from time 0 to infinite time (AUC_{∞}), for esketamine were approximately 48% and 31% higher, respectively, in the elderly compared with younger adult subjects. Differences were greater based on median C_{max} and AUC_{∞} values (97% and 63% higher in the elderly, respectively).

Study ESKETINTRD2003 is an ongoing 2-panel, doubly randomized, double-blind, placebo-controlled, multicenter study.⁸ 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 (ongoing) is 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.

1.1.2.2. 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).³² This recent meta-analysis of studies suggests that ketamine has a rapid onset (within 1 day) of antidepressant efficacy, including in those who have not benefitted from other antidepressants used as monotherapy or in combination with oral antidepressants.

Esketamine (0.2 and 0.4 mg/kg administered over 40 minutes) has similar, rapid, and robust antidepressant effect 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).¹⁴ 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 esketamine dose groups was statistically significant (1-sided $p = 0.001$ 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 esketamine 0.20 mg/kg group, and -17.8 (9.45) in the esketamine 0.40 mg/kg group.

The studies listed above assessed the efficacy of ketamine or 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 ketamine given twice a week would also maintain the antidepressant response; the data from this study suggest that ketamine (0.50 mg/kg IV over 40 minutes) administered twice a week was sufficient for maintaining the initial effect over a 4 week treatment period.¹⁵

As noted above, Study ESKETINTRD2003 is a 2-panel, doubly randomized, double-blind, placebo-controlled, multicenter study.⁸ 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 (ongoing) is 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). An initial analysis of the 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) (data on file). Subjects eligible for re-randomization had to have a Quick Inventory of Depressive Symptomatology – Self Report (QIDS-SR₁₆) 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 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 mg and 84 mg doses appears to support twice-a-week dosing.

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. Based on PK data from ESKETINTRD1012 it is also possible that the 28 mg dose in the elderly may overlap with the 56 mg dose in younger patients, so addition of the 28 mg dose in the elderly may provide an efficacious dose while improving safety.

1.1.2.3. 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[®] United States Prescribing Information [USPI] 2011; Ketanest[®]S Summary of Product Characteristics [SmPC] 2011).^{35,44,45,71,86}

In 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 [Table 1](#) for details.

Table 1: 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^{44,a}	"Very Common" or "Common" Reactions Per Anesthetic Esketamine SmPC^{90,b}
Psychiatric disorders	<u>Frequency:</u> Emergence reactions occurred in approximately 12% of patients. <u>Characteristics:</u> 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.	<u>Frequency:</u> Recovery reactions were common. When esketamine was the sole anesthetic, up to 30% of patients displayed dose-dependent recovery reactions. <u>Characteristics:</u> 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 $\geq 1/10$ and "common" was defined as $\geq 1/100$ to $< 1/10$.

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

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

According to the SmPC for esketamine,⁴⁵ 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.⁵³

Administration of esketamine is associated with a number of adverse events, which are transient in nature and typically resolve in 2 hours or less from the start of drug administration. The Phase 1 study ESKETINTRD1003 evaluated the pharmacokinetics and safety of a single intranasal esketamine 28 mg in 14 healthy elderly subjects (≥ 65 years of age, with 3 subjects ≥ 75 years of age) and 20 healthy younger adult subjects (18 to 55 years of age, inclusive).¹³ The incidences of the treatment emergent adverse events (TEAEs) were slightly higher in young subjects (100% [20 subjects]) as compared with elderly subjects (85.7% [12 subjects]). The most

commonly reported TEAEs by preferred term (>20%) in elderly subjects were dysgeusia and vertigo (9 [64%], of 14 subjects each).

Additionally, another recently completed Phase 1 study, ESKETINTRD1012, evaluated the pharmacokinetics and safety of a single intranasal 84 mg dose, which was self-administered by 8 healthy elderly subjects who were ≥ 75 years of age (Cohort 1) and 8 healthy younger adults (18 to 55 years of age – Cohort 2). An initial review noted TEAEs occurred in all subjects in both cohorts (100% [16 subjects – 8 in each cohort]). The TEAE of illusions was reported in 5 younger subjects (62.5%) and in none of the elderly subjects. In elderly subjects, the incidence of TEAEs of vascular disorders (6 subjects [75%] including hot flush [2 subjects, 25%] and hypertension [3 subjects, 37.5%]) was higher than in younger adults (hypertension in 1 subject, 12.5%). Vertigo and vertigo positional were more common in elderly subjects (5 subjects, 62.8% and 1 subject, 12.5%, respectively) than in younger adults (vertigo – 3 subjects, 37.5%).

In both cohorts, the maximal mean increase in systolic and diastolic blood pressure as well as heart rate was observed at 32 minutes post dose measurement time point. The mean increase in supine systolic blood pressure and pulse rate was slightly greater in Cohort 1 (elderly) than in Cohort 2 (young adult), while the mean increase in the supine diastolic blood pressure was greater in Cohort 2. In both Cohort 1 and Cohort 2, the mean systolic and diastolic blood pressure returned to baseline within 4 hours post dose. Mean blood pressure and heart rate for Cohort 1 is provided in [Table 2](#)

Table 2: Mean Supine Blood Pressure and Heart Rate - Cohort 1 (ESKETINTRD1012)

	Mean	Range	Mean Change from Baseline	Range
Supine SBP (mm Hg)				
Day 1, predose	133.5	104; 164		
Day 1, 32 min	165.3	141; 194	31.8	16; 44
Day 1, 50 min	154.1	127; 177	20.6	-5; 38
Day 1, 1.5 h	145.6	123; 177	12.1	-11; 32
Day 1, 4 h	130.4	130; 170	-3.1	-36; 31
Supine DBP (mm Hg)				
Day 1, predose	68.0	54; 79		
Day 1, 32 min	81.5	64; 93	13.5	3; 20
Day 1, 50 min	77.1	65; 87	9.1	-3; 17
Day 1, 1.5 h	76.5	63; 81	8.5	-6; 14
Day 1, 4 h	68.5	57; 81	0.6	-16; 17
Supine Heart Rate (beats/min)				
Day 1, predose	60.0	48; 79		
Day 1, 32 min	74.8	53; 102	14.8	3; 38
Day 1, 50 min	70.9	53; 96	10.9	1; 32
Day 1, 1.5 h	62.9	46; 81	2.9	-7; 17
Day 1, 4 h	78.0	55; 97	18.0	-6; 39

DBP = diastolic blood pressure; h = hours; min = minutes; SBP = systolic blood pressure

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.⁷⁷ Dissociative symptoms were the most typical of these adverse events observed post dose and were characterized 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 ESKETINTRD2003 study during the double-blind and open-label study phase. One subject experienced a serious adverse event of esophagitis in Panel A (double-blind phase, placebo/placebo treatment group). A total of 3 subjects withdrew during the double-blind phase because of adverse events. One subject in esketamine 28 mg group experienced a TEAE of syncope of severe intensity on Day 2 of Period 1, 1 day after receiving the first dose of study medication. The subject discontinued from the study and the study agent was permanently withdrawn due to this event, which resolved on the same day. The investigator considered the event to be possibly related to the study agent. Another subject in the placebo/esketamine 56 mg group experienced a TEAE of headache of moderate intensity on Day 11 of Period 2 and the study agent was permanently withdrawn due to this event, which resolved on the same day. The investigator considered the event to be very likely related to the study agent. A third subject in the esketamine group (esketamine 84 mg) experienced a TEAE of dissociative disorder (verbatim term: Dissociative syndrome) of moderate intensity on Day 8 of Period 2 (day of the third esketamine 84 mg dose in the study). The subject discontinued from the study and the study agent was permanently withdrawn due to the event of dissociative disorder, which resolved on the same day. The investigator considered the event to be very likely related to the study agent.⁷⁷

Dissociative symptoms measured on the Clinician Administered Dissociative States Scale (CADSS) were dose-dependent and were observed to reduce significantly with multiple doses over 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 (mean [SD] increase of 5.4 [7.84] mmHg)
- 28 mg: 131.8 (15.49) mmHg (mean [SD] increase of 10.4 [10.44] mmHg)
- 56 mg: 130.4 (18.64) mmHg (mean [SD] increase of 11.2 [15.01] mmHg)
- 84 mg: 146.1 (19.9) mmHg (mean [SD] 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 (mean [SD] increase of 3.8 [7.99] mmHg)
- 28 mg: 85.7 (9.16) mmHg (mean [SD] increase of 6.5 [7.00] mmHg)

- 56 mg: 86.5 (11.34) mmHg (mean [SD] increase of 7.2 [9.67] mmHg)
- 84 mg: 87.8 (10.62) mmHg (mean [SD] 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.⁵⁹ Eighty percent of the participants were retested at the end of 1 year. Cognitive deficits 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.⁵⁸

The principal action of ketamine is at the NMDA receptor, and the consequences of ketamine use on cognition have been fairly widely investigated. Several studies have examined cognitive function in infrequent and frequent ketamine users.^{19,56,57,62} Overall, infrequent or recreational ketamine use does not appear to be associated with long-term cognitive impairment.⁵⁹ The most robust findings are that frequent ketamine users (more than 5 times a week) exhibit impairments in both short- and long-term memory.⁵⁶ 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.⁵⁹

Ketamine-induced ulcerative cystitis is a recently identified complication.⁵⁸ The most common symptoms are frequency and urgency of urination, dysuria, urge incontinence, and occasionally painful hematuria (blood in urine). In the series of 9 patients with ketamine-associated ulcerative cystitis, computerized tomography scans revealed a marked thickening of the bladder wall, a small bladder capacity, and perivesicular stranding consistent with severe inflammation⁸². 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 resolved after stopping ketamine use, one-third remaining static⁸⁴.

Abuse Liability, Dependence, and Withdrawal

There are a number of reports of ketamine dependence in the literature^{40,42,55,66} but no large-scale studies, and so the incidence of ketamine dependence is largely unknown.⁵⁸ 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.⁶⁰ 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.⁸⁵ There is conflicting evidence of the existence of a "withdrawal syndrome" after cessation of ketamine use.⁵⁸ 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.⁵⁸ 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.^{18,50} However, a specific ketamine withdrawal syndrome has not yet been described.⁵⁸

Please refer to the Investigator's Brochure for a summary of the adverse events reported in ketamine and esketamine studies.⁴¹

1.1.3. Marketing Experience

No intranasal formulation of esketamine is currently marketed.

1.2. Oral Antidepressants: Study Medication

This study will evaluate 3 doses of intranasal esketamine (28 mg, 56 mg, or 84 mg) plus a newly initiated oral antidepressant. In the open-label induction phase, direct-entry subjects will be assigned to receive 1 of the 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]). For direct-entry subjects, the oral antidepressant medication will be started on Day 1 of the induction phase and continued in the optimization, maintenance, and follow-up (if clinically indicated) phases. The transferred-entry subjects (both responder and non-responder subjects) should continue oral antidepressant medication previously assigned to them in the ESKETINTRD3005 study during their entire participation in the ESKETINTRD3004 study.

The indications and safety information provided below for each oral antidepressant are from the USPI.^{22,27,80,89} For further information, please refer to the appropriate package insert or SmPC applicable to the local country in which the study is being conducted.

In the US, all of the oral antidepressant options include a black box warning in the prescribing information regarding suicidality and antidepressant drugs. The black box warning informs the prescriber that antidepressant treatments increased 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 prescribing information for the entire content of the black box warning.^{22,27,80,89}

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.²⁷

The adult starting dosage for MDD in the USPI is 10 mg once daily, with a maximum of 20 mg once daily. If the dosage is increased to 20 mg, this should occur after a minimum of 1 week. No additional benefits have been seen at the 20 mg/day dose. In the current study, for subjects <65 years old, maximum daily dose is 20 mg/day. The 10 mg/day dose is recommended for most elderly subjects, and, for subjects aged ≥65 years 10 mg/day will be the maximum dose used in the current study.

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 pimozone; 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.⁸⁰

According to the USPI, 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, posttraumatic stress disorder (PTSD), or social anxiety disorder, subjects were dosed in a range of 50 to 200 mg/day in the clinical trials demonstrating the effectiveness of sertraline for the treatment of these indications. Given the 24 hour elimination half-life of sertraline, dose changes should occur in at least weekly intervals. In the current study, patients not tolerating higher doses of sertraline may have the dose reduced to a minimum of 50 mg/day.

In the current study the dosing is as follows:

- For subjects <65 years, the starting dose is 50 mg, administered once daily and the maximum dose in the current study is 150 mg/day.
- For subjects aged ≥65 years, the starting dose will be 25 mg and the maximum dose will be 150 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 pimozone; 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.²²

The starting dosage for MDD in the United States Prescribing Information (USPI) is 40 to 60 mg/day. The dosage for acute treatment is 40 to 60 mg/day, with maintenance treatment at 60 mg/day. An initial starting dose of 30 mg/day has also been evaluated.⁹³ For some subjects, 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.

In the current study, subjects should be initiated with 60 mg/day. Subjects who have in the past shown increased sensitivity towards SSRI/SNRI's, 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 open-label induction phase.

In Taiwan and South Korea (only), all subjects (ie, including those <65 years of age) should receive an initial dose of 30 mg during Week 1 of the open-label induction phase (see Attachment 3)

Per, USPI no dose adjustment is recommended for elderly patients on the basis of age. As with any drug, caution should be exercised in treating the elderly. When individualizing the dosage in elderly patients, extra care should be taken when increasing the dose. The maximum dosage per USPI is 120 mg/day, although there is no evidence that dosages greater than 60 mg/day confer any additional benefits.

In the current study the dosing is as follows:

- For subjects <65 years, the starting dose is 60 mg; and the maximum dose in this study.
- For improved tolerability, the starting dose for those ≥65 years is 30 mg/day and the maximum dose is 60 mg.

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.⁸⁹

The starting dosage for MDD in the USPI is 75 mg/day (in elderly subjects and in some Asian countries e.g, Taiwan, South Korea, and Malaysia the starting dose is 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. No dose adjustment is recommended for the elderly subjects on the basis of age alone, although other clinical circumstances, such as renal or hepatic impairment would require a dose adjustment.

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

In the current study the dosing is as follows:

- For those <65 years the starting dose is 75 mg and the maximum dose is 225 mg/day.
- For subjects ≥65 years, the starting dose of venlafaxine is 37.5 mg and the maximum dose attained is 150 mg/day.

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 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 hydrochloride 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

In contrast to available data about short-term antidepressant effects of esketamine/ketamine, much less is known about safety of the long term administration of esketamine and how to sustain the antidepressant effect over the long term. No systematic studies have yet characterized long term safety and sustaining the response to esketamine administered at subanesthetic doses in patients with treatment-resistant depression. The long term safety reports summarizing data from recreational ketamine users may not be a reliable source as the dose used was either unknown or several times greater. The only available clinical data are case reports and anecdotal reports from clinicians who have been using ketamine over extended periods of time to sustain the initial response to ketamine.⁴ On average, the duration of response from a single IV dose of ketamine is approximately 5 to 7 days.¹⁰⁰ The duration of response after the last IV session

following repeated administration studies (up to 6 sessions over 2 weeks) varies highly between subjects; the time to relapse has been reported as a median of 18 days (range, 2 to >83 days)⁶¹ or a mean of 16 days (range, 7 to 28 days).⁸⁴

In the abovementioned Study KETIVTRD2002, in the group that received IV ketamine twice per week for 2 weeks, all subjects maintained the response for at least 15 days following the last IV ketamine dose. Similarly, in the abovementioned Study ESKETIVTRD2001, subjects maintained their response for approximately 2 weeks following the last IV esketamine dose.

Long term maintenance of efficacy could be achieved either through repeated intranasal dosing as is the case with most antidepressant medications or possibly by an oral antidepressant alone. Studies to assess whether venlafaxine or lithium may be able to maintain the antidepressant response induced by ketamine are underway by other sponsors.^{16,17}

No systematic studies have yet described sustaining the response to ketamine. The safety of long-term use needs to be systematically assessed with repeated interval dosing. This study will address the long term safety and efficacy of repeated dose esketamine.

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

The primary objective of this study is to assess the long-term safety and tolerability of intranasal esketamine plus a newly initiated oral antidepressant in subjects with TRD, with special attention to the following:

- Potential effects on cognitive function
- Potential treatment-emergent symptoms of cystitis and/or lower urinary tract symptoms
- Potential withdrawal and/or rebound symptoms following cessation of intranasal esketamine treatment

Secondary Objective

To assess the effect of intranasal esketamine plus a newly initiated oral antidepressant in subjects with TRD on

- Safety and tolerability with special attention to the following:

Treatment-emergent adverse events, including TEAEs of special interest

Local nasal tolerability

Effects on heart rate, blood pressure, respiratory rate and blood oxygen saturation,

Effects on alertness and sedation

Potential psychosis-like effects

Dissociative symptoms

Potential effects on suicidal ideation/behavior

- Long-term efficacy, including effects on:

Depressive symptoms (clinician and self-reported), overall severity of depressive illness, functional impairment and associated disability, anxiety symptoms, and health-related quality of life and health status

- Response rate over time, defined as:
 - percentage of subjects with $\geq 50\%$ reduction from baseline (induction phase) in the MADRS total score,
 - percentage of subjects with $\geq 50\%$ reduction from baseline (induction phase) in the Patient Health Questionnaire, 9-item (PHQ-9) total score

Remission rate over time, defined as:

- percentage of subjects with MADRS total score ≤ 12 ,
- percentage of subjects with PHQ-9 total score ≤ 5

Exploratory Objectives

- To assess the potential relationship of biomarkers with response/non-response to intranasal esketamine plus an oral antidepressant in subjects with TRD
- To assess medical resource utilization.
- To assess subject tradeoff preferences for key benefit and harm outcomes associated with TRD treatment, using a stated-choice conjoint analysis survey. Reporting of these survey results may be conducted separately from this study.

2.2. Hypothesis

There is no formal hypothesis for this safety study.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is an open-label multicenter, long-term study to evaluate the safety and efficacy of intranasal esketamine plus a newly initiated oral antidepressant in subjects with TRD. Subjects will enter the study either directly (referred to as ‘direct-entry subjects’) or after completing the double-blind induction phase of ESKETINTRD3005, a short-term efficacy study, in elderly subjects with TRD (referred to as ‘transferred-entry subjects’). Approximately 750 direct entry subjects will be enrolled in this study, plus transferred-entry subjects from study ESKETINTRD3005. At total of at least 100 subjects 65 years or older (who are either direct entry subjects or transferred entry subjects from the ESKETINTRD3005 study) will be enrolled.

ESKETINTRD3005 is a randomized, double-blind, active-controlled, 4 week study in male and female elderly subjects (≥ 65 years) with TRD to assess the efficacy, safety, and tolerability of flexibly dosed intranasal esketamine (28 mg, 56 mg, or 84 mg) plus a newly initiated oral antidepressant, compared with a newly initiated oral antidepressant (active comparator) plus intranasal placebo.⁹

Transferred-entry subjects, who are non-responders (defined as <50% reduction in the MADRS total score from baseline [Day 1] at the end of the 4 week double-blind induction phase of ESKETINTRD3005 study), will be referred to as ‘transferred-entry non-responder subjects’ in the subsequent sections of the protocol. Transferred-entry subjects, who are responders (defined as \geq 50% reduction in the MADRS total score from baseline [Day 1] at the end of the 4 week double-blind induction phase of ESKETINTRD3005 study), will be referred to as ‘transferred-entry responder subjects’ in the subsequent sections of the protocol.

An Independent Data Monitoring Committee (IDMC) will be commissioned for this study to review safety data periodically (see Section 11.8, Independent Data Monitoring Committee, for details).

This study (ESKETINTRD3004) will have 4 phases:

Up to 4-week screening phase (direct-entry subjects only)

A 4-week open-label induction phase (direct-entry subjects and transferred-entry non-responders)

A 48-week open-label optimization/maintenance phase (all responder subjects from the open label induction phase of the current study and transferred-entry responder subjects)

A 4-week follow-up phase (for all subjects treated with intranasal esketamine)

The maximum duration of the subject’s participation in ESKETINTRD3004 study will be 60 weeks for direct-entry subjects, 56 weeks for transferred-entry non-responder subjects, and 52 weeks for transferred-entry responder subjects. The end of the study will occur when at least 300 subjects have received treatment with intranasal esketamine for 6 months and at least 100 subjects for 12 months (Note: the total number of subjects will be based on subjects from this study and subjects from other intranasal esketamine Phase 3 studies).

Detailed description of the study phases are provided below.

3.1.1. Study Phases

Subjects may participate in up to 4 phases. Study treatment phases are detailed below.

Screening Phase

After giving informed consent, direct-entry subjects with TRD who are \geq 18 years of age (or older if the minimum legal age of consent in the country in which the study is taking place is >18 years), will be screened to determine eligibility for study participation. Transferred-entry subjects from ESKETINTRD3005 study will not participate in this 4-week screening phase.

Direct-entry subjects will be eligible for screening regardless of whether or not they are currently taking oral antidepressant treatments. At screening, subjects must have had a non-response to \geq 2 oral antidepressants treatments in the current episode of depression, as assessed by the Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire

(MGH-ATRQ), and confirmed by documented records (eg, medical//pharmacy/prescription records or a letter from a treating physician, etc.).

Eligible subjects who are entering the open-label induction phase will discontinue all of their current oral antidepressant medication(s), being used for depression treatment, including adjunctive/augmentation therapies, prior to the start of the induction phase. 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) during the screening phase can continue these medications. No dose increases beyond the equivalent of 6 mg/day of lorazepam, or new benzodiazepine or non-benzodiazepine sleep medications are permitted during the screening phase, with the exception of the use of permitted benzodiazepine as rescue medication (where required). If clinically indicated, the antidepressant medication(s) may either be tapered and discontinued during the screening phase, or discontinued and switched directly to 1 of the 4 new oral antidepressant medication(s) on Day 1 of the open-label induction phase, per clinical judgment.

Subjects not currently taking oral antidepressant medication(s) at screening will start 1 of the 4 selected new oral antidepressants medication (duloxetine, escitalopram, sertraline, or venlafaxine extended release [XR]) on Day 1 of the open-label induction phase.

Subjects meeting the inclusion/exclusion criteria are eligible to proceed to the open-label induction phase.

Open-label Induction Phase

Direct-entry subjects and transferred-entry non-responder subjects will participate in this phase.

Direct-entry subjects: Intranasal esketamine treatment will be self-administered at scheduled treatment sessions in the clinic/study site, twice weekly for 4 weeks. Subjects who are <65 years old will start intranasal esketamine with an initial dose of 56 mg on Day 1, with the dose adjusted based on efficacy and tolerability in the subsequent visits of the induction phase, (flexible dose: 56 mg or 84 mg). Subjects who are ≥65 years old will start intranasal esketamine with a dose of 28 mg on Day 1 with the dose adjusted based on efficacy and tolerability (28, 56, or 84 mg) in the subsequent visits of the induction phase. In addition, all direct-entry subjects will initiate a new, open-label oral antidepressant on Day 1, which should be taken daily during the study.

The oral antidepressant will be 1 of 4 oral antidepressant medications (duloxetine, escitalopram, sertraline, or venlafaxine XR), that the subject has not previously had a non-response to in the current episode, has not been previously intolerant to (lifetime), and is available in the participating country.

Transferred-entry non-responder subjects from ESKETINTRD3005 study (all will be ≥65 years old), will join at the start of the open-label induction phase. These subjects will start intranasal esketamine with a dose of 28 mg on Day 1 with the dose adjusted based on efficacy and tolerability (28, 56, or 84 mg) in the subsequent visits of the induction phase. These subjects

should continue taking the same oral antidepressant during the study, at the same dose as taken in the last week of the double-blind induction phase of ESKETINTRD3005 study.

Transferred-entry subjects may participate in this study only if this is clinically appropriate in the opinion of the investigator.

For transferred-entry non-responder subjects, results of all assessments performed on Day 28 of the induction phase of that study (Visit 2.9 of ESKETINTRD3005 study) will not be repeated as part of Visit 2.1 of the current study. For these subjects, the Day 28 visit of the ESKETINTRD3005 study will coincide with Day 1 (Visit 2.1) for the current study. There is no gap allowed between studies.

If a subject withdraws from the study before the end of the open-label induction phase for reasons other than withdrawal of consent, an early withdrawal visit should be conducted followed by the follow-up phase.

Optimization/Maintenance Phase

Responder subjects at the end of the induction phase of the ESKETINTRD3004 study, will be eligible to proceed to the optimization/maintenance phase; and continue receiving open-label intranasal esketamine treatment (at the same dose; 28 mg, 56 mg, or 84 mg) and should continue to take the same oral antidepressant medication(s) (at the same dose) as taken in the last week of the induction phase of ESKETINTRD3004 study, unless poorly tolerated, in which case the oral antidepressant may be discontinued after review with sponsor.

Non-responders at the end of the induction phase of the current study will complete an early withdrawal visit and proceed to the follow-up phase.

Eligible transferred-entry responder subjects from the ESKETINTRD3005 study (all will be ≥ 65 years old) will join the current study starting from the optimization/maintenance phase. These subjects will all start intranasal esketamine with a dose of 28 mg (Week 5; Study Day 32) and have their dose adjusted over the following 3 weeks of the optimization/maintenance phase as described under the section “Dosing and Administration” Subjects should continue to take the same oral antidepressant (at the same dose) during the study, that they received at the end of the induction phase of ESKETINTRD3005 study, unless poorly tolerated, in which case the oral antidepressant may be discontinued after review with sponsor.

For transferred-entry responder subjects, results of all assessments performed on Day 28 of the induction phase (Visit 2.9 of ESKETINTRD3005 study) will not be repeated as part of Visit 3.1 of the current study. The Day 28 visit of the ESKETINTRD3005 study will coincide with Day 28 (Visit 3.1) for the current study. There is no gap allowed between studies.

For all subjects, the intranasal treatment session frequency will be reduced from that in the induction phase (twice weekly) to weekly for the first 4 weeks of the optimization/maintenance phase (ie, Week 5 to Week 8). After the first 4 weeks, the frequency of intranasal treatment sessions will be adjusted to once weekly or once every other week based on the severity of

depressive symptoms, as assessed by the MADRS total score. A maximum of 3 changes in intranasal treatment session frequency from weekly to every other week is permitted during the optimization/maintenance phase.

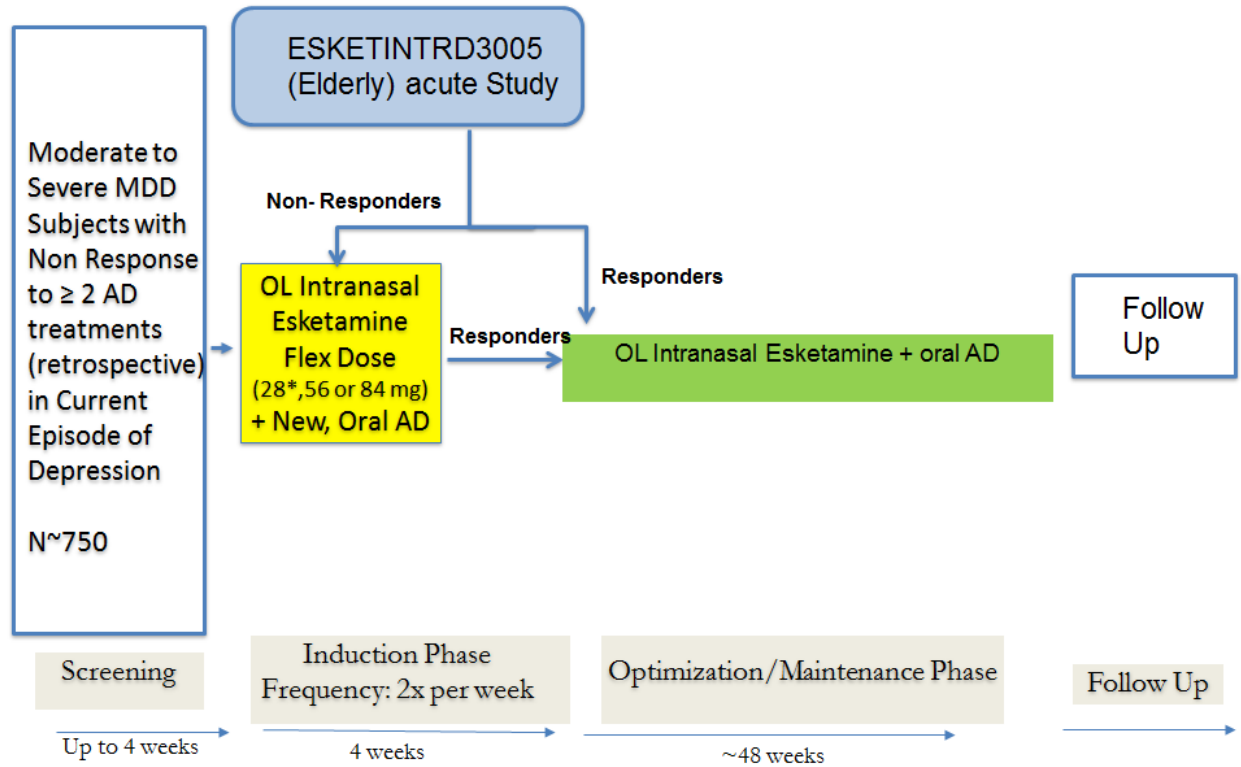
If a subject withdraws from the study before the end of the optimization/maintenance phase for reasons other than withdrawal of consent, an early withdrawal visit should be conducted, followed by the follow-up phase.

Follow-up Phase

This phase will include all subjects who have received at least 1 dose of intranasal study medication in this study. Follow-up visits will be performed at 1, 2 and 4 weeks after the last dose of intranasal study drug. 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. There will be no intranasal esketamine administered during this phase. Subjects will be provided with an additional 4-week supply of the oral antidepressant medication to ensure that there is no interruption of oral antidepressant therapy during the transition to further clinical/standard of care.

The decision to continue the oral antidepressant in this phase will be at the discretion of the investigator, but in order to better assess potential withdrawal symptoms from intranasal study drug and facilitate maintenance of clinical benefit, it is strongly recommended that the oral antidepressant medication(s) be continued for the duration of the follow-up phase unless determined as not clinically appropriate. An open label safety extension study, 54135419TRD3008, may be available (pending country and site approval) for eligible subjects participating in the ESKETINTRD3004 study. Please refer to the 54135419TRD3008 protocol for full details, when available.

A diagram of the study design is provided in [Figure 1](#).

Figure 1: Schematic Overview of the Study

^a Intranasal esketamine 28 mg dose is the only option for subjects ≥ 65 years.

^b At entry to the ESKETINTRD3004, transferred entry subjects will continue to receive the same oral antidepressant initiated in the ESKETINTRD3005 study. The new oral AD is for direct entry subjects only.

3.2. Study Design Rationale

3.2.1. Study Population

The study population will include adult men and women who meet Diagnostic and Statistical Manual of Mental Disorders (5th edition) (DSM-5) diagnostic criteria for single episode MDD (duration of episode must be ≥ 2 years) or recurrent MDD.

Subjects will enter the study either directly (referred to as direct-entry subjects) or after completing the double-blind induction phase of a short-term study in elderly subjects (ESKETINTRD3005) (referred to as “transferred-entry non-responder subjects”, or “transferred entry responder subjects”). The direct-entry subjects will include both younger (≥ 18 and < 65 years) and elderly (≥ 65 years old) subjects while the transferred-entry subjects include only elderly subjects (≥ 65 years old). Enrichment of study population with elderly subjects is important to evaluate the safety of intranasal esketamine in this long-term safety study as elderly subjects may be more vulnerable to any adverse drug effects than younger adults (elderly subjects are known to have more comorbidities and need to administer more concomitant medications than younger subjects). Also prevalence of depression in the over 65 years age group is higher than in the general adult population.

Direct-entry subjects

The direct-entry study population will include adult men and women, ≥ 18 years of age (or older if the minimum legal age of consent in the country in which the study is taking place is > 18), who meet DSM-5 diagnostic criteria for recurrent MDD or single episode MDD (duration of episode must be ≥ 2 years), without psychotic features, based upon clinical assessment, and confirmed by the Mini International Neuropsychiatric Interview (MINI).

Treatment-resistant depression is defined as a lack of clinically meaningful improvement after treatment with at least 2 different antidepressant agents prescribed in adequate dosages for adequate duration. At screening, subjects must have had nonresponse to ≥ 2 oral antidepressant treatments taken at adequate dosage and for adequate duration (including currently taken oral antidepressant, if applicable), as assessed on the MGH-ATRQ and documented by medical history and/or prescription/pharmacy records, in the current episode of depression. Subjects who have had some initial response, but then lost 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 antidepressant treatment prior to patient enrollment in an antidepressant treatment study is considered practical and valid. The MGH-ATRQ is a validated tool assessing treatment response. Direct-entry subjects will be eligible for screening regardless of whether or not they are currently taking oral antidepressant medications.

Transferred-entry responder subjects

The transferred-entry responder subjects are the elderly (≥ 65 years old) subjects who have completed the double-blind induction phase and demonstrated response at the end of the induction phase in the short-term study (ESKETINTRD3005). To maintain the blinding of intranasal treatment in the ongoing ESKETINTRD3005 study, this group will consist of responders to intranasal esketamine plus oral antidepressant (anticipated to be the majority), and responders to intranasal placebo plus oral antidepressant. Responders to intranasal esketamine plus oral antidepressant from ESKETINTRD3005 can continue to receive intranasal esketamine in ESKETINTRD3004 to maintain the treatment response.

For subjects who are responders to intranasal placebo and oral antidepressant there may be no additional benefit to such subjects in participating in ESKETINTRD3004. However, as these subjects were documented to be treatment-resistant prior to the study, the probability of responding to a new oral antidepressant is considered relatively low and so it is expected that much less subjects would be responders to the oral antidepressant plus intranasal placebo in ESKETINTRD3005 compared to those receiving intranasal esketamine plus an oral antidepressant.

Transferred-entry non-responder subjects

These are the elderly (≥ 65 years old) subjects who completed the double-blind induction phase without demonstrating a response at the end of induction phase in the short-term study (ESKETINTRD3005). This group will consist of non-responders to intranasal placebo and oral antidepressant (anticipated to be the majority), and non-responders to intranasal esketamine plus an oral antidepressant.

The rationale for the participation of subjects who are non-responders to the intranasal placebo plus oral antidepressant is that they may benefit from open-label esketamine therapy in the open label induction phase in the current study.

Subjects who are non-responders to intranasal esketamine who decide to participate in the ESKETINTRD3004 study may not benefit from additional treatment with esketamine. However, time to response to oral antidepressants in elderly may take longer than 4 weeks and the potential benefit of additional treatment with esketamine in terms of efficacy remains unknown.

As the blind of the ESKETINTRD3005 study will be maintained, further participation of non-responder transfer-entry subjects will be decided by the subject and the investigator, after individual evaluation of the risk-benefit, based on the experience from the ESKETINTRD3005 study.

3.2.2. Study Phases

Screening Phase

The 4-week screening phase for direct-entry subjects will provide adequate time to assess subject eligibility according to the study entry criteria.

If a subject is taking an oral antidepressant medication(s) at the start of screening, the 4-week duration of the screening phase will provide adequate time to taper and discontinue these medication(s). Otherwise, oral antidepressant medication(s) can be discontinued directly and subjects can be switched to a new oral antidepressant in the open-label induction phase, per clinical judgment.

Open-label Induction Phase

As described in Section 1.1.2, the duration of the 4 week open-label induction phase for direct-entry subjects was selected based upon the onset of effect of typical antidepressants, with a 4 week duration required to consolidate the initial response beyond which a lower frequency can be attempted without losing the antidepressant effects of treatment.

Optimization/Maintenance Phase

The duration of 48 weeks for the optimization/maintenance phase for both direct-entry and transferred-entry subjects allows for a reduction in the frequency of intranasal treatment sessions and subsequent individualization and stabilization of the treatment session frequency (weekly or every other week) for a given subject (using the MADRS total score to assess depressive symptoms). In total, the maximal duration of exposure to intranasal esketamine and newly initiated oral antidepressant in completers of this study will be 1 year (52 weeks), which is in line with the requirements for long-term safety assessments by Health Authorities. The required duration of exposures and number of subjects exposed to intranasal esketamine and oral antidepressant (i.e. 300 subjects with 6 months exposure and 100 subjects with 1 year exposure) will provide sufficient long term safety data to support regulatory approval of intranasal esketamine and will be used as a milestone determining the time point of completion of the study.

Follow-up Phase

The 4 week duration of the follow-up phase will allow sufficient time to assess safety and tolerability after cessation of intranasal dosing. Given the frequency of esketamine administration, the 4 week follow-up should be sufficient to assess potential withdrawal symptoms and reversibility of any drug related adverse events and/or laboratory abnormalities. During this 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.

3.2.3. Blinding and Controls

Blinding will not be used in the study. An open-label design has been selected for this study as this is preferred for a patient population with a large unmet medical need and severe condition (TRD) which makes it difficult to justify administration of placebo only for up to 52 weeks from an ethical perspective.

The blind of the ESKETINTRD3005 study will be maintained for transferred-entry subjects, and all eligible subjects can participate in the current study, thereby the decision to participate in the ESKETINTRD3004 will be independent from subject's treatment response, to either intranasal esketamine plus an oral antidepressant, or intranasal placebo plus an oral antidepressant in the ESKETINTRD3005 study.

3.2.4. Treatment Groups and Dose Selection

Intranasal Study Drug

Open-label Induction Phase

All direct-entry subjects and transferred-entry non-responder subjects will receive intranasal esketamine during this phase. The dose selection (56 mg or 84 mg) and administration interval (2 treatment sessions per week for 4 weeks) for this phase were based on the sponsor's previous clinical data; in particular the results from Studies ESKETIVTRD2001, KETIVTRD2002, ESKETINTRD1001, ESKETINTRD1012, and Panel A of the Study ESKETINTRD2003,

described above in Section 1.1.2. Of note, to improve tolerability, subjects ≥ 65 years who are assigned to esketamine will start with 28 mg of intranasal esketamine on Day 1.

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 open-label induction phase. In addition, the 56 mg and 84 mg dosages were generally well tolerated by subjects. More recently, Study ESKETINTRD1012 evaluated the pharmacokinetics and safety of a single intranasal 84 mg dose in elderly subjects ≥ 75 years of age. Preliminary data showed the means of the C_{max} and AUC_{∞} were approximately 48% and 31% higher, respectively, in the elderly compared with younger adult subjects. Differences were greater based on median C_{max} and AUC_{∞} values (97% and 63% higher in the elderly, respectively).

Based on PK data from ESKETINTRD1012 it is also possible that the 28 mg dose in the elderly may overlap with the 56 mg dose in younger patients, so addition of the 28 mg dose in the elderly may provide an efficacious dose while improving safety.

The use of flexible dosing for intranasal esketamine may provide 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 antidepressant medication.

In the current study, all subjects ≥ 65 years of age will start intranasal esketamine at a dose of 28 mg on Day 1, thereafter adjusting the dose (28 mg, 56 mg, or 84 mg) in a flexible fashion based on efficacy and tolerability up to Day 15 (see Section 6 Dosage and Administration). Starting with a lower dose (28 mg) initially and then adjusting the dose in increments of 28 mg based on efficacy and tolerability may allow these elderly subjects to adjust to the effects of the lower dose before going to higher doses. Similarly for those < 65 years the lower dose, 56 mg, will be the starting dose on Day 1, thereby providing the subjects time to tolerate the lower dose before the higher dose (84 mg). For example, internal data from the CADSS suggest a dose response, with the greatest effect seen initially on the 84 mg dose (ESKETINTRD2003). However, on subsequent repeated dosing, dissociative symptoms lessen. Starting with the lower dose may therefore limit the number of elderly subjects discontinuing the study because of intolerance.

The dose will be flexible (28 mg, 56 mg, or 84 mg) in the first part of the induction phase. This approach is aimed to resemble clinical practice where the investigator can modify the dose of the medication depending on tolerability and efficacy for each subject individually.

The objective is that the dose remains stable from Day 18 onwards so that subjects are on a stable dose at the end of the open-label induction phase. However, if needed for tolerability, one additional dose down-titration of 28 mg is permitted from Day 15 until Day 25.

Optimization/maintenance Phase

All responder subjects from the open-label induction phase of ESKETINTRD3004 study and eligible transferred-entry responder subjects from ESKETINTRD3005 study will participate in this phase.

Subjects entering the optimization/maintenance phase following the open-label induction phase may have the dose down titrated during this phase for tolerability.

As the blind will be maintained to the intranasal treatment received in ESKETINTRD3005 study for transferred-entry responder subjects, within that group there may be responders to intranasal placebo and oral antidepressant who did not receive intranasal esketamine before. For this reason, all transferred-entry responder subjects will start at a dose of 28 mg of intranasal esketamine.

Eligible transferred-entry responder subjects from ESKETINTRD3005 will join the study at this phase. The first intranasal treatment session for these subjects will begin on Study Day 32 of the optimization/maintenance phase. Transferred-entry responder subjects who enter the ESKETINTRD3004 study from the optimization/maintenance phase will start intranasal dosing sessions starting at the 28 mg dose and will titrate the dose to 56 mg in the second week of the phase and then adjust the dose (28 mg, 56 mg, or to 84 mg) thereafter based on efficacy and tolerability (see Section 6 for dosing administration details). For the first 4 weeks of optimization/maintenance phase, these subjects will receive weekly treatment sessions with open-label intranasal esketamine as described Section 6.1.2, Table 7.

For all subjects, the intranasal treatment session frequency will be reduced from that in the induction phase (twice weekly) to weekly for the first 4 weeks of the optimization/maintenance phase. After the first 4 weeks, the frequency of intranasal treatment sessions will be individualized to once weekly or once every other week based on the severity of depression, as assessed by the MADRS total score. This reduction in frequency and subsequent individualization is intended to allow subjects to sustain the antidepressant response while minimizing the frequency of intranasal treatment sessions required.

The selected dose frequencies were guided by clinical experience with the use of IV ketamine for the treatment of MDD/TRD in the community and the (albeit) limited Panel A data from the phase 2 study in treatment-resistant depression ESKETINTRD2003 study, where subjects after an initial induction phase, in a subsequent optional open label phase and, after an additional 2 weeks of dosing twice weekly, had their dosing frequency reduced to weekly for 3 weeks and then every other week for 4 weeks. The ESKETINTRD2003 Panel A data suggests that even after reducing to weekly and every other week dosing, the majority of subjects were able to maintain their antidepressant response/remission.

Oral Antidepressant

On Day 1 of the open-label induction phase, a new, open-label oral antidepressant treatment will be initiated for all direct-entry subjects.

Each subject will be either assigned (for direct-entry subject) or will continue (for transferred-entry subjects) to receive 1 of the 4 oral antidepressant medications from 2 different classes of antidepressant treatments, an SSRI (escitalopram or sertraline) or an SNRI (duloxetine or venlafaxine XR). The assignment of the oral antidepressant treatment will be done by the investigator based on review of the MGH-ATRQ and relevant prior antidepressant medication information.

These 2 antidepressant 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 nonresponse to in the current episode, has not been previously intolerant to (lifetime), and is available in the participating country.

Dosing of the oral antidepressant will follow the country-specific prescribing information for the respective product, with a forced titration to the maximally tolerated dosage to ensure that the oral antidepressant is taken at an adequate dosage and duration for assessment of potential maintenance of effect. A protocol-specified titration schedule is provided in [Attachment 3](#). If higher doses are not tolerated, a down-titration is permitted based on clinician's judgment.

For all subjects, the same oral antidepressant treatment initiated in the induction phase is continued throughout the optimization/maintenance, and follow-up (if clinically indicated) phases, unless poorly tolerated, in which case the oral antidepressant may be discontinued after review with sponsor.

Refer to Section [1.3](#) (Overall Rationale for study) the rationale of initiating and continuing an oral antidepressant along with intranasal esketamine treatment.

3.2.5. Safety Evaluations

Physical examination, body weight, vital signs (including blood pressure measurements), 12-lead ECG, pulse oximetry, clinical laboratory tests, nasal examinations, and evaluation of TEAEs and concomitant therapies will be performed throughout the study to monitor subject safety.

TEAEs of special interest will be examined separately grouped in the following categories: drug abuse, dependence and withdrawal (standardized Medical Dictionary for Regulatory Activities [MedDRA] queries [SMQ]), increased blood pressure, increased heart rate, transient dizziness/vertigo; impaired cognition; anxiety and cystitis.

A subject-completed nasal symptom questionnaire will also be to assess for any treatment-emergent nasal tolerability symptoms.

The Columbia Suicide Severity Rating Scale (C-SSRS) will be performed to assess suicidal ideation and behavior, the CADSS will be administered to assess treatment-emergent dissociative symptoms, the Brief Psychiatric Rating Scale (BPRS+; four-item positive symptom subscale) will be administered to assess treatment-emergent psychotic symptoms, the MOAA/S will be used to measure treatment-emergent sedation, the CGADR will be used to measure the

subject's readiness for discharge based on parameters including sedation, blood pressure, and adverse events, and the PWC-20 will be administered (as applicable) to assess potential withdrawal symptoms after cessation of esketamine treatment.

Given the potential for treatment emergent transient elevation in systolic and diastolic blood pressure, heart rate and blood pressure will be monitored throughout the study and at multiple time points on dosing days. Specific guidance to be followed on intranasal dosing days is provided in Section 6.1.

Even though it is anticipated that the potential risk for treatment-emergent cystitis is very low based upon the doses to be used in this study, subjects will be monitored for symptoms of cystitis, bladder pain, and interstitial cystitis using the subject-completed BPIC-SS at specific time points.³⁹ A score >18 on the BPIC-SS scale is considered as probable cystitis, and any subjects meeting this cut-off will have a urinalysis and culture conducted at that visit to assess for potential urinary tract infection. Those without evidence of an ongoing urinary tract infection will be referred to a specialist for diagnostic workup. There are no definitive tests for diagnosing ulcerative cystitis. If a subject is diagnosed with ulcerative cystitis, the subject must be discontinued from the study and followed up with appropriate medical care.

The effect of intranasal esketamine on cognition will be assessed using the computerized cognitive battery and Hopkins Verbal Learning Test-Revised (HVLTR). The cognitive battery will provide assessment of multiple cognitive domains, including attention, visual learning and memory, and executive function. The HVLTR is a measure of verbal learning and memory.

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](#) for general guidance for the investigator (not all-inclusive).

3.2.6. Efficacy Measures

The efficacy measures were chosen for their reliability, validity, and ability to measure depression severity (including changes due to antidepressant treatment).

MADRS

The 10-item clinician-administered MADRS was designed to be used in subjects with MDD to measure the overall severity of depressive symptoms.^{53,54} The MADRS scale is a validated, reliable scale and acceptable to regulatory health authorities as a primary scale to determine efficacy in major depression.

Efficacy endpoints include assessment of depression symptoms using the MADRS individual scores and total score, as well as response and remission rate over time.

Direct-entry subjects and transferred-entry non-responder subjects (from ESKETINTRD3005) with a $\geq 50\%$ reduction from baseline (Day 1) at the end of the 4 week open-label induction phase in ESKETINTRD3004 will be considered responders and eligible to proceed into the optimization/maintenance phase.

PHQ-9

The PHQ-9 will be used as a patient-reported measure of depressive symptomatology.⁸⁸ Refer to Section 9.3.1.3 for additional information regarding PHQ-9.

SDS

The Sheehan Disability Scale (SDS) is a patient reported measure included as an assessment of functional impairment and associated disability.^{48,83} Refer to Section 9.3.1.6 for additional information regarding SDS.

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.³⁴ Refer to Section 9.3.1.2 for additional information regarding CGI-S.

GAD-7

GAD-7 is included as a brief and validated measure of overall anxiety.⁸⁷ Refer to Section 9.3.1.4 for additional information regarding GAD-7.

EQ 5D-5L

The EQ-5D-5L is included as a standardized patient self-completed instrument for use as a measure of health-related quality of life and health status.^{29,30} Refer to Section 9.3.1.5 for additional information regarding EQ-5D-5L.

3.2.7. Medical Resource Utilization

Superior and sustained response and remission rates to the current antidepressant medication(s) are expected to result in low utilization of services, whereas nonresponse is expected to result in higher utilization of healthcare services (such as outpatient visits, emergency room visits, or hospitalization), as assessed using the Healthcare Resource Use Questionnaire (HRUQ) during the follow-up phase. The HRUQ includes information regarding utilization of healthcare services, including the timing of services, enabling changes in level and quantity of services to be considered as a variable in economic models.

3.2.8. Patient Stated-choice Preference Survey

Stated-choice conjoint analysis is a method specifically designed to provide information about an individual's willingness to accept tradeoffs between treatments with multiple outcomes. It has been used in many therapeutic areas and with many types of patients, including patients with depression. The Patient Stated-choice Preference Survey will be used as an exploratory tool to

assess the manner and degree to which the study subjects value or weigh the clinical outcome associated with esketamine treatment, thus allowing assessment of the maximum acceptable treatment-related risk subjects would accept for various degrees of benefit.

3.2.9. Biomarker and DNA Collection

Assessment of biomarkers and their potential relationship to maintenance/optimization of response and non-response 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 DNA and biomarker 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 pharmacokinetics, pharmacodynamics, efficacy, safety, or tolerability of intranasal esketamine and oral antidepressant comedication 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 (HPA axis, inflammation, growth factors, monoamine transporters, ion channels, circadian rhythm) will be evaluated.

Protein, DNA and metabolic biomarkers may aid in the elucidation of the mechanism of action of intranasal esketamine and oral antidepressant co-medication or help to explain interindividual 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 biomarker analyses is to evaluate the pharmacodynamics of intranasal esketamine and oral antidepressant comedication, 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, since moderately or grossly lipemic specimens may interfere with assay results.

4. SUBJECT POPULATION

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 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.

Screening for eligible direct-entry subjects will be performed within 4 weeks (28 days) before the first administration of study drug.

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

4.1. Inclusion Criteria

4.1.1. Direct-Entry Subjects

The following criteria apply only to those subjects entering directly into the study

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

1. Subject must be a man or woman, ≥ 18 years of age.
2. At the start of the screening phase, each subject must meet DSM-5 diagnostic criteria of single-episode MDD (if single episode MDD, the duration must be ≥ 2 years) or recurrent MDD, without psychotic features, based on clinical assessment and confirmed by the MINI.
3. Criterion modified per amendment 2
 - 3.1 Criterion modified per amendment 3
 - 3.2 At the start of the screening phase, each subject must have had non-response to ≥ 2 antidepressant treatments in the current episode of depression, as assessed using the MGH-ATRQ and confirmed by documented records (eg, medical/pharmacy/prescription records or a letter from treating a physician, etc.).
 - Note: 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.
4. Criterion modified per amendment 3.
 - 4.1 At screening, subject must have a MADRS total score of ≥ 22 .
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 at screening. If there are any abnormalities that are not specified in the inclusion and exclusion criteria, their clinical significance must be determined by the investigator and recorded in the subject's source documents and initialed by the investigator.
6. Criterion modified per amendment 1
 - 6.1 Criterion modified per amendment 2
 - 6.2 Criterion modified per amendment 3
 - 6.3 Subject must be medically stable on the basis of clinical laboratory tests performed at screening. If the results of the serum chemistry panel, hematology, or urinalysis are outside the normal reference ranges, the subject may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for the population under study. This determination must be recorded in the subject's source documents and initialed by the investigator.

- 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.
 - 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 phase.
7. Subject must be comfortable with self-administration of intranasal medication and be able to follow the intranasal administration instructions provided.
 8. Criterion modified per amendment 2
 - 8.1. Criterion modified per amendment 3
 - 8.2. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

Before the start of the screening phase, a woman must be either:

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 (sexual abstinence is considered a highly effective method **only** if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study 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, or the risk of pregnancy changes (eg, woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

Women must agree to continue using these methods of contraception throughout the study and for at least 6 weeks after the last dose of study drug.

9. Criterion modified per amendment 2

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

10. Criterion deleted per amendment 2

4.1.2. Transferred-Entry Subjects (From Study ESKETINTRD3005)

11. Criterion modified per amendment 2

11.1. All subjects who completed the double-blind induction phase of ESKETINTRD3005 study, regardless of their response status, will be eligible to participate in this study, if they meet the study specific eligibility criteria in Sections 4.1.2, 4.1.3 and 4.2.2.

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 at entry into the study. If there are any abnormalities that are not specified in the inclusion and exclusion criteria, their clinical significance must be determined by the investigator and recorded in the subject's source documents and initialed by the investigator.

Subject must be medically stable on the basis of clinical laboratory tests performed at screening. If the results of the serum chemistry panel, hematology, or urinalysis are outside the normal reference ranges, the subject may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate

and reasonable for the population under study. This determination must be recorded in the subject's source documents and initialed by the investigator.

4.1.3. Both Types of Subjects (Direct-entry and Transferred-entry Subjects)

12. Each subject must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.
13. Each subject must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and is willing to participate in the study.
14. Criterion modified per amendment 3

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

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

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

4.2. Exclusion Criteria

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

4.2.1. Direct-Entry Subjects

The following exclusion criteria only apply to those subjects entering directly into the study:

1. Criterion modified per amendment 3

1.1 Subject's depressive symptoms have previously not responded to:

Esketamine or ketamine in the current major depressive episode per clinical judgment, or

All of the 4 oral antidepressant treatment options available in the respective country for the open-label induction phase (ie, duloxetine, escitalopram, sertraline, and venlafaxine XR) in the current major depressive episode (based on MGH-ATRQ).

2. Criterion modified per amendment 1

2.1 Criterion modified per amendment 2

2.2. 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 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.

3. 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 phase, per the investigator's clinical judgment or based on the C-SSRS, corresponding to response of "Yes" on Item 4 (active suicidal ideation with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent) for suicidal ideation on the C-SSRS, or a history of suicidal behavior within the past year prior to the start of the screening phase. Subjects reporting suicidal ideation with intent to act or suicidal behavior prior to the start of the open-label induction phase should be excluded.
4. 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 Screening.
A history (lifetime) of ketamine, phencyclidine, lysergic acid diethylamide (LSD), or 3,4-methylenedioxy-methamphetamine (MDMA) hallucinogen-related use disorder is exclusionary.
5. Subject has a current or past history of seizures (uncomplicated childhood febrile seizures with no sequelae are not exclusionary).
6. Criterion deleted per amendment, duplicate to exclusion criterion #10.
7. Criterion modified per amendment 2
 - 7.1. Subject who:
 - Has a Mini Mental State Examination (MMSE) <25
 - Has neurodegenerative disorder (eg, Alzheimer's disease, vascular dementia, Parkinson's disease), or evidence of mild cognitive impairment (MCI).
8. Criterion modified per amendment 2.
 - 8.1 Criterion modified per amendment 3
 - 8.2 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 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 (see [Attachment 2](#))
9. Criterion modified per amendment 2.
- 9.1. Criterion modified per amendment 3
- 9.2 Subject has a history of uncontrolled hypertension despite diet, exercise, or antihypertensive medications at the start of the screening phase or 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 for those <65 years during screening phase which continues to be above this range with repeated testing during this phase. For those ≥65 years uncontrolled hypertension is defined as a supine systolic blood pressure (SBP) >150 mm Hg or diastolic blood pressure DBP >90 mmHg during screening phase which continues to be above this range with repeated testing during this phase. Note: On Day 1 of the open-label induction phase, a supine SBP >140 mmHg or DBP >90 mm Hg is exclusionary for those <65 years; and for those ≥65 years a SBP >150 mm Hg or DBP >90 mmHg is exclusionary.
- A potential subject may have his/her current antihypertensive medication(s) adjusted during the screening phase and be re-evaluated to assess their blood pressure control. The subject must be on a stable regimen for at least 2 weeks before Day 1 of the open-label induction phase.
10. Subject has a current or past history of significant pulmonary insufficiency/condition or an arterial blood oxygen saturation (SpO₂) of <93% at the start of the screening phase or Day 1 of the open-label induction phase prior to the first intranasal treatment session.
11. Criterion modified per amendment 2
- 11.1 Criterion modified per amendment 3
- 11.2 Criterion modified per amendment 4
- 11.3 Subject has clinically significant ECG abnormalities at the start of screening or on Day 1 of the open-label induction phase prior to the first intranasal treatment session, defined as:
- During screening, a QT interval corrected according to Fridericia's formula (QTcF): ≥450 msec; 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): ≥450 msec 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.
 - Evidence of 2nd or 3rd degree AV block.
 - Features of new ischemia.
 - Arrhythmia (except premature atrial contractions [PACs] and premature ventricular contractions [PVCs]).

12. Criterion modified per amendment 2

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

13. Criterion modified per amendment 2

13.1. Subject has 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 $\geq 2x$ the upper limit of normal or total bilirubin >1.5 times the ULN in the during the screening phase.

- Repeat of screening test for abnormal ALT and AST is permitted once during the screening period, provided per investigator discretion and provided that 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.

14. Criterion modified per amendment 2

14.1 Criterion modified per amendment 3

14.2 Subject has positive test result(s) for drugs of abuse (including barbiturates, methadone, opiates, cocaine, phencyclidine, and amphetamine/methamphetamine) at the start of the screening phase or Day 1 of the open-label induction phase prior to the first intranasal treatment session.

- Subjects who have a positive test result at screening due to prescribed psychostimulants taken for an indication other than MDD (e.g. amphetamine, methylphenidate etc.) are permitted to continue to take this medication during the study in accordance with Attachment 1.
- 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 phase if the medication is discontinued at least 1 week or 5 half-lives, whichever is longer, before Day 1 of the open-label induction phase prior to the first intranasal treatment session in accordance with [Attachment 1](#) restrictions (for opiates). The result of the Day 1 (prior to the first intranasal treatment session) test for drugs of abuse must be negative for the subject to have the first intranasal treatment session.
- 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 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 phase is not exclusionary however a positive test result for cannabinoids on Day 1 (predose) of the open-label induction phase is exclusionary.

15. Subjects who are taking a total daily dose of benzodiazepines greater than the equivalent of 6 mg/day of lorazepam at the start of the screening phase.

16. Criterion modified per amendment 2

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

17. Subject has untreated glaucoma, current penetrating or perforating eye injury, brain injury, hypertensive encephalopathy, intrathecal therapy with ventricular shunts, or any other condition associated with increased intracranial pressure or increased intraocular pressure or planned eye surgery.

18. Criterion modified per amendment 2

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

19. Criterion deleted per amendment 2

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

21. Subject has known allergies, hypersensitivity, intolerance, or contraindications to esketamine/ketamine, and/or excipients or all of the available oral antidepressant treatment options for the open-label induction phase.

22. Subject has taken any prohibited therapies that would not permit dosing on Day 1, as noted in Section 8 (Pre study and Concomitant Therapy) and [Attachment 1](#).23. If a subject has a score of ≥ 5 on the STOP-Bang questionnaire, in which case, obstructive sleep apnea must be ruled out (eg, apnea-hypopnea index [AHI] <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 his or her sleep apnea.

24. Criterion modified per amendment 2.

24.1. 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 phase, or has participated in 2 or more MDD or other psychiatric condition interventional clinical studies (with different investigational medication) in the previous 1 year before the start of the screening phase, or is currently enrolled in an investigational interventional study.

25. Criterion modified per amendment 2

25.1. 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.

26. Subject has a diagnosis of acquired immunodeficiency syndrome (AIDS). No human immunodeficiency virus (HIV) testing is required for this study.

27. Criterion modified per amendment 1

27.1 Subject has had major surgery (eg, requiring general anesthesia) within 12 weeks before the start of the screening phase, or will not have fully recovered from surgery.

28. 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

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.

NOTE: the following criterion is intentionally not numbered sequentially.

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

4.2.2. Transferred-Entry Subjects

30. Subject has taken any prohibited therapies that would not permit dosing on Day 1, as noted in Section 8 (Prestudy and Concomitant Therapy) and [Attachment 1](#).

31. 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.

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

NOTE: Investigators should ensure that, all study enrollment criteria have been met prior to Day 1 of the induction phase (for direct-entry and transferred-entry non-responder subjects) or the start of the optimization phase (for transferred-entry responder subjects). If a subject's status changes (eg, laboratory results or receipt of additional medical records) after the start of screening but before the first dose of intranasal study drug is given in this study, such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

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

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:

- Refer to Section 4.1 (Inclusion Criteria) and Section 4.2 (Exclusion Criteria) for information regarding contraception requirements.
- Refer to Section 8 (Prestudy and Concomitant Therapy) and [Attachment 1](#) (Prohibited Concomitant Medications for Intranasal Study Medication) for further information on prohibited therapies.

- A positive urine drug screen for use of phencyclidine, or cocaine from Day 1 of the induction phase through the final visit in the final treatment phase (open-label induction, optimization, or maintenance phase) will lead to discontinuation.
- 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).
- 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 and 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.
- Electroconvulsive therapy (ECT), deep brain stimulation (DBS), transcranial magnetic stimulation (TMS), and vagal nerve stimulation (VNS) are prohibited from study entry through the end of the last treatment phase (open-label induction, or optimization/maintenance phase)
- Subjects receiving psychotherapy (including cognitive behavioral therapy; CBT) can continue receiving psychotherapy. New psychotherapy is allowed during this study. Any change in existing therapy or new therapy must be documented on the concomitant therapies form.
- 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) during the screening phase can continue these medications during the study. No dose increases beyond the equivalent of 6 mg/day lorazepam or new benzodiazepine medications are permitted during the study, with the exception of the use of permitted benzodiazepine rescue medication. Benzodiazepines and non-benzodiazepine sleeping medication (e.g., zolpidem, zaleplon, eszopiclone, and ramelteon) are prohibited within 12 hours prior to the start of each intranasal treatment session or cognition testing.

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

There will be no randomization for subjects enrolled in this study. All direct-entry subjects who meet the entry criteria will start intranasal esketamine treatment as well as newly assigned oral antidepressant medication on Day 1 of the open-label induction phase. Transferred-entry non-responder subjects will join this study from the induction phase and will receive intranasal esketamine in open-label manner, and continue the same oral antidepressant treatment that they started in the double-blind induction phase of ESKETINTRD3005 study. Transferred-entry responder subjects will join this study from the optimization/maintenance phase and will receive intranasal esketamine in open-label manner, and continue the same oral antidepressant treatment (at the same dose) that they were taking at end of the double-blind induction phase of ESKETINTRD3005 study. The details of treatment for direct-entry subjects and transferred-entry non-responder subjects are included in Section 6.1.1. and treatment for transferred-entry responder subjects are included in Section 6.1.2.

Blinding

Blinding procedures will not be applicable for this study. All the subjects will self-administer intranasal esketamine and an oral antidepressant in an open label manner.

The blind of intranasal treatment (from ESKETINTRD3005 study) will not be broken.

6. DOSAGE AND ADMINISTRATION**6.1. Intranasal Study Drug**

On all intranasal treatment days, a site staff member with recent training in cardiopulmonary resuscitation (eg, Basic Life Support course or equivalent course) that is up to date per local regulations must be present with the subject during the intranasal treatment session and the postdose observation period. 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 study drug.

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, direct-entry subjects will practice spraying (into the air, not intranasally) a demonstration intranasal device that is filled with a placebo solution.
- All subjects will self-administer the intranasal study drug at treatment sessions at the study site. Intranasal treatment sessions cannot be given on consecutive days.
- After Day 1, all dosing decisions are to be determined by the investigator based on efficacy and tolerability.

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 may be used to reduce congestion, but it cannot be used within 1 hour prior to intranasal study drug dosing.

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.

Guidance for Blood Pressure Monitoring on Intranasal Treatment Session Days (Subjects <65 years of age)

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 inclusion and exclusion criteria on Day 1 (ie, applicable for all other 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 mm Hg, 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 mm Hg, 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 (PCP) prior to further dosing.
- If at any post-dose 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 cardiologist, other specialist, or primary care physician for a follow-up assessment.
 - After the assessment by 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 provided the pre-dose blood pressure at the next scheduled visit is within the acceptable range (see bullet above).
- If at any post-dose 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 be referred for cardiologist, other specialist or primary care physician for a follow up assessment.

During the open-label induction 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 is clinically stable and can be discharged from the study site, or
- the subject is referred for appropriate medical care if clinically indicated.
- If the blood pressure remains ≥ 180 mmHg SBP and/or ≥ 110 mmHg DBP, 2 hours after dosing, the subject should be referred for immediate medical treatment.

Guidance for Blood Pressure Monitoring on Intranasal Treatment Session Days (Subjects ≥ 65 years of age)

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

- Prior to any dose escalation, subjects must have had a post-dose blood pressure, on the prior intranasal dosing day, of <180 mmHg systolic and <100 mm Hg diastolic blood pressure.
- 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 subjects pre-dose SBP is >150 mmHg and/or 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 >150 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 a primary care physician, prior to further dosing.

- If at any postdose time point on the dosing day the SBP is ≥ 180 mmHg but < 190 mmHg and/or the DBP is ≥ 100 mmHg but < 110 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 above).

- If at any postdose time point on the dosing day the SBP is ≥ 190 mmHg and/or the DBP is ≥ 110 mmHg, the subject must discontinue from further dosing and be referred to a cardiologist, other specialist, or primary care physician for a follow-up assessment.

During the open-label induction 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 is clinically stable and can be discharged from the study site, or
- the subject is referred for appropriate medical care, if clinically indicated.
- If the blood pressure remains ≥ 180 mmHg SBP and/or ≥ 110 mmHg DBP, 2 hours after dosing, the subject should be referred for immediate medical treatment.

6.1.1. Open-label Induction Phase

This phase is only for direct-entry and transferred-entry non-responder subjects. All subjects will self-administer open-label intranasal esketamine twice a week for 4 weeks as a flexible dose regimen at the study site.

For direct-entry subjects <65 years, the dose titration of intranasal esketamine is described in [Table 3](#):

Table 3: Open-label Induction Phase Dose Titration of Intranasal Esketamine for Direct-entry Subjects <65 Years

Day	Dose	Dose Titration Guidance
Day 1	56 mg	
Day 4	56 or 84 mg	The dose may be increased to 84 mg or remain at 56 mg, as determined by the investigator based on efficacy and tolerability
Day 8	56 or 84 mg	The dose may be increased to 84 mg (if Day 4 dose was 56 mg), remain the same as Day 4, or be reduced to 56 mg (if Day 4 dose was 84 mg), as determined by the investigator based on efficacy and tolerability
Day 11	56 or 84 mg	The dose may be increased to 84 mg (if Day 8 dose was 56 mg), remain the same as on Day 8, or be reduced to 56 mg (if Day 8 dose was 84 mg), as determined by the investigator based on efficacy and tolerability.
Day 15	56 or 84 mg	A dose reduction from 84 mg to 56 mg is permitted, if required for tolerability. If the dose is 56 mg on Day 11, no dose increase is permitted on Day 15.
Day 18, 22, 25	56 or 84 mg	No dose increase from 56 mg is permitted beyond Day 15. If needed for tolerability, one additional dose down-titration from 84 mg to 56 mg is permitted from Day 15 until Day 25.

For direct-entry subjects <65 years, the intranasal treatment will be administered as described in [Table 4](#).

Table 4: Open-Label Induction Phase Intranasal Treatment Sessions for Subjects <65 Years

Intranasal Treatment	Time of Administration ^a		
	0 ^a	5 minutes	10 minutes
Intranasal Device ^b	First	Second	Third
Esketamine 56 mg	1 spray of esketamine to each nostril	1 spray of esketamine to each nostril	No device required.
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 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).

For direct-entry and transferred-entry non-responder subjects ≥ 65 years, the dose titration of intranasal esketamine is described in [Table 5](#).

Table 5: Open-Label Induction Phase Dose Titration of Intranasal Esketamine for Direct-entry and Transferred-entry Non-responder Subjects ≥ 65 Years

Day	Dose	Dose Titration Guidance*
Day 1	28 mg	
Day 4	28 or 56 mg	The dose may remain at 28mg or be increased to 56mg , as determined by the investigator based on efficacy and tolerability
Day 8, 11, 15	28, 56 or 84 mg	The dose may be maintained, or increased or reduced by 28mg from the previous dosing session, as determined by the investigator based on efficacy and tolerability. .
Days 18, 22 and 25	28, 56 or 84 mg	No dose increase is permitted beyond Day 15. If needed for tolerability, a dose reduction by 28 mg from the previous dose is permitted on Days 18, 22, and 25.

* Dose changes are determined by the investigator based on efficacy and tolerability and in accordance with blood pressure guidelines.

From Day 8 to Day 15, inclusive, for subjects who have had a prior down titration from a higher dose, a dose increase by 28 mg is allowed based on clinical judgment. Instructions for intranasal dosing for subjects ≥ 65 years:

- Prior to intranasal dosing, subjects must have a blood pressure $\leq 150/90$ mm Hg
- Prior to any dose escalation, subjects ≥ 65 years must have had a post-dose blood pressure, on the prior intranasal dosing day, of <180 mmHg systolic and <100 mm Hg diastolic blood pressure.

For direct-entry and transferred-entry non-responder subjects ≥ 65 years, the intranasal treatment sessions will be administered as described in [Table 6](#).

Table 6: Open-Label Induction Phase Intranasal Treatment Sessions for Subjects ≥ 65 Years

Intranasal Treatment	Time of Intranasal Device Administration		
	0 ^a	5 minutes	10 minutes
Intranasal Device ^b	First	Second	Third
Esketamine 28 mg	1 spray of esketamine to each nostril	No device required	No device required
Esketamine 56 mg	1 spray of esketamine to each nostril	1 spray of esketamine to each nostril	No device required
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).

6.1.2. Optimization/Maintenance Phase

Subjects who meet the response criteria at the end of the 4-week open-label induction phase of ESKETINTRD3004 study will participate in the optimization/maintenance phase. Subjects will

receive weekly treatment sessions of intranasal esketamine for the first 4 weeks of optimization/maintenance phase at the same dose from the open-label induction phase.

Subjects entering the optimization/maintenance phase following the open-label induction phase may have the dose down titrated during this phase for tolerability.

Eligible transferred-entry responder subjects from ESKETINTRD3005 study will join the study at this phase. The first intranasal treatment session for these subjects will begin on Study Day 32 of the optimization/maintenance phase. For the first 4 weeks of optimization/maintenance phase, these subjects will receive weekly treatment sessions with open-label intranasal esketamine as described in [Table 7](#) below:

Table 7: Optimization/Maintenance Phase Dose Titration of Intranasal Esketamine for Transferred-entry Responder Subjects

Week	Dose	Dose Titration Guidance
Week 5	28 mg	
Week 6	28 or 56 mg	The dose may remain at 28mg or increased to 56mg as determined by the investigator based on efficacy and tolerability
Week 7, 8	28, 56 or 84 mg	The dose maybe maintained, increased or reduced by 28mg from the previous dosing session For those who have had a prior down titration from a higher dose, a dose increase by 28 mg is allowed based on clinical judgment.
Week 9 through end of phase	28, 56 or 84 mg	No dose increase is permitted after week 8. If needed for tolerability, a dose reduction by 28mg from the previous dose is permitted from Week 9 through the end of the phase.

Instructions for intranasal dosing for subjects ≥ 65 years:

- After week 5 all dosing decisions are to be determined by the investigator based on efficacy and tolerability.
- Prior to intranasal dosing, subjects must have a blood pressure $\leq 150/90$ mm Hg
- Prior to any dose escalation, subjects ≥ 65 years must have had a post-dose blood pressure, on the prior intranasal dosing day, of <180 mmHg systolic and <100 mm Hg diastolic blood pressure.

Intranasal Treatment Session Frequency

As described above, for all subjects, the frequency of intranasal treatment sessions will be reduced from the twice-weekly frequency used in the induction phase to weekly for the first 4 weeks of the optimization/maintenance phase (Week 5 to Week 8).

During the optimization/maintenance phase, the MADRS will be performed weekly for all subjects either at the clinic visit (prior to intranasal treatment session) or remotely during a telephone contact visit (if no intranasal treatment session planned that week). After the first 4 weeks of this phase (ie, starting from Week 8), the intranasal treatment session frequency will be adjusted (if applicable) at fixed, 4-week intervals (starting at Week 8, and subsequently at Weeks. 12, 16, 20, 24, 28, 32, 36, 40, 44, 48), based on the guidance below.

Week 8:

- If the MADRS total score is ≤ 12 :

The esketamine treatment session frequency will be changed to every other week. (ie, the next intranasal treatment session after Week 8 will be at Week 10).

- If the MADRS total score is >12 :

There will be no change in esketamine treatment session frequency.

- If the MADRS assessment at Week 8 is missed, the last MADRS total score available prior to Week 8 will be used to determine if a change in treatment session frequency is indicated at Week 8. In this case:

If the MADRS total score is ≤ 12 , the subject will reduce the frequency to receive intranasal treatment sessions every other week for the next 4 weeks (ie, next treatment sessions will be at Weeks 10 and 12).

If the MADRS total score is >12 , the subject will continue to receive weekly intranasal treatment sessions and no further change to the treatment session frequency is permitted for the next 4 weeks.

From Week 12 onwards and at subsequent visits every 4 weeks:

- If the MADRS total score is ≤ 12 :

If esketamine treatment session frequency is weekly, the frequency will be changed to every other week. (e.g. If this is Week 12, the next intranasal treatment session after Week 12 will be at Week 14).

If esketamine treatment session frequency is every other week, there will be no change in frequency.

- If the MADRS total score is >12 :

If esketamine treatment session frequency is weekly, there will be no change in frequency.

If esketamine treatment session frequency is every other week, the frequency will be changed to weekly.

- If the MADRS is missed at that week, the last MADRS total score available prior to that week will be used to determine if a change in treatment session frequency is indicated at that week:

If the MADRS total score is ≤ 12 :

- If esketamine treatment session frequency is weekly, the frequency will be changed to every other week. (eg, If this is Week 12, the next intranasal treatment session after Week 12 will be at Week 14).
- If esketamine treatment session frequency is every other week, there will be no change in frequency.

If the MADRS total score is >12:

- If esketamine treatment session frequency is weekly, there will be no change in frequency.
- If esketamine treatment session frequency is every other week, the frequency will be changed to weekly.

A maximum of 3 changes in intranasal treatment session frequency from weekly to every other week is permitted during the optimization/maintenance phase. After this time, if a given subject is unable to sustain improvement on every other week treatment sessions, they will remain on a weekly frequency for the remainder of the study.

Table 8 describes the administration of intranasal study drug from Week 6 of the optimization/maintenance phase for all subjects.

Table 8: Intranasal Esketamine Treatment Sessions: Optimization/Maintenance Phase

	Time of Administration		
	0 ^a	5 minutes	10 minutes
Intranasal Device ^b	First	Second	Third
Esketamine 28 mg ^c	1 spray of esketamine to each nostril	No device required	No device required
Esketamine 56 mg	1 spray of esketamine to each nostril	1 spray of esketamine to each nostril	No device required.
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 designated time point. Each 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 28 mg dose will be administered only for transferred-entry responder subjects, at Week 5.

If a subject misses >4 consecutive intranasal treatment sessions and/or ≥ 4 MADRS consecutive assessments in the optimization/maintenance phase, the subject will be discontinued from the study, complete the early withdrawal visit, and proceed to the follow-up phase.

If a subject misses a study visit (clinic or telephone visit) in the optimization/maintenance phase without notifying the site of the reason, the site personnel will attempt to contact the subject to confirm if the subject is still interested in participating in the study and if so, to schedule their next visit. During this contact the information on adverse events and concomitant medication will be collected.

6.1.3. Follow-up Phase

No intranasal study medication will be administered during this phase, but to facilitate maintenance of clinical benefit the oral antidepressant medication should continue if clinically indicated.

6.2. Oral Antidepressants

Study-site personnel will instruct subjects on how to take/use and store the oral antidepressants supplied during this study for at-home use. A subject diary to capture oral antidepressant study medication use will be provided.

If the oral antidepressant is taken in the morning on a dosing day, intranasal dosing may proceed provided acceptable blood pressure based on pre-dose blood pressure guidance.

On intranasal treatment sessions days, it is recommended that oral antidepressant treatment not be taken until at least 3 hours after the intranasal treatment session.

6.2.1. Screening Phase for Direct-entry Subjects

Subjects will be eligible for screening regardless of whether or not they are currently taking oral antidepressant medication(s) at screening visit. Subjects taking oral antidepressant medication(s) at screening will discontinue their current antidepressant medications(s) prior to the start of the induction phase. If clinically indicated, the antidepressant medication(s) can be either tapered and discontinued during the screening period, or discontinued and switched directly to the new oral antidepressant on Day 1 of the open-label induction phase, per clinical judgment.

Subjects currently not taking any oral antidepressant medication(s) at screening will start 1 of the 4 oral antidepressant medication(s) on Day 1 of the induction phase.

6.2.2. Open-label Induction and Optimization/Maintenance Phases

Direct-entry subjects: Starting on Study Day 1 of the open-label induction phase, a new, open-label oral antidepressant treatment will be initiated and will be continued during the induction and optimization/maintenance phases of this study. 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 and will be one that the subject has not previously had a nonresponse to in the current episode (per MGH-ATRQ), has not been previously intolerant to (lifetime), and that is available in the participating country.

Dosing of the new oral antidepressant will begin on Day 1 and will follow the local prescribing information for the respective product, with a forced titration to the maximally tolerated dose. A protocol-specified titration schedule is provided in [Attachment 3](#) of the protocol. As subjects may not be able to tolerate the higher doses of the oral antidepressant during the induction phase, a down titration of the dose is permitted based on clinician's judgment.

Transferred-entry subjects (responder and non-responder subjects): These subjects will continue taking the same oral antidepressant medication(s) (duloxetine, escitalopram, sertraline,

or venlafaxine XR) which they were taking at the end of the double-blind induction phase of ESKETINTRD3005 study, at the same dose, during their participation in the optimization/maintenance phase of this ESKETINTRD3004 study.

6.2.3. Follow-up 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.

No intranasal esketamine will be administered during this phase.

All subjects will be provided with an additional 4-week supply of the oral antidepressant medication at the last clinic visit prior to entering the follow-up phase, to ensure there is no interruption of antidepressant therapy during the transition to further clinical/standard of care.

The decision to continue the oral antidepressant in this phase will be at the discretion of the investigator, however, in order to better assess potential withdrawal symptoms from intranasal study drug and to facilitate maintenance of clinical benefit, it is strongly recommended that the oral antidepressant be continued for the duration of the follow-up phase unless determined as not clinically appropriate.

7. TREATMENT COMPLIANCE

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

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.

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 (see Section 14.5 Drug Accountability).

Antidepressant treatment compliance will be assessed by performing pill counts (ie, compliance check) and drug accountability.

8. PRESTUDY AND CONCOMITANT THERAPY

Prestudy non-antidepressants therapies administered up to 30 days before the start of the screening 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 phase) will be recorded at the start of the screening phase. In addition, information will

also be obtained regarding any history of intolerance to any of the 4 antidepressant choices (ie, duloxetine, venlafaxine XR, escitalopram, sertraline). Antidepressant treatments which are not listed on the MGH-ATRQ, but were used, or are currently being used as antidepressant treatment in the current depressive episode, must be recorded under ‘Concomitant Medication’ in the eCRF.

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 and Attachment 1 should be taken into account. Of note, if a subject routinely takes his/her oral antihypertensive medications in the morning on dosing days, the morning dose should be taken prior to intranasal esketamine on intranasal dosing.

Subjects receiving psychotherapy (including cognitive behavioral therapy; CBT), can continue receiving psychotherapy. 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; non-pharmacologic 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, 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
- 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 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 Schedules summarize the frequency and timing of efficacy, biomarker, pharmacogenomic, health economic, medical resource utilization and safety measurements applicable to this study.

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

Actual dates and times of assessments will be recorded in the source documentation and eCRF.

The approximate total blood volume to be collected from each subject will depend on whether a subject is a direct-entry subject, or transferred-entry responder or transferred-entry non-responder subject, from a short-term study (ESKETINTRD3005), and on sex/gender (since women will have pregnancy tests). Approximate calculations indicate that the maximum amount of blood drawn from each subject in this study during a full year of study participation will be approximately 139 mL ([Table 9](#)) and will not exceed the amount of blood donated by a volunteer for a single charitable blood donation in 1 day (about 500 mL). 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 required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

Table 9: Volume of Blood to be Collected From Each Subject

Phase Type of Sample	Volume per Sample(s), mL	Number of Samples per Subject	Total Volume of Blood (mL) ^a
Screening Phase			
TSH,	3.5	1	3.5
HbA1C	2	1	2
Hematology	2	1	2
Serum chemistry ^b	5	1	5
Biomarkers (protein) ^c	10	1	10
Biomarker (DNA)	6	1	6
Tricyclic Antidepressant Blood level ^d	6	1	6
Free thyroxine (FT4) ^e	3.5	1	3.5
Open-label Induction Phase			
Hematology	2	2	4
Serum Chemistry	2.5	2	5
Biomarkers: Protein (v 2.1, v 2.3, v 2.9)	10	3	30
Biomarkers: DNA	6	1	6
Optimization/Maintenance Phase			
Hematology	2	7	14
Serum Chemistry	2.5	7	17.5
Biomarkers: Protein (v 3.4)	10	1	10
Follow-up Phase			
Hematology	2	1	2
Serum Chemistry	2.5	1	2.5
Biomarkers: Protein	10	1	10
Approximate volume of blood collected during the study			139 mL

Abbreviations: DNA= deoxyribonucleic acid; TSH=thyroid-stimulating hormone, EW-O/M=early withdrawal – optimization/stabilization phase

^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.

^d For specific tricyclic antidepressants which are 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.

^e For any subject (regardless of thyroid history), if the TSH value is out of normal range, a free thyroxine (FT4) will be conducted.

Note: 10 mL of blood for protein biomarkers represents the volume of several tubes combined

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 Phase

This phase is for direct-entry subjects only.

Prior to conducting any study procedure, the investigator (or designated study personnel) will review and explain the written ICF to each direct-entry subject. After signing the ICF, subjects who are 18 years of age (or older if the minimum legal age of consent in the country in which the study is taking place is >18 years) will begin to 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 single (if a single episode, duration of episode must be ≥ 2 years) or recurrent MDD, without psychotic features, based upon clinical assessment and confirmed by the MINI.

At the start of this phase, subjects must have had nonresponse to ≥ 2 oral antidepressant treatments in the current episode of depression, as assessed by the MGH-ATRQ and confirmed by documented records (eg, medical/pharmacy/prescription records or a letter from a treating physician, etc.).

Subjects will be screened regardless of whether or not they are currently taking oral antidepressant medication(s). Subjects taking antidepressant medication(s) during screening phase will discontinue their current antidepressant medication(s) prior to the start of the induction phase.

Benzodiazepines or nonbenzodiazepine sleep medications will be allowed to continue but will have specific restrictions regarding the administration time relative to the intranasal treatment sessions (see [Attachment 1](#)).

Since all eligible subjects will be starting a new oral antidepressant during the open-label induction phase, no washout or drug-free period is required after discontinuing the current antidepressant treatment; however, if clinically indicated, the antidepressant treatment can be tapered and discontinued during the screening phase.

All other subjects who do not participate in the open-label induction phase will end study participation at this time. No further study visits or follow-up is required.

9.1.3. Open-label Induction Phase

This phase is for direct-entry and transferred-entry non-responder subjects.

Transferred-entry non-responder subjects will join this study starting from Day 1 of the induction phase. Prior to conducting any study procedure for ESKETINTRD3004, the investigator (or designated study personnel) will review and explain the written ICF to each transferred-entry non-responder subject. The ICF will be signed at the start of this phase (after completion of Day 28 study procedures of the double-blind induction phase for ESKETINTRD3005). After signing the ICF, transferred-entry subjects will be evaluated to determine eligibility for study participation.

During this phase, all subjects will self-administer open-label treatment with intranasal esketamine treatment twice a week for 4 weeks as a flexible dose regimen. Direct-entry subjects will initiate a new, open-label oral antidepressant. Transferred-entry subjects will continue the same oral antidepressant as they received in the induction phase of ESKETINTRD3005. Refer to Section 6, Dosage and Administration for details regarding intranasal and oral study medication.

At the end of the open-label induction phase of ESKETINTRD3004, responder subjects (defined as $\geq 50\%$ reduction in the MADRS total score from baseline [Day 1]) will enter the optimization/maintenance phase.

Refer to Section 9.1.6 for information regarding early withdrawal subjects and subjects that are currently in this phase at the time the study is terminated. For direct-entry and transferred-entry non-responder subjects, results for all assessments performed on Day 28 of the induction phase (Visit 2.9 of ESKETINTRD3005 study) will serve as the baseline values for the optimization/maintenance phase and will not be repeated as part of Visit 3.1 in the current study.

9.1.4. Optimization/Maintenance Phase

Transferred-entry responder subjects may participate in this study only if it is clinically appropriate in the opinion of the investigator.

Prior to conducting any study procedure for ESKETINTRD3004, the investigator (or designated study personnel) will review and explain the written ICF to each transferred-entry responder subject. The ICF will be signed at the start of this phase (after completion of Day 28 study procedures of the double-blind induction phase for ESKETINTRD3005). After signing the ICF, transferred-entry subjects will be evaluated to determine eligibility for study participation.

The intranasal treatment session frequency will be reduced from that in the induction phase (twice weekly) to weekly for the first 4 weeks of the optimization/maintenance phase. After the first 4 weeks, the frequency of intranasal treatment sessions will be individualized to once weekly or once every other week based on the severity of depression, as assessed by the MADRS total score. All subjects will continue taking the same oral antidepressant treatment that was initiated in their respective induction phases (for direct-entry subjects, the oral antidepressant initiated in the open-label induction phase of the ESKETINTRD3004 study; and for transferred entry responder and non-responder subjects, the oral antidepressant initiated in the double-blind induction phase of ESKETINTRD3005 study, unless poorly tolerated, in which case the oral antidepressant may be discontinued after review with sponsor). Refer to Section 6 Dosing and Administration for further details regarding intranasal and oral antidepressant study medication.

Refer to Section 9.1.6 for information regarding early withdrawal subjects and subjects that are currently in this phase at the time the study is terminated.

If a subject misses a study visit (clinic or telephone contact) in the optimization/maintenance phase without notifying the site of the reason, the site personnel will attempt to contact the subject to confirm if the subject is still interested in participating in the study and if so, to schedule their next visit. During this contact the information on adverse events and concomitant medication will be collected.

9.1.5. Follow-up Phase

This phase will include all subjects who have received at least 1 dose of intranasal study medication in this study. Follow-up visits will be performed at 1, 2 and 4 weeks after the last dose of intranasal study drug.

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

No intranasal study medication will be administered during this phase. Subjects will be provided with an additional 4-week supply of their oral antidepressant medication, to ensure there is no interruption of oral antidepressant therapy during the transition to further clinical/standard of care. The decision to continue the oral antidepressant in this phase will be at the discretion of the investigator, however, in order to better assess potential withdrawal symptoms from intranasal study drug and to facilitate maintenance of clinical benefit, it is strongly recommended that the oral antidepressant be continued for the duration of the follow-up phase, unless determined as not clinically appropriate.

An open-label safety extension study, 54135419TRD3008, may be available (pending country and site approval) for eligible subjects participating in the ESKETINTRD3001 study. Please refer to the 54135419TRD3008 protocol for full details when available.

If information is obtained via telephone contact, written documentation of the communication must be available for review in the source documents.

Investigators may contact the subject after study completion to obtain long-term follow-up information to determine the subject's safety or survival status (refer to Section 16.2.3, Informed Consent).

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

9.1.6. Early Withdrawal or End of Optimization/Maintenance Phase VisitEarly Withdrawal

If a subject withdraws before the end of the open-label induction or optimization/maintenance phase for reasons other than withdrawal of consent, an early withdrawal visit should be conducted, followed by the follow-up phase.

Subjects in the induction phase at the time of study termination, will be permitted to complete the phase, will have an early withdrawal visit conducted, 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.

End of Optimization/Maintenance Phase

Subjects in the optimization/maintenance phase at the time of study termination, will have an End of Optimization/Maintenance Phase visit conducted, followed by the follow up phase. If the End of Optimization/Maintenance Phase visit occurs on the same day as a scheduled visit, the End of Optimization/Maintenance Phase 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 will continue.

Subjects will receive additional oral antidepressant medication, if applicable, and it will be recommended that they continue taking the oral antidepressant medication for the duration of the follow-up phase, unless determined as not clinically appropriate.

If a subject discontinues the follow-up phase prior to completion of all visits, an early withdrawal visit is not required.

9.2. Safety

9.2.1. Safety Evaluations

Details regarding the Independent Data Monitoring Committee (IDMC) are provided in section [11.8](#).

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 Schedules:

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), MOAA/S, pulse oximetry, BPRS+, and CADSS.

Adverse Events

Treatment-emergent adverse events (TEAE) will be assessed.

TEAEs of special interest will be examined separately grouped in the following categories: drug abuse, dependence and withdrawal (SMQ), increased blood pressure, increased heart rate, transient dizziness/vertigo; impaired cognition; anxiety and cystitis.

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.

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology and urine samples 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 count
- white blood cell count with differential
- platelet count

- **Serum chemistry panel:**

- sodium
- potassium
- chloride
- bicarbonate
- blood urea nitrogen
- creatinine
- glucose (only done if subject is fasted)
- aspartate aminotransferase
- alanine aminotransferase
- gamma-glutamyltransferase
- total bilirubin
- alkaline phosphatase
- creatine phosphokinase
- calcium
- phosphate
- albumin
- total protein
- fasting lipid panel

- **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:

- Lipid panel: total cholesterol, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, and triglycerides
- 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/methamphetamine
- Alcohol breath test
- Thyroid-stimulating hormone (TSH)
- Free thyroxine (FT4) if applicable (TSH is out of normal range)
- Calculation of creatinine clearance
- HbA1c
- 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 Electrocardiogram (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 prior to dosing.

The subject must be discontinued 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 (blood pressure, pulse/heart rate, temperature, and respiratory rate)

Blood pressure and pulse/heart rate measurements will be assessed supine with a completely automated device. Manual techniques will be used only if an automated device is not available.

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

For further details regarding blood pressure, please see Guidance for Blood Pressure Monitoring on Intranasal Dosing Days (Section 6.1).

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 at prespecified time points. Any arterial oxygen saturation (SpO₂) $< 93\%$ 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 $\geq 93\%$ or until the subject is referred for appropriate medical care, if clinically indicated.

Physical Examination, Height, Body Weight and Neck Circumference

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

In addition body mass index (BMI) will be calculated and neck circumference measured as part of the information required for the STOP-Bang questionnaire, at screening.

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.

Nasal Symptom Questionnaire

Subjects will complete a nasal symptom questionnaire. The nasal symptom questionnaire was developed by the Sponsor to assess nasal tolerability following intranasal administration of study drug. The questionnaire asks about nasal symptoms, which are rated by the subject as none, mild, moderate, or severe, based on how he or she feels at the time of the assessment.

Columbia Suicide Severity Rating Scale (C-SSRS)

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

The C-SSRS is a low-burden measure of the spectrum of suicidal ideation and behavior that was developed in the National Institute of Mental Health Treatment of Adolescent Suicide Attempters Study to assess severity and track suicidal events through any treatment.⁷⁰ 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 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.

Clinician Administered Dissociative States Scale (CADSS)

The CADSS is an instrument for the measurement of present-state dissociative symptoms,⁵ and will be administered to assess treatment-emergent dissociative symptoms.

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 and 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.

Positive-symptom Subscale of the Brief Psychiatric Rating Scale (BPRS+)

Four items of the BPRS will be administered to assess potential treatment-emergent psychotic symptoms.

The BPRS is an 18-item rating scale that is used to assess a range of psychotic and affective symptoms, rated from both observation of the subject and the subject’s own report.^{64,65} It reportedly provides a rapid and efficient evaluation of treatment response in clinic drug studies and in clinical settings.⁷³

Only the 4-item positive symptom subscale BPRS+ (ie, suspiciousness, hallucinations, unusual thought content, and conceptual disorganization) will be used in this study. It is highly sensitive

to change, and excellent inter-rater reliability can be achieved with training and a standard interview procedure.

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

The MOAA/S will be used to measure treatment-emergent sedation, with correlation to levels of sedation defined by the American Society of Anesthesiologists continuum.

The MOAA/S scores range from 0=no response to painful stimulus (corresponds to ASA continuum for general anesthesia) to 5=readily responds to name spoken in normal tone (awake; corresponds to ASA continuum for minimal sedation).

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

- If the score is ≤ 3 at any time during the 1.5 hour postdose interval, the MOAA/S will be performed every 5 minutes until a score of 4 is reached (at which point a frequency of every 15 minutes can be resumed until t=+1.5 hours post dose).
- If a subject does not have a score of at least 5 at t=+1.5 hours postdose, they should continue to be monitored. For subjects with a score of 4, the assessment should be repeated every 15 minutes. And for subjects with a score of ≤ 3 , the assessment should be repeated every 5 minutes until the score returns to 5 or the subject is referred for appropriate medical care, if clinically indicated.

Clinical Global Assessment of Discharge Readiness (CGADR)

The CGADR will be used to measure the subject's current clinical status and is the clinician's assessment of the readiness to be discharged from the study site.

The clinician will answer "Yes" or "No" to the question "Is the subject considered ready to be discharged based on their overall clinical status (eg, sedation, blood pressure, and other adverse events)?"

On each intranasal dosing day, the CGADR will be performed at 1 hour and 1.5 hours postdose; if the response is not "Yes" at 1.5 hours postdose, the assessment will be repeated every 15 minutes until a "Yes" response is achieved or until the subject is referred for appropriate medical care, if clinically indicated.

A subject should not be discharged prior to the 1.5 hour time point.

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

Physician Withdrawal Checklist, 20-item (PWC-20)

The PWC-20 will be administered to assess potential withdrawal symptoms following cessation of intranasal esketamine treatment. An assessment will be performed pre-dose 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 the duration 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.⁷² Discontinuation symptoms occur early and disappear rather swiftly, depending upon speed of taper, daily medication dose, and drug elimination half-life.

Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS)

The BPIC-SS will be used to monitor subjects for potential symptoms of cystitis, bladder pain, and interstitial cystitis.

The BPIC-SS is a patient-reported outcome measure that was developed to identify an appropriate bladder pain syndrome/interstitial cystitis population for clinical studies to evaluate new treatments for bladder pain syndrome.³⁹

The BPIC-SS contains 8 questions with a recall period of the past 7 days, and addresses key symptoms identified by subjects with BPS including symptom concepts of pain and/or pressure of the bladder and urinary frequency. Subjects respond to items using a 5-point scale (0=never, 1=rarely, 2=sometimes, 3=most of the time, 4=always for frequency-based questions, and 0=not at all, 1=a little, 2=somewhat, 3=moderately, and 4=a great deal for items related to bother associated with symptoms). Question 8 records the worst bladder pain in the last 7 days using a 0-10 numerical rating scale. A total score is calculated by adding up the numbers beside the response options chosen by the subject. The range of scores for the scale is 0 to 28.

A total score of 19 or more has demonstrated good sensitivity/specificity and is considered a relevant cut-off to distinguish those with significant bladder symptoms or cystitis.³⁹

If any items are missing, a total score cannot be calculated.

If a subject has a score greater than 18 on the BPIC-SS scale and urinalysis and microscopy indicate no evidence of urinary tract infection then the subject will be referred to a specialist for further evaluation. If a subject is diagnosed with ulcerative cystitis, the subject must be discontinued from the study and followed up with appropriate medical care. As such, in addition to urinalysis, a urine culture should also be obtained if the BPIC-SS score on an applicable study day is greater than 18.

Cognition Testing

Computerized Cognitive Battery

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

- Simple and choice reaction time tests; scored for speed of response (mean of the log 10-transformed reaction times for correct responses)
- Visual episodic memory; visual recall test scored using arcsine transformation of the proportion of correct responses
- Working memory (n back); scored for speed of correct response (mean of the log 10-transformed reaction times for correct responses)
- Executive function; maze/sequencing test, scored for total number of errors

All measures have been validated against traditional neuropsychological tests and are sensitive to the effects of various drugs on cognitive performance, including alcohol and benzodiazepines. Completing the cognitive battery requires approximately 25 minutes.

Hopkins Verbal Learning Test-Revised (HVLTR)

The HVLTR, a measure of verbal learning and memory, is a 12-item word list recall test. Administration includes 3 learning trials, a 24-word recognition list (including 12 target and 12 foil words), and a delayed recall trial (20-minute).³ The test administrator reads instructions and word lists aloud, and records words recalled/recognized by the subject. Scores include learning, delayed recall, and recognition. The HVLTR is a well-validated and widely used measure of verbal episodic memory.

The tests will be administered in the following order: HVLTR, computerized cognitive test battery, and HVLTR Delayed.

All subjects will complete a practice session for the computerized cognitive battery during the screening phase. There is no practice session for the HVLTR.

9.2.2. Safety Endpoints

Safety endpoints will include:

- Monitoring of TEAEs, including TEAEs of special interest
- Clinical laboratory tests, including hematology, serum chemistry, and urinalysis
- Physical examination, and body weight measurements
- Serum and urine pregnancy testing (for women of childbearing potential)
- Urine drug screen
- Alcohol breath test

Safety evaluations to assess short-term effects following intranasal esketamine dosing will include:

- 12-lead electrocardiogram
- Vital signs
- Pulse oximetry
- Clinician Administered Dissociative States Scale (CADSS), to assess treatment-emergent dissociative symptoms
- Four-item positive symptom subscale of the BPRS+, to assess treatment-emergent psychotic symptoms
- Modified Observer's Assessment of Alertness/Sedation, to measure treatment-emergent sedation
- Clinical Global Assessment of Discharge Readiness (CGADR), to document the subject's current clinical status based on the clinician's assessment of the readiness to be discharged from the study site

Safety evaluations will also include assessment of any long-term adverse events, with special attention to:

- Nasal examination and nasal symptom questionnaire to local assess nasal tolerability
- Columbia Suicide Severity Rating Scale (C-SSRS), to assess suicidal ideation and behavior
- Bladder Pain/ Interstitial Cystitis Symptom Score (BPIC-SS), to monitor for symptoms of cystitis, bladder pain, and interstitial cystitis
- Physician Withdrawal Checklist (PWC-20) to assess potential withdrawal symptoms following cessation of intranasal esketamine treatment
- Computerized cognitive battery and HVLT-R, to assess the effect of intranasal esketamine on cognition

9.3. Efficacy

9.3.1. Efficacy Evaluations

Every effort should be made to ensure that all clinician-administered efficacy assessments are completed by the same individual who made the initial baseline determinations.

9.3.1.1. Montgomery-Asberg Depression Rating Scale (MADRS)

The MADRS is a clinician-rated scale designed to measure depression severity and detects changes due to antidepressant treatment.⁵³ 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 structured interview guide for the MADRS (SIGMA) will be used for each administration.

The typical recall period for the MADRS is 7 days.

The MADRS will be used to measure the secondary objectives of effects on depressive symptoms.

9.3.1.2. 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.³⁴ 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.

9.3.1.3. Patient Health Questionnaire, 9-Item (PHQ-9)

The PHQ-9 is a 9-item, patient-reported outcome measure to assess depressive symptoms.⁸⁸ The scale scores each of the 9 symptom domains of the DSM-5 MDD criteria and it has been used both as a screening tool and a measure of response to treatment for depression. Each item is rated on a 4-point scale (0=not at all, 1=several days, 2=more than half the days, and 3=nearly every day). The subject's item responses are summed to provide a total score (range of 0 to 27) with higher scores indicating greater severity of depressive symptoms. The recall period is 2 weeks.

9.3.1.4. Generalized Anxiety Disorder, 7-item (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; and 3 = nearly every day).⁸⁷ Item responses are summed to yield a total score with range of 0 to 21, where higher scores indicate more anxiety. The recall period is 2 weeks.

9.3.1.5. European Quality of Life (EuroQol) Group, 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).^{29,30}

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.

9.3.1.6. Sheehan Disability Scale (SDS)

The Sheehan Disability Scale will be used to assess the secondary objective of functional impact and associated disability. The SDS, a patient-reported outcome measure, is a 5 item questionnaire which has been widely used and accepted for assessment of functional impairment and associated disability.^{48,82} 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.

9.3.2. Efficacy Endpoints

Efficacy endpoints include the mean total score over time, individual scores over time as well as change from baseline in the total score and individual scores for the following rating scales:

- Depressive symptoms, using the MADRS and the self-reported PHQ-9
- Overall severity of illness, using the CGI-S
- Symptoms of anxiety, using the GAD-7 scale
- Health-related quality of life and health status, using the EQ-5D-5L questionnaire
- Functioning and associated disability, using the SDS
- Long-term efficacy will also be assessed by:

Response rate over time, defined as:

- percentage of subjects with $\geq 50\%$ reduction from baseline (induction phase) in the MADRS total score,
- percentage of subjects with $\geq 50\%$ reduction from baseline (induction phase) in the PHQ-9 total score

Remission rate over time, defined as:

- percentage of subjects with MADRS total score ≤ 12 ,
- percentage of subjects with PHQ-9 total score ≤ 5

9.4. Biomarker and Pharmacogenomic Evaluations

During the study, blood will be collected for the assessment of biomarkers (protein and metabolite) 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, and metabolites) 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.

Pharmacogenomics

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 etc).

Genotyping will be conducted only on the screening/baseline 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.

9.5. Medical Resource Utilization

Medical resource utilization data, associated with healthcare encounters, will be collected using the HRUQ during the optimization/maintenance and follow up phases of the study. Protocol-mandated procedures, tests, and encounters are excluded. The data collected may be used to conduct exploratory economic analyses and will include:

- Number, duration and type of healthcare encounters (inpatient and outpatient).
- Duration of hospitalization (total days length of stay, including duration by wards)

9.6. Other Evaluations

Menstrual Cycle Tracking

Menstrual cycle tracking (start date of last menstrual period) will be documented for female subjects with a menstrual cycle at the study visits specified in the Time and Events Schedule.

MINI

The MINI is a brief, structured diagnostic interview to confirm the diagnosis of MDD and to determine if there are other psychiatric conditions present.

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

The MGH-ATRQ is used to determine treatment resistance in MDD.²⁰

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

Snoring, Tiredness, Observed Apnea, High Blood Pressure, Body Mass Index, Age, Neck Size, Gender (STOP-Bang) Questionnaire

The STOP-Bang Questionnaire is a concise, easy-to-use, validated, and sensitive screening tool for obstructive sleep apnea (OSA). This questionnaire has 8 items which address key risk factors for obstructive sleep apnea: snoring, tiredness, observed breathing interruption during sleep, high blood pressure, body mass index, age, neck size, and gender. The STOP-Bang questions do not specify a recall period. Subjects will answer yes or no to questions about snoring, tiredness, observed breathing interruption, and high blood pressure (these are the “STOP” items in the STOP-BANG acronym); this takes approximately 1 minute.⁷

Study site staff will answer yes or no to questions about body mass index (more than 35 kg/m²?), age (older than 50 years?), neck circumference (larger than 17 inches [43 cm] in men, or larger than 16 inches [41 cm] in women?), and gender (male?).

The total STOP-BANG score is calculated by summing the number of positive responses, yielding a score range of 0 to 8. A score of ≥ 5 on the STOP-Bang indicates a moderate to severe risk for Obstructive Sleep Apnea (apnea hypopnea index of >30).⁷

MMSE

The MMSE is a validated, brief examination that rates subjects on orientation (total score, 10), registration (total score, 3), attention and calculation (total score, 5), recall (total score, 3), and language (total score, 9).³¹ The MMSE is effective as a screening tool for cognitive impairment with older community dwelling, hospitalized and institutionalized adults. The maximum score is 30. The MMSE will be completed at screening only. A total score <25 will be used in the current study in order to exclude subjects with potential neurodegenerative disorder.

Patient Stated-choice Preference Survey

Stated-choice conjoint analysis is a method specifically designed to provide information about an individual's willingness to accept tradeoffs between treatments with multiple outcomes^{43, 46, 75, 76} Preference studies have been performed with patients with depression and other mental illnesses.^{49, 95} The Patient Stated-choice Preference Surveys will be used as an exploratory tool to assess

the manner and degree to which subjects' value or weigh the benefit and harm clinical outcomes associated with esketamine.

The intent is to have the subject complete the survey after having some experience with esketamine. The survey will be administered once and only at sites in the United States, United Kingdom and Australia and only for English speakers. Subjects at any other site, regardless of whether they speak English, will not be surveyed. It is expected that subjects will require 20 to 25 minutes to complete the survey. Since subjects may be in different stages of the trial when the survey becomes available, trial sites should have subjects complete the survey as noted in the T&E schedule. Specifically, the survey should be completed during or shortly after Visit 2.9, or if the subject completed this visit prior to when the survey becomes available, trial sites should have the subject complete the survey at the earliest possible opportunity. Note, for transferred-entry responder subjects from the ESKETINTRD3005 study who enter directly to the optimization/maintenance phase, the survey should be completed during or shortly after Visit 3.5, or if the subject completed this visit prior to when the survey becomes available, the subject should complete the survey at the earliest possible opportunity. Subjects who completed the Patient Stated-choice preference survey while enrolled in ESKETINTRD3005 should not be issued the survey. The survey should be administered predose (if/when performed on intranasal dosing days).

If the patient indicates a desire to discontinue the study, the patient should be asked to complete the survey by his or her last visit if, in the study coordinator's judgment, the patient will give the survey the required time and attention. If the study coordinator believes a patient will not give the survey the required time and attention on this last visit, the survey should not be administered.

The survey will be administered on a table-based computer during a site visit prior to administration of study drug if dosing is scheduled to occur on that day.

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/WITHDRAWAL

10.1. Criteria for Completion

A subject will be considered to have completed the study if he or she has completed safety assessments at Week 52 of the optimization/maintenance phase.

Subjects in the induction phase of the study at the time of study completion will be allowed to complete the phase, will complete an early withdrawal visit, and continue into the follow-up phase but will not be considered completers.

Subjects in the optimization/maintenance phase of the study at the time of study completion will complete an End of Optimization/Maintenance visit, and continue into the follow-up phase but will not be considered completers.

An open label safety extension study, 54135419TRD3008, may be available (pending country and site approval) for eligible subjects participating in the ESKETINTRD3004 study. Please refer to the 54135419TRD3008 protocol for full details, when available.

10.2. Criteria for Withdrawal from the Study

During any phase of the study, a subject will be withdrawn from the study for any of the following reasons:

- The investigator believes that for safety reasons (eg, an adverse event) it is in the best interest of the subject to stop treatment.

See Section 6.1 for discontinuation criteria related to blood pressure

- The subject does not meet response criteria for continuing into the optimization/maintenance phase at the end of the open-label induction phase (direct-entry subjects and transferred-entry non-responder subjects only).
- The subject must be discontinued 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.
- Lack of efficacy, as determined by the investigator
- Violation of protocol procedures (determined on a case-by-case basis)
- The subject becomes pregnant
- The subject is lost to follow-up
- Death
- The sponsor terminates the study.
- Withdrawal of consent (Note: See “Withdrawal 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)

- The subject misses ≥ 4 consecutive MADRS assessments or >4 consecutive intranasal treatment sessions in the optimization/maintenance phase

Refer to Section 9.1.6 for further information on the Early Withdrawal or End of Optimization/Maintenance Phase Visit.

If a subject misses a study visit (clinic or telephone visit) in the optimization/maintenance phase without notifying the site of the reason, the site personnel will attempt to contact the subject to confirm if the subject is still interested in participating in the study and if so, to schedule their next visit. During this contact the information on adverse events and concomitant medication will be collected. These contacts will be repeated weekly until successful scheduling of the next dosing session or otherwise until discontinuation from the study (up to 4 contacts will be made).

If the subject withdraws from the study before the end of the open-label induction phase or optimization/maintenance phase, an Early Withdrawal visit is to be performed.

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 site personnel 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. In addition, the study site should emphasize the importance of follow-up information to the subject before initiation of the open-label induction phase. The measures taken to follow up must be documented.

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

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 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 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 open-label induction phase or the optimization/maintenance phase with the reason noted as “Other” and will specify the reason why.

For a subject who “withdraws consent”, it is recommended that the subject withdraw consent in writing; if the subject refuses or is physically unavailable, the study site should document and sign the reason for the subject’s failure to withdraw consent in writing and maintain it with the subjects 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 (SAP).

11.1. Subject Information

The following analysis sets will be used to summarize efficacy and safety data.

- Full Analysis Set for open-label induction phase: will be defined as all subjects who receive at least 1 dose of intranasal esketamine or 1 dose of oral antidepressant during this phase.
- Full Analysis Set for Optimization/Maintenance phase: will be defined as all subjects who receive at least 1 dose of intranasal esketamine or 1 dose of oral antidepressant during this phase.

11.2. Sample Size Determination

No formal sample size calculation was performed for the study. The projected sample size of 750 direct entry subjects plus transferred entry subjects is considered adequate to obtain at least 300 subjects who have received treatment with esketamine for 6 months and at least 100 subjects for 12 months (Note: the total number of subjects will be based on subjects from this study and subjects from other intranasal esketamine Phase 3 studies). The number of transferred entry subjects is based on predictions related to discontinuation rate and efficacy, and therefore may vary.

The sample size will include at least 100 older subjects (who are either direct entry subjects or transferred entry subjects from the ESKETINTRD3005 study) aged ≥ 65 years.

11.3. Safety Analyses

Safety data for the open-label induction phase, the optimization/maintenance phase and follow-up phase will be analyzed separately for each phase as well as for the entire treatment period (induction and optimization/maintenance phase). The baseline for safety assessments will be defined in the Statistical Analysis Plan.

Cognitive Function

- Computerized cognitive test battery and HVLT-R: Descriptive statistics of each of the cognitive domain scores and changes from baseline will be summarized at each scheduled time point.
- Reversibility of any potential changes from baseline to end of treatment visit in cognitive test battery and HVLT-R will be assessed at follow-up phase.

Treatment-emergent lower urinary tract symptoms

- **BPIC-SS+**: Descriptive statistics of scores and their changes from predose or baseline will be summarized at each scheduled time point.
- Adverse events related to lower urinary tract symptoms will be summarized descriptively. Reversibility of any changes from baseline to end of treatment visit in BPIC-SS, and reversibility of any ongoing adverse events related to LUTS will be assessed during the follow-up phase.

Withdrawal and/or rebound symptoms

- **PWC-20**: Descriptive statistics of scores and their changes from predose on the last day of dosing will be summarized at each scheduled time point during the follow-up phase.
- Adverse events related to withdrawal and/or rebound symptoms will be summarized descriptively. Reversibility of any ongoing adverse events related to withdrawal and/or rebound symptoms will be assessed during the follow-up phase.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are adverse events with onset during the treatment phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported adverse events with onset during the treatment phase (ie, TEAEs, and adverse events that have worsened since baseline) will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized.

TEAEs of special interest will be examined separately grouped in the following categories: drug abuse, dependence and withdrawal (SMQ), increased blood pressure, increased heart rate, transient dizziness/vertigo; impaired cognition; anxiety and lower urinary tract symptoms SMQ including cystitis.

Adverse events occurring during the follow-up phase will be summarized separately. For transferred-entry subjects, adverse events ongoing at the time of entry into the study will be summarized separately.

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 SAP) 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 provided. Frequency tabulations of the abnormalities will be provided. Listings of subjects with laboratory results outside the reference ranges and markedly abnormal laboratory results will be provided.

Electrocardiogram (ECG)

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

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

The ECG variables that will be analyzed are heart rate, PR interval, QRS interval, QT interval, and QT interval corrected (QTc) according to Bazett's formula (QTcB) and Fridericia's formula (QTcF).^{2,78}

Descriptive statistics of QTc intervals and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with QTc interval >450 msec, >480 msec, or >500 msec will be summarized, as will the percentage of subjects with QTc interval increases from baseline <30 msec, 30 to 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 body weight, temperature, pulse/heart rate, respiratory rate, pulse oximetry and supine blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time point. Any treatment-emergent abnormalities will be listed.

Nasal Examination and Nasal Symptom Questionnaire

Changes in findings from the baseline nasal examination (including the upper respiratory tract/throat) will be listed. Examinations will provide ratings (none, mild, moderate, or severe) that are based on a visual inspection of the nostrils, nasal mucosa, and throat for nasal erythema, rhinorrhea, rhinitis, capillary/blood vessel disruption and epistaxis. A shift table for changes from baseline in ratings for each examination will be presented. Percentage of subjects having findings in the nasal exam and tolerability questionnaire will be assessed over time.

In addition, scoring from the nasal symptom questionnaire will be summarized descriptively for each scheduled time point.

Other Safety and Tolerability Questionnaires and Assessments

- C-SSRS: Suicide-related thoughts and behaviors based on the C-SSRS will be summarized in incidence and shift tables. Separate endpoints for suicidal ideation and suicidal behavior will be defined and summarized descriptively. Missing scores will not be imputed.
- CADSS, CGDAR, BPRS+ and MOAA/S: Descriptive statistics of scores and their changes (and/or percent changes) from predose or baseline will be summarized at each scheduled time point.

11.4. Efficacy Analyses

Depression symptoms using the MADRS as well as a patient reported outcome (PHQ-9), global change in severity (CGI-S), social, occupational and family functioning related disability (SDS), anxiety (GAD-7), and health status (EQ-5D-5L) will be summarized descriptively at each scheduled visit for each phase, using both last observation carried forward and observed data. The proportion of subjects who responded and remitted based on the MADRS total score as well as PHQ-9 total score will be provided over time for each phase.

11.5. Biomarker and Pharmacogenomic Analysis

Baseline biomarker values and changes from baseline biomarker values to the time points specified in the Time and Events Schedule will be summarized. Exploratory analyses may include correlation of biomarker values at baseline and change from baseline in biomarker values with the efficacy parameters 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 and non-response.

Pharmacogenomic analyses may include candidate gene analyses or genome-wide association analyses in relation to treatment response, maintenance/stabilization of response, non-response and MDD/TRD.

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

11.6. Medical Resource Utilization Analysis

Medical resource utilization data (including HRUQ results) will be descriptively summarized.

11.7. Patient Stated-choice Preference Survey

The conjoint analysis based patient stated-choice preference survey will be used as an exploratory tool to assess the outcomes with esketamine.

The patient stated-choice preference survey, generate data that can be used to estimate relative preference weights for specified levels of treatment-related benefits and harms. A regression model described in a SAP will be used to estimate a distribution of preferences around each model parameter. All estimates will be reported with 95% confidence intervals. A key result will be the maximum acceptable risk for each harm, defined as the largest increase in probability or severity of that harm that a patient is willing to accept for a given degree of benefit. Reporting of the survey results may be conducted separately from this study.

11.8. Independent Data Monitoring Committee

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

The IDMC will consist of at least 1 medical expert in the relevant therapeutic area and at least 1 statistician. The IDMC responsibilities, authorities, and procedures will be documented in its charter.

12. ADVERSE EVENT REPORTING

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

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

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

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

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

Serious Adverse Event

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

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

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

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

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For, intranasal esketamine 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.

For oral antidepressants with marketing authorizations (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 USPI.

Adverse Event Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section [12.1.2](#)

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.

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

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 for some part of the duration of 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 1 business day after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

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

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drugs

14.1.1. 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 mL spray. Each individual nasal spray pump (device) contains a total of 28 mg (ie, 2 sprays).

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

14.1.2. Oral Antidepressant Medications

Duloxetine

Duloxetine 30 mg will be obtained from commercial stock and provided under the responsibility of the sponsor. Refer to the SmPC/USPI for the physical description and a list of excipients.^{22,23}

Escitalopram

Escitalopram 10 mg will be obtained from commercial stock and provided under the responsibility of the sponsor. Refer to the SmPC/USPI for the physical description and a list of excipients.^{27,28}

Sertraline

Sertraline 25 mg and 50 mg (as applicable) will be obtained from commercial stock and provided under the responsibility of the sponsor. Refer to the SmPC/USPI for the physical description and a list of excipients.^{80,81}

Venlafaxine XR

Venlafaxine 37.5 mg and 75 mg (as applicable) will be obtained from commercial stock and provided under the responsibility of the sponsor. Refer to the SmPC/USPI for the physical description and a list of excipients.^{89,90}

14.2. Packaging

Intranasal Study Drug

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

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

Device for Practicing Intranasal Study Drug Administration (Direct-entry subjects only)

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

Oral Antidepressant Medication

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

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

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

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

14.5. Drug Accountability

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

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

The study drug administered to the subject must be documented on the drug accountability form. All study drugs 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, 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
- SmPC/USPI and local prescribing information for oral antidepressant study medications: duloxetine, escitalopram, sertraline, and venlafaxine XR.
- Investigational Product (IP) Binder, including the IP Procedures investigational product procedures manual
- Laboratory manual and materials
- Clinician-administered and subject-completed/patient-reported outcomes 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
- Subject diary
- Computerized cognitive battery and HVLTR-R, and all associated equipment and materials
- Device to measure respiratory rate
- Guidance on recommended order of study procedures
- Guidance document for the use of the MGH-ATRQ.
- Web-based Patient Stated-choice Preference Survey.

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 major depression.

Studies with esketamine have shown robust antidepressant effects in several clinical studies and it has been well tolerated in these clinical studies.

Selection of Subjects

The primary aim of the study is to evaluate long-term safety and tolerability of intranasal esketamine plus an oral antidepressant in subjects with TRD. Thus, the study cannot be conducted 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.

As part of study entry criteria, at screening subjects must have a history of TRD (inadequate response to at least 2 antidepressants at adequate doses and for adequate duration of time). Transferred-entry non-responder subjects from ESKETINTRD3005 will join this study starting from Day 1 of the induction phase and transferred-entry responder subjects will join this study on the first day of the optimization/maintenance phase.

The blind for transferred entry subjects will not be broken. This results in 4 cohorts:

- 1) Subjects who are non-responders to placebo have the potential of receiving esketamine in this study,

- 2) Subjects who are non-responders to esketamine in the ESKETINTRD3005 study who decide to participate in this study may not benefit from additional treatment with esketamine. However, the time to response to oral antidepressants in elderly takes typically longer than 4 weeks. The benefit of additional treatment with esketamine remains unknown. In case of no perceived benefit of esketamine to the subjects after 2-3 dosing sessions they may choose to discontinue from this study,
- 3) Subjects who are responders to esketamine are expected to benefit from longer term treatment to maintain their treatment response,
- 4) Subjects who are responders to the oral antidepressant. These subjects were documented to be treatment-resistant prior to the study, and the probability of responding to a new oral antidepressant is very limited. In case of no additional benefit over that achieved during the induction phase in this study after 2-3 dosing session, subjects may choose to discontinue from this study.

Direct entry subjects will receive 4 weeks of treatment in the open-label induction phase; those who are responders will be eligible to participate in the optimization/maintenance phase.

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. At any time during the study, subjects may discontinue and proceed to the 4 week follow-up phase; they will be provided with an additional 4 week supply of oral antidepressant and appropriate follow-up care will be arranged.

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. 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 subject and the study investigator and/or the subject's physician.

Compensation for any procedure will be fair per local standards and approved by the participating site's IRB, in order to avoid offering any undue incentive to participate in the study.

Subjects will be carefully monitored during the study and subjects who are unable to tolerate study drugs 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 dosing days (see Section 6.1).

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

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 total blood volume to be collected during a full year of study participation is approximately 148 mL, 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 is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

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

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- 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. The reapproval 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 not to 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 recontact 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 DNA and biomarker 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 10.2 Criteria for Withdrawal From the Study).

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 subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)

- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.3. Subject Identification, Enrollment, and Screening Logs

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

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

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

17.4. Source Documentation

At a minimum, source documentation 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 to confirm data collected in the eCRF: 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).

Some subject-completed and clinician-completed scales and assessments designated by the sponsor) will be recorded directly into an electronic device and will be considered source data.

The minimum source documentation requirements for Section 4.1, Inclusion Criteria and Section 4.2, Exclusion Criteria that specify a need for documented medical history are as follows:

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

- 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.

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 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 subject measurements (eg, clinician reported questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

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 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 database. 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 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

The end of the study will occur when at least 300 subjects have received treatment with intranasal esketamine for 6 months and at least 100 subjects for 12 months (Note: the total number of subjects will be based on subjects from this study and subjects from other intranasal esketamine Phase 3 studies).

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

17.9.2. Study Termination

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

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

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

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

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection 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 transfers 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 substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and/or 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. Benedict RHB, Schretlen D, Groninger L, Brandt J. Hopkins Verbal Learning Test-Revised: normative data and analysis of inter-form and test-retest reliability. *Clin. Neuropsychologist*. 1998;12:43-55.
4. Blier P, Zigman D, Blier J. On the safety and benefits of repeated intravenous injections of ketamine for depression. *Biol Psychiatry*. 2012;72:e11-e12.
5. 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.
6. 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.
7. Chung F, Yegneswaran B, Liao P, et al. STOP questionnaire: a tool to screen patients for obstructive sleep apnea. *Anesthesiology*. 2008;108:812-821.
8. Clinical Study 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). Document ID No. EDMS-ERI-71950055 (28 Apr 2014).
9. Clinical Study 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. Janssen Research & Development (10 March 2015). Document No. EDMS-ERI-93094734:1.0.
10. Clinical Study Protocol ESKETINTRD1012. An Open-Label, Single-Dose Study to Assess the Pharmacokinetics, Safety, and Tolerability of Intranasally Administered Esketamine in Elderly (≥75 Years of Age) and Healthy Younger Adult Subjects (18 to 55 Years of Age, Inclusive). Document No. EDMS-ERI-92316094 (03 December 2014).
11. 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. Document No. EDMS-ERI-73676925 (21 Aug 2014).
12. 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. Document No. EDMS-ERI-74234860 (21 Aug 2014).
13. 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. Document No. EDMS-ERI-81854053 (30 Dec 2014).
14. 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. Document No. EDMS-ERI-63623355 (01 May 2014).
15. Clinical Study Report KETIVTRD2002. A double-blind, randomized, placebo-controlled, parallel group, dose frequency study of ketamine in subjects with treatment-resistant depression. Document No. EDMS-ERI-63976766 (5 Sep 2014).
16. ClinicalTrials.gov Registry Entry NCT01557712. Estimate the efficiency of the association of an injection of ketamine and the venlafaxine in the severe major depressive disorder for six weeks (KETADEP). Sponsor: University Hospital, Grenoble. <http://clinicaltrials.gov/ct2/show/NCT01557712>. Last updated 16 Mar 2012. Accessed 16 Dec 2014.
17. ClinicalTrials.gov Registry Entry NCT01880593. Ketamine plus lithium in treatment-resistant depression. Sponsor: Mount Sinai School of Medicine. <https://clinicaltrials.gov/ct2/show/NCT01880593>. Last updated 6 Dec 2014. Accessed 16 Dec 2014.

18. Critchlow DG. A case of ketamine dependence with discontinuation symptoms. *Addiction*. 2006;101(8):1212-1213.
19. 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.
20. 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.
21. DeWilde KE, Levitch CF, Murrough JW, Mathew SJ, Iosifescu DV. The promise of ketamine for treatment-resistant depression: current evidence and future directions. *Ann N Y Acad Sci*. 2015 Feb 3. (17)
22. Duloxetine (Cymbalta®): US Prescribing Information. Lilly USA, LLC, Indianapolis, Indiana, USA; December 2014. <http://pi.lilly.com/us/cymbalta-pi.pdf> (accessed 9 February 2015).
23. Duloxetine (Cymbalta®): Summary of Product Characteristics. Eli Lilly Nederland, Houten, The Netherlands; August 2014. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000572/WC500036781.pdf (accessed 6 March 2015).
24. Duman RS, Aghajanian GK. Synaptic dysfunction in depression: potential therapeutic targets. *Science*. 2012 Oct 5;338(6103):68-72.
25. 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.
26. 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.
27. Escitalopram (Ciprallex®): US Prescribing Information. Lundbeck Canada Inc., Quebec, Canada; 12 November 2014. http://www.lundbeck.com/upload/ca/en/files/pdf/product_pi/Ciprallex_November_2013/Ciprallex.pdf (accessed 9 February 2015).
28. Escitalopram: Summary of Product Characteristics. Actavis Group PTC ehf., Iceland; July 2014. <http://www.medicines.org.uk/emc/medicine/28956> (accessed 6 March 2015).
29. EuroQol Group. About EQ-5D. <http://www.euroqol.org/about-eq-5d.html> (accessed 18 June 2014).
30. EuroQol Group. EQ-5D-5L User Guide: basic information on how to use the EQ-5D-5L instrument. Version 2.0; October 2013. http://www.euroqol.org/fileadmin/user_upload/Documenten/PDF/Folders_Flyers/UserGuide_EQ-5D-5L_v2.0_October_2013.pdf (accessed 6 August 2014).
31. Fava M. Diagnosis and definition of treatment-resistant depression. *Biol Psychiatry*. 2003 Apr 15;53(8):649-659. Review.
32. 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
33. 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.
34. Guy W. ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: U.S. Department of Health, Education, and Welfare; 1976.
35. Haas DA, Harper DG. Ketamine: a review of its pharmacologic properties and use in ambulatory anesthesia. *Anesth Prog*. 1992;39(3):61-68.
36. 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.
37. 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.
38. Holtman JR, Crooks PA, Johnson-Hardy JK, Hojomat M, Kleven M, Wala EP. Effects of norketamine enantiomers in rodent models of persistent pain. *Pharmacol Biochem Behav*. 2008; 90: 676-685.

39. Humphrey L, Arbuckle R, Moldwin R, et al. The Bladder Pain/Interstitial Cystitis Symptom Score: development, validation, and identification of a cut score. *Eur Urology*. 2012;61:271-279.
40. Hurt PH, Ritchie EC. A case of ketamine dependence. *Am J Psychiatry*. 1994 May;151(5):779.
41. Investigator's Brochure, JNJ-54135419-AAC (esketamine hydrochloride),. Document ID: EDMS-ERI-49489196.
42. Jansen KL. Ketamine--can chronic use impair memory? *Int J Addict*. 1990 Feb;25(2):133-9.
43. Johnson FR, Hauber B, Özdemir S, Siegel CA, Hass S, Sands BE. Are gastroenterologists less tolerant of treatment risks than patients? Benefit-risk preferences in Crohn's disease management. *J Manag Care Pharm*. 2010; 16: 616-628.
44. Ketamine HCl Injection: US Prescribing Information; March 2012. JHP Pharmaceuticals, LLC. Rochester, Minnesota, USA. <http://www.drugs.com/pro/ketalar.html> (accessed 25 February 2015).
45. Ketanest-S®: Summary of Product Characteristics. Ankeveen, The Netherlands: Eurocept BV; 2011.
46. Kinter ET, Schmeding A, Rudolph I, dosReis S, Bridges JF. Identifying patient-relevant endpoints among individuals with schizophrenia: an application of patient-centered health technology assessment. *Int J Technol Assess Health Care*. 2009; 25: 35-41.
47. Lapidus KA, Levitch CF, Perez AM, et al. A randomized controlled trial of intranasal ketamine in major depressive disorder. *Biol Psychiatry*. 2014;76(12):970-6.
48. 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.
49. Levitan B, Markowitz M, Mohamed AF, Johnson FR, Alphas L, Citrome L, Bridges JF. Patients' Preferences Related to Benefits, Risks, and Formulations of Schizophrenia Treatment. *Psychiatr Serv*. 2015; 66(7):719-726.
50. Lim DK. Ketamine associated psychedelic effects and dependence. *Singapore Med J*. 2003;44(1):31-34.
51. McGirr A, Berlim MT, Bond DJ, Fleck MP, Yatham LN, Lam RW. A systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials of ketamine in the rapid treatment of major depressive episodes. *Psychol Med*. 2015 Mar;45(4):693-704.
52. Monteggia LM, Zarate C Jr. Antidepressant actions of ketamine: from molecular mechanisms to clinical practice. *Curr Opin Neurobiol*. 2015 Feb;30C:139-143.
53. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134:382-389.
54. Montgomery SA. Clinically relevant effect sizes in depression. *Eur Neuropsychopharmacology*. 1994;(4)283-284.
55. Moore NN, Bostwick JM. Ketamine dependence in anesthesia providers. *Psychosomatics*. 1999 Jul-Aug;40(4):356-9.
56. Morgan CJ, Curran HV. Acute and chronic effects of ketamine upon human memory: a review. *Psychopharmacology*. 2006;188:408-424.
57. Morgan CJ, Muetzelfeldt L, Curran HV. Ketamine use, cognition and psychological wellbeing: a comparison of frequent, infrequent and ex-users with polydrug and non-using controls. *Addiction*. 2009;104:77-87.
58. Morgan CJ, Curran HV; Independent Scientific Committee on Drugs. Ketamine use: a review. *Addiction*. 2012 Jan;107(1):27-38.
59. 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.
60. 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.
61. Murrough JW, Perez AM, Pillemer S, et al. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. *Biol Psychiatry*. 2013; 74:250-256.

62. 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.
63. Opler LA, Opler MG, Arnsten AF. Ameliorating treatment-refractory depression with intranasal ketamine: potential NMDA receptor actions in the pain circuitry representing mental anguish. *CNS Spectr*. 2015 Jan 26:1-11.
64. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale (BPRS): recent developments in ascertainment and scaling. *Psychopharmacol Bull*. 1988;24:97-99.
65. Overall JE; Gorham D R. The Brief Psychiatric Rating Scale. *Psychol Rep*. 1962;10:799-812.
66. Pal HR, Berry N, Kumar R, Ray R. Ketamine dependence. *Anaesth Intensive Care*. 2002 Jun;30(3):382-4.
67. Persson J. Wherefore ketamine? *Curr Opin Anaesthesiol*. 2010 Aug;23(4):455-60.
68. Pharmacokinetic Report KET-PK-007. A randomized, open label, single center, single-dose, cross-over study to determine the absolute bioavailability and the nasopharyngeal absorption of PMI-150 (intranasal ketamine) in healthy adult volunteers. Javelin Pharmaceuticals, Inc. Document No. EDMS-ERI-44757121 (31 Oct 2008).
69. 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.
70. 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.
71. Reich DL, Silvey G. Ketamine: An update on the first twenty-five years of clinical experience. *Can J Anaesth*. 1989;36(2):186-197.
72. Rickels K, Garcia-Espana F, Mandos L, Case GW. Physician Withdrawal Checklist (PWC-20). *J Clin Psychopharmacol*. 2008;28(4):447-451.
73. Rugani F, Bacciardi S, Rovai L, et al. Symptomatological Features of patients with and without ecstasy use during their first psychotic episode. *Int. J. Environ. Res. Public Health*. 2012;9(7):2283-2292.
74. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. 2006 Nov;163(11):1905-17.
75. Ryan M, Hughes J. Using conjoint analysis to assess women's preferences for miscarriage management. *Health Econ*. 1997; 6(3): 261-273.
76. Ryan M, Gerard K. Using discrete choice experiments to value health care programmes: current practice and future research reflections. *Appl Health Econ Health Policy*. 2003; 2(1): 55-64.
77. 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). Document ID No. EDMS-ERI-97270375 (6 February 2015).
78. Sagie A, Larson MG, Goldberg RJ, Bengtson 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.
79. Saveanu R, Etkin A, Duchemin AM, et al. The International Study to Predict Optimized Treatment in Depression (iSPOT-D): Outcomes from the acute phase of antidepressant treatment. *J Psychiatr Res*. 2015 Feb;61:1-12
80. Sertraline (Zoloft®): US Prescribing Information. Pfizer, Inc., New York, New York, USA; August 2014. <http://labeling.pfizer.com/ShowLabeling.aspx?id=517> (accessed 9 February 2015).
81. Sertraline: Summary of Product Characteristics. Sandoz Limited, Surrey, United Kingdom; September 2012. <http://www.medicines.org.uk/emc/medicine/28749/SPC> (accessed 6 March 2015).
82. Shahani R, Streutker C, Dickson B, Stewart RJ. Ketamine-associated ulcerative cystitis: a new clinical entity. *Urology*. 2007;69(5):810-2.
83. Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. *Int Clin Psychopharmacol*. 1996 Jun;11 Suppl 3:89-95. Review.

84. Shiroma PR, Johns B, Kuskowski M, et al. Augmentation of response and remission to serial intravenous subanesthetic ketamine in treatment resistant depression. *J Affect Disord.* 2014; 155: 123-129.
85. 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.
86. Sinner B, Graf BM. Ketamine. In: Schüttler J, Schwilden H, eds. *Modern Anesthetics: Handbook of Experimental Pharmacology.* Berlin: Springer-Verlag; 2008; 182: 313-333.
87. 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.
88. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. *JAMA.* 1999; 282:1737-1744.
89. Venlafaxine Extended-release: US Prescribing Information. Pfizer, Inc., New York, New York, USA; August 2014. <http://labeling.pfizer.com/ShowLabeling.aspx?id=612> (accessed 9 February 2015).
90. Venlafaxine: Summary of Product Characteristics. Actavis Group PTC ehf, Iceland; May 2012. <http://www.medicines.org.uk/emc/medicine/24329> (accessed 6 March 2015)
91. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* 2012 Dec 15;380(9859):2163-96.
92. Walker E, McGee R, Druss B. Mortality in Mental Disorders and Global Disease Burden Implications: A Systematic Review and Meta-analysis. *JAMA Psychiatry.* 2015. (new ref for the first sent)
93. Whitmyer VG, Dunner DL, Kornstein SG, et al. A comparison of initial duloxetine dosing strategies in patients with major depressive disorder. *J Clin Psychiatry.* 2007 Dec; 68(12):1921-30.
94. Wieber J, Gugler R, Hengstmann JH, Dengler HJ. Pharmacokinetics of ketamine in man. *Anaesthesist.* 1975 Jun;24(6):260-3.
95. Wittink MN, Cary M, Tenhave T, Baron J, Gallo JJ. Towards patient-centered care for depression: conjoint methods to tailor treatment based on preferences. *Patient.* 2010; 3(3): 145-157.
96. Woolf TF, Adams JD. Biotransformation of ketamine, (Z)-6-hydroxyketamine, and (E)-6-hydroxyketamine by rat, rabbit, and human liver microsomal preparations. *Xenobiotica.* 1987; 17: 839-847.
97. World Health Organization. Depression (fact sheet). October 2012. <http://www.who.int/mediacentre/factsheets/fs369/en/> (accessed 5 February 2015).
98. 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.
99. Zarate CA Jr, Quiroz JA, Singh JB, et al. An open-label trial of the glutamate-modulating agent riluzole in combination with lithium for the treatment of bipolar depression. *Biol Psychiatry.* 2005; 57: 430-432.
100. Zarate CA Jr, Singh JB, Carlson PJ, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry.* 2006; 63: 856-864.

ATTACHMENTS**Attachment 1: Prohibited Concomitant Medications with Intranasal Study Medication (Esketamine)**

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 this table are prohibited from 1 week (or 5 half-lives, whichever is longer) prior to the first dose of intranasal study medication until at least 1 day (24 hours) after the last dose of intranasal study medication. Of note, other than for MAOIs (see table below), for all antidepressants being taken at the start of or during the screening phase, no washout or drug-free period is required after discontinuing the antidepressant treatment; however, if clinically indicated, the antidepressant treatment can be tapered and discontinued during the screening phase.

N = Prohibited, Y = Permitted (see Comments column for additional guidance)

Drug Class	Episodic Use (as needed)	Continuous Use	Comments	Reason for Prohibition
Amantadine	N	N		PD interaction
Anorexiant (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 <i>(other than the specific antidepressant started in the induction phase of the study)</i>	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 phase, there must be a minimum washout interval of 2 weeks prior to the first dose of intranasal study medication. – Even if used primarily for sleep, trazodone use 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 equal to or less than the equivalent of 6 mg/day of 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 or cognition testing	Safety and PD interaction
Benzotropine	Y	N	Prohibited if use is continuous and prohibited within 12 hours prior to the start of cognition testing	Safety and PD interaction.
Chloral hydrate, melatonin, valerian	N	N		Safety and PD interaction
Clonidine	N	N		Safety and PD interaction
Corticosteroids (systemic)	Y	N	Inhaled, intranasal, topical, and ophthalmic steroids are not prohibited. Intermittent IM/IV corticosteroids are permitted (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
Methyl dopa	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, and modafinil, armodafinil)	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
St. John's Wort	N	N		PD interaction and PK
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: IM, intramuscular; IV, intravenous; 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

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 Schedules for Open-label Induction Phase

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

Titration schedule for subjects <65 years (except for Taiwan, South Korea and Malaysia)

Oral Antidepressant (Active Comparator)	Titration Schedule			
	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	150 mg
Venlafaxine XR	75 mg	150 mg	225 mg	225 mg

Titration schedule for subjects <65 years in Taiwan and South Korea

Oral Antidepressant (Active Comparator)	Titration Schedule			
	Week 1 (Starting Day 1)	Week 2 (Starting Day 8)	Week 3 (Starting Day 15)	Week 4 (Starting Day 22)
Duloxetine	30 mg	60 mg	60 mg	60 mg
Escitalopram	10 mg	20 mg	20 mg	20 mg
Sertraline	50 mg	100 mg	150 mg	150 mg
Venlafaxine XR	37.5 mg	75 mg	150 mg	225 mg

Titration schedule for subjects <65 years in Malaysia

Oral Antidepressant (Active Comparator)	Titration Schedule			
	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	150 mg
Venlafaxine XR	37.5 mg	75 mg	150 mg	225 mg

Titration schedule for subjects' ≥65 years old – all countries

Oral Antidepressant (Active Comparator)	Titration Schedule			
	Week 1 (Starting Day 1)	Week 2 (Starting Day 8)	Week 3 (Starting Day 15)	Week 4 (Starting Day 22)
Duloxetine	30 mg	60 mg	60 mg	60 mg
Escitalopram	10 mg	10 mg	10 mg	10 mg
Sertraline	25 mg	50 mg	100 mg	150 mg
Venlafaxine XR	37.5 mg	75 mg	150 mg	150 mg

^aDuloxetine: Subjects should be initiated with 60 mg/day. Subjects that have in the past shown increased sensitivity towards serotonin reuptake inhibitors (SSRI) and 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

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.^{22,23,27,28,41,80,81,89,90} 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
- Excessive happiness
- Irritability, anger, and impulsive behavior
- Agitation, feeling anxious/anxiety, 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

These events will be captured on the CRF and in the database, 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-AAC (esketamine)

Clinical Protocol ESKETINTRD3004 Amendment 4

INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Jaskaran Singh, MD

Institution: Janssen Research & Development, LLC

Signature: _____ Date: 6 July, 2016
(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.