

**Janssen Research & Development\***

**Clinical Protocol**

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**A Randomized, Double-blind, Multicenter, Active-controlled Study of Intranasal Esketamine Plus an Oral Antidepressant for Relapse Prevention in Treatment-resistant Depression**

Sustenance of Esketamine Treatment Response With Repeated Doses at Intervals Determined by Symptom Severity (SUSTAIN-1)

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**Protocol ESKETINTRD3003; 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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**Prepared by:** Janssen Research & Development, LLC  
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**GCP Compliance:** This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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## PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	26 March 2015
Amendment INT-1	21 April 2015
Amendment 2	13 January 2016
Amendment 3	9 June 2016
Amendment 4	4 April 2017

Amendments below are listed beginning with the most recent amendment.

### **Amendment 4** (4 April 2017)

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

**The overall reason for the amendment:** In order to enhance the number of clinically valid subjects proceeding to the Maintenance phase as stable remitters, the stable remission criteria have been revised.

Applicable Section(s)	Description of Change(s)
<b>Rationale:</b>	The justification for allowing a single excursion of the MADRS total score or one missed MADRS assessment was made on the basis that it could be due to a life event and not the underlying illness, eg, having a bad day, difficulty in a family relationship, a setback at work or school, or a scheduling conflict.
Synopsis: Overview of Study Design, Definitions of Terms; 3.1.2. Definitions of Terms: Optimization Phase	<p>The definition of stable remission was modified (bold text added; strikethrough text deleted):</p> <p><del>Remission: MADRS total score <math>\leq 12</math></del></p> <ul style="list-style-type: none"> <li>Stable remission: <ul style="list-style-type: none"> <li><del>MADRS total score <math>\leq 12</math> for the last 4 weeks of the optimization phase</del></li> <li>MADRS total score <math>\leq 12</math> for at least 3 of the last 4 weeks of the optimization phase, but one excursion of a MADRS total score <math>&gt; 12</math> or one missing MADRS assessment is permitted at Optimization week 13 or 14 only. The MADRS total score at weeks 15 and 16 must be <math>\leq 12</math>.</li> </ul> </li> </ul>
3.2.2. Study Phases: Optimization Phase	For the primary analysis, a subject must be in stable remission (MADRS total score $\leq 12$ for 4 consecutive weeks) for the last 4 weeks of this phase (see full definition, section 3.1.2) to enter the maintenance phase.
<b>Rationale:</b>	The definition of stable response was modified, as there is no longer a requirement to have a MADRS score of $> 12$ at one of the last 2 weeks of the Optimization phase.
Synopsis: Overview of Study Design, Definitions of Terms; 3.1.2. Definitions of Terms: Optimization Phase	<p>The definition of stable response was modified as follows (bold text added; strikethrough text deleted):</p> <p>Stable response: <math>\geq 50\%</math> reduction in the MADRS total score from baseline (Day 1 of induction phase; pre-randomization/prior to the first intranasal dose) in each of the last 2 weeks of the optimization phase, <b>but does not meet criteria for stable remission.</b> <del>with at least 1 MADRS total score of <math>&gt; 12</math> in these 2 weeks.</del> Note: For transferred-entry subjects, Day 1 of the open-label induction phase will take place in ESKETINTRD3001 or ESKETINTRD3002.</p>

Applicable Section(s)	Description of Change(s)
3.2.2. Study Phases: Optimization Phase	Subjects with stable response ( $\geq 50\%$ reduction in the MADRS total score from baseline [Day 1 of induction phase; pre-randomization/prior to the first intranasal dose]) in each of the last 2 weeks of the optimization phase <del>with at least 1 MADRS total score of <math>&gt;12</math> in these 2 weeks but who do are</del> not <b>meet criteria for</b> in stable remission, will also enter the maintenance phase, but will not be part of the primary analysis.
<b>Rationale:</b> Missing MADRS assessments during Weeks 5 to 12 of the Optimization phase will no longer be considered in determining subject's eligibility to participate in the maintenance phase of the study. This modification has been made to reduce the impact of missing MADRS assessments, given the lengthiness of the trial and need for weekly assessments. The justification for removing this criterion is made on the basis that, in general, rather than indicating poor compliance to study procedure, missing assessments may often be due to a family emergency or illness, vacation or travel plans, or change in work or school schedule. In order to enhance the number of clinically valid subjects proceeding to the Maintenance phase, the criterion has been removed.	
Synopsis: Dosage and Administration, Optimization phase; 6.1.2.3. Intranasal Treatment Session Frequency: All Subjects	The following text was modified (strikethrough text deleted):  <del><i>Missed MADRS Assessments:</i></del> <ul style="list-style-type: none"> <li>• <del>If <math>\geq 3</math> MADRS assessments are missed during the first 8 weeks of the optimization phase (Week 5 to Week 12), the subject can complete the optimization phase but is not eligible to participate in the maintenance phase.</del></li> </ul>
9.1.4. Optimization Phase; 10.2. Withdrawal From the Study	A subject will not be eligible to proceed into the maintenance phase if he or she: <ul style="list-style-type: none"> <li>• Misses <math>\geq 21</math> days of the oral antidepressant doses (total daily dose)</li> <li>• <del>Misses <math>\geq 3</math> MADRS assessments in the first 8 weeks (Weeks 5 to 12)</del></li> </ul>
<b>Rationale:</b> Clarification that subjects in the Optimization phase at the time study closes are not required to complete the Optimization phase.	
Synopsis: Optimization Phase; 3.1.1. Study Phases: Optimization Phase	The following text was modified (bold text added; strikethrough text deleted):  At the time the study is stopped <del>(for efficacy)</del> , subjects in the optimization phase <del>will be able to complete the phase. After completing the phase, these subjects</del> will have an Early Withdrawal Visit conducted and proceed directly to the follow-up phase.
10.1. Criteria for Completion	<b>Subjects in the Screening Prospective Observational phase at the time of study termination may be eligible to proceed to the 54135419TRD3008 study.</b>  Subjects in the induction <del>or optimization</del> phase of the study at the time of study termination will be allowed to complete their <del>current induction</del> phase, <del>will complete an Early Withdrawal Visit, and continue into the follow up phase but will not be considered completers.</del>  <b>These subjects, after completing the Early Withdrawal visit, may proceed to the 54135419TRD3008 study, but will not be considered completers for this study. Subjects in the optimization phase at time of study termination will not need to complete this phase, and will complete an Early Withdrawal Visit, and continue into the follow up phase, but they will not be considered completers.</b>



Applicable Section(s)	Description of Change(s)
<b>Rationale:</b> Clarification for subjects in different phases of the study at the time study is stopped (for efficacy) regarding whether they will complete their current phase.	
Synopsis: Overview of Study Design; 3.1.1. Study Phases; 16.1. Study-specific Design Considerations	<p>The following text was modified (bold text added; strikethrough text deleted):</p> <p>The study will be stopped once 84 relapses (in the subjects with stable remission) occur during the maintenance phase, or earlier, based on the results of the interim analysis for efficacy <del>or futility</del>. At the time the study is stopped (<del>for efficacy</del>), subjects in the induction phase <del>or optimization phase</del> will be able to complete the <del>Induction</del><del>respective</del> phase.</p> <p><b>Those subjects who are responders after completing an Early Withdrawal Visit may proceed to the 54135419TRD3008 study without completing the follow up phase. Those who are not responders will have an Early Withdrawal Visit and proceed directly to the follow-up phase. After completing the respective phase, these subjects and S</b>ubjects who are in the <b>optimization or</b> maintenance phase at the time the study is terminated will <b>have an Early Withdrawal Visit/End of Maintenance Visit conducted and</b> proceed directly to the follow-up phase.</p>
Synopsis: Open-label Induction Phase; 3.1.1. Study Phases: Open-label Induction Phase	<p>At the time the study is stopped (<del>for efficacy</del>), subjects in the induction phase will be able to complete the phase.</p> <p><b>Those who are responders, after completing an Early Withdrawal Visit, may proceed to the 54135419TRD3008 study without completing the follow up phase. Those who are not responders</b> <del>After completing the phase, these subjects will</del> have an Early Withdrawal Visit conducted and proceed directly to the follow-up phase.</p>
<b>Rationale:</b> To allow earlier access to open label esketamine treatment, subjects who relapse in the Maintenance phase and those who are responders at the end of induction at the time the study is stopped, will be allowed to proceed to the open-label safety extension study, 54135419TRD3008, without completing the follow up phase (if clinically indicated).	
Synopsis: Follow-up Phase; Time and Events Schedule (Early Withdrawal/End of Maintenance Phase Visit and Follow-up Phase) footnote a; 3.1.1. Study Phases: Follow-up Phase; 9.1.6. Early Withdrawal/End of Maintenance Phase; 9.1.7. Follow-up Phase;	<p>The following text was modified (bold text added; strikethrough text deleted):</p> <p>This phase will include all subjects who have received at least 1 dose of intranasal study medication in this study. <b>For those subjects who relapse in the Maintenance phase, if clinically indicated based on investigator’s judgment, after completing the end of maintenance visit, the subject may proceed to the open-label safety extension study, 54135419TRD3008, without completing the follow up phase. Similarly, when the study is stopped, (<del>for efficacy</del>) subjects in the Induction phase who are responders, after completing the early withdrawal visit, if clinically indicated based on the investigator’s judgment, may proceed to the 54135419TRD3008 study, without completing the follow up phase.</b></p>

Applicable Section(s)	Description of Change(s)
Synopsis: Maintenance Phase; 3.1.1. Study Phases: Maintenance phase	<p>The following text was modified (bold text added; strikethrough text deleted):</p> <p>Subjects who meet the relapse criteria and subjects who remain relapse-free at study termination will have an End of Maintenance Phase Visit conducted and <b>may</b> proceed to the follow-up phase. <b>If clinically indicated, subjects who have met relapse criteria after completing the End of Maintenance visit may proceed to the open-label safety extension study, 54135419TRD3008, without completing the follow up phase.</b> Subjects who are participating in the maintenance phase at the time the study is stopped (<del>for efficacy</del>) will have an Early Withdrawal Visit conducted and proceed directly to the follow-up phase.</p>
9.1.6. Early Withdrawal/End of Maintenance Phase;	<p>The following text was modified (bold text added):</p> <p>A subject meeting relapse criteria during the maintenance phase is not considered an early withdrawal. These subjects, and subjects in the maintenance phase who remain relapse-free at study termination, will have an End of Maintenance Phase Visit conducted, followed by the follow up phase. <b>If clinically indicated, subjects who relapse in the Maintenance phase may proceed to the open-label safety extension study, 54135419TRD3008, without completing the follow up phase.</b></p>
10.2. Withdrawal from Study	<p>The following text was modified (bold text added; strike through text deleted):</p> <p>A subject meeting relapse criteria during the maintenance phase is not considered an early withdrawal. <b>If clinically indicated, after completing the End of Maintenance visit, subjects who have met relapse criteria may proceed to the open-label safety extension study, 54135419TRD3008, without completing the follow up phase.</b> <del>For these subjects, and</del> Subjects who remain relapse-free at study termination, will have an End of Maintenance Phase Visit conducted, followed by the follow-up phase.</p>
<p><b>Rationale:</b> Early termination of the maintenance phase for futility, based on interim analysis results, is no longer applicable, because these results could indicate that once subjects become stable remitters on esketamine, the intranasal placebo plus oral antidepressant arm can be as good or potentially better at maintaining response as intranasal esketamine + oral antidepressant arm. This potential outcome is not a negative outcome, but rather may inform how to use esketamine in long term. As such, the study would not be considered futile.</p>	
Synopsis: Overview of Study Design, Synopsis: Statistical Methods, Interim Analysis; 3.1.1. Study Phases; 11.3. Efficacy Analyses; 11.7. Interim Analysis; 11.8. Independent Data Monitoring Committee; 16.1. Study-specific Design Considerations	<p>Clarified that the results of the interim analysis would no longer be used to stop the study due to futility; the results could only indicate stopping due to efficacy (ie, futility was deleted).</p>

Applicable Section(s)	Description of Change(s)
<b>Rationale:</b> Clarification on Dosage and Administration of Intranasal Study Drug. Dose adjustment will be permitted on Days 15, 18, and 22 to allow more time for dosing to be optimized based on efficacy and tolerability	
Synopsis: Dosage and Administration: Open-label Induction Phase; 6.1.1. Open-label Induction Phase	<p>Modified the following text (bold text added; strikethrough text deleted):</p> <p>On Day 1, subjects will start with a dose of 56 mg. On Day 4, the dose may be increased to 84 mg or remain at 56 mg, as determined by the investigator based on efficacy and tolerability. On Day 8, the dose may be increased to 84 mg (if Day 4 dose was 56 mg), remain the same, or be reduced to 56 mg (if Day 4 dose was 84 mg), as determined by the investigator based on efficacy and tolerability. Similarly, on Days 11, <b>15, 18, and 22</b>, the dose may be increased to 84 mg (<del>if Day 8 dose was 56 mg</del>), remain the same, or be reduced to 56 mg (<del>if Day 8 dose was 84 mg</del>), <b>if applicable</b> as determined by the investigator based on efficacy and tolerability. <del>On Day 15, a dose reduction from 84 mg to 56 mg is permitted, if required for tolerability; no dose increase is permitted on Day 15.</del> On Days 18, 22, and 25, <b>a dose reduction from 84 mg to 56 mg is permitted if required for tolerability; no dose increase is permitted. the dose must remain stable (unchanged).</b> If there is no intranasal treatment session on Day 15 (eg, visit is missed), a dose reduction from 84 mg to 56 mg is permitted on Day 18 if required for tolerability; <del>no dose increase is permitted.</del></p>
<b>Rationale:</b> Added information about 54135419TRD3008, an open-label safety extension study, that may be available for eligible subjects participating in ESKETINTRD3003.	
Synopsis: Follow-up Phase; 3.1.1. Study Phases: Follow-up Phase; 9.1.7. Follow-up Phase	<p>The following text was modified (bold text added; strikethrough text deleted):</p> <p>An open-label safety extension study, 54135419TRD3008, may be available (pending country and site approval) for eligible subjects participating in the ESKETINTRD3003 study. Please refer to the 54135419TRD3008 protocol for full details <del>when available</del> <b>of potential pathways for entry.</b></p>
<b>Rationale:</b> Restrictions for Day 28 of the Induction phase and visit 3.1 of the Optimization phase were relaxed to allow for some flexibility.	
Time and Events Schedule (Optimization Phase, footnote b); 9.1.3. Open-label Induction Phase; 9.1.4. Optimization Phase	<p>The following text was modified (bold text added; strikethrough text deleted):</p> <p>Results for all assessments performed on Day 28 of the induction phase for direct-entry subjects (Visit 2.9) and transferred-entry subjects (Visit 2.10 of Study ESKETINTRD3001 or ESKETINTRD3002) will serve as the baseline values for the optimization phase and will not be repeated as part of Visit 3.1. The Day 28 visit <del>should</del> <b>must</b> coincide <del>exactly</del> with Day 28 (Visit 3.1) for this study. <del>There is no gap allowed between studies.</del> All transferred-entry subjects must meet all of the transferred-entry subject-specific inclusion criteria and none of the exclusion criteria in order to be enrolled.</p>

Applicable Section(s)	Description of Change(s)
<b>Rationale:</b> Clarified the approach for collection of duplicate assessments during Optimization Phase and Maintenance Phase.	
Time and Events Schedule (Optimization Phase, footnote a);	The following text was modified (bold text added):  If a subject withdraws before the end of the optimization phase for reasons other than withdrawal of consent, or is not eligible to continue into the maintenance phase, an Early Withdrawal Visit (Refer to Time and Events Schedule: Early Withdrawal/End of Maintenance Phase Visit and follow up phase) should be conducted. <b>If the Early Withdrawal Visit is conducted on the same day as a scheduled visit, duplicate assessments are not required.</b>
Time and Events Schedule (Maintenance Phase, footnote b)	If a subject withdraws before the end of the maintenance phase for reasons other than withdrawal of consent, an Early Withdrawal Visit should be conducted. A subject meeting relapse criteria is not considered to be an early withdrawal subject; for relapse subjects, and those subjects remaining relapse-free at the time of study termination, an End of Maintenance Phase Visit should be conducted. <b>If the End of Maintenance Visit is conducted on the same day as a scheduled visit, duplicate assessments are not required.</b> Refer to the Time and Events Schedule: Early Withdrawal/End of Maintenance Phase Visit and Follow-up Phase.
<b>Rationale:</b> Given the potential to cause increased sedation and potential impact on efficacy, benzodiazepine rescue medication is permitted only post-dose on the dosing day.	
3.1.1. Study Phases: Open-label Induction Phase; 4.3. Prohibitions and Restrictions; 9.1.2. Screening/Prospective Observational Phase	The following text was modified (bold text added):  No dose increases beyond the equivalent of 6 mg/day of lorazepam, or new benzodiazepine medications are permitted during the induction phase, with the exception of the use of permitted benzodiazepine rescue medication ( <b>post-dose on the dosing day only</b> ).
8. Prestudy and Concomitant Therapy	For agitation or anxiety: As required, midazolam (maximum dose 2.5 mg orally or IM) or short acting benzodiazepine ( <b>only permitted post-dose on the day of dosing</b> ).
<b>Rationale:</b> Updated language in Attachment 1 to align with the changes made regarding oral antidepressant requirements under INT-3 of 3003. Under that amendment, the dose of oral antidepressant medications can be adjusted in the screening/prospective phase.	
Attachment 1	The following text was modified (bold text added; strikethrough text deleted):  Except where specifically noted, the prohibited medications listed in the following table are prohibited from 1 week (or 5 half-lives, whichever is longer) prior to the first dose of intranasal study medication until after the last dose of intranasal study medication. Note: If a medication is part of the antidepressant treatment regimen being taken at the time of signing the ICF (ie, start of screening/prospective observational phase), <b>per protocol, the medication is continued</b> <del>it must be continued unchanged</del> until the end of Week 4 of the screening/prospective observational phase, therefore this requirement is not applicable. In such cases the investigator may choose to taper the relevant medication during the up to 3-week taper period based on their clinical judgment.

Applicable Section(s)	Description of Change(s)
<b>Rationale:</b> As clonidine is considered a safe and effective treatment option for blood pressure elevation, it is now permitted as a treatment for blood pressure control in the study.	<p data-bbox="181 296 1442 359">Attachment 1                      Episodic and continuous course of clonidine is now allowed as a treatment option for blood pressure control.</p> <p data-bbox="634 386 1268 449">The following text was deleted (strikethrough text deleted): <del>Safety and PD Interaction</del></p> <p data-bbox="634 476 1146 539">The following text was added (bold text added): <b>Use for blood pressure control is allowed</b></p> <p data-bbox="634 567 1393 630">Episodic Use (As Needed) and Continuous Use were changed from No (N) to <b>Yes (Y)</b>.</p>
<b>Rationale:</b> (brief course of corticosteroids may be permitted to treat conditions including rash, asthma etc.): The Company considered that there is no increased risk in terms of safety or efficacy in allowing a brief course of corticosteroids, if clinically indicated, to treat an acute medical condition.	<p data-bbox="181 764 1442 795">Attachment 1                      The following text was added (bold text added):</p> <p data-bbox="634 823 1341 886">Intermittent IM/IV/<b>PO</b> corticosteroids are permitted <b>with sponsor approval</b> (chronic use prohibited).</p>
<b>Rationale:</b> (allowing brief course of opiates): Company considered that there is no increased risk in terms of safety or efficacy in allowing a brief course of opiates, if clinically indicated, to treat pain associated with recent surgery or acute injury.	<p data-bbox="181 1018 1442 1050">Attachment 1                      The following text was added (bold text added):</p> <p data-bbox="634 1077 1390 1140"><b>Note: With Sponsor approval, brief treatment with opiates may be allowed for treatment of acute injuries etc.</b></p>
<b>Rationale:</b> Modafinil and armodafinil are deleted from the psychostimulants row of Attachment 1 (they are no longer permitted as psychostimulants) because they are potent CYP 3A4 inducers and therefore should be prohibited during the study.	<p data-bbox="181 1272 1442 1304">Attachment 1                      The following text was modified (strikethrough text deleted):</p> <p data-bbox="634 1331 1289 1394">Psychostimulants (eg, amphetamines, methylphenidate, <del>modafinil, armodafinil</del>)</p>
<b>Rationale:</b> Minor grammatical, formatting, and spelling errors were noted	Throughout the document                      Minor errors were corrected. Minor formatting changes were made.

**Amendment 3** (9 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:** Based on feedback received from Investigators involved in the study, the subject entry criteria have been revised to improve recruitment.

Applicable Section(s)	Description of Change(s)
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	<p><b>Rationale:</b> To improve recruitment, the antidepressant treatment requirements at study entry (ie, time of signing the ICF) in inclusion criterion no. 3.1 were changed. In addition, the definition of non-response at the end of the screening/prospective observational phase was revised.</p>
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4.1.1. Direct-entry Subjects	<p>Inclusion criterion no. 3.1 was revised as follows (bold text added; strikethrough text deleted):</p> <p>At the start of the screening/prospective observational phase, subject must have had non-response (<math>\leq 25\%</math> improvement) to <math>\geq 12</math> but <math>\leq 5</math> (if current episode is <math>&gt; 2</math> years, upper limit is applicable to only the last 2 years) oral antidepressant treatments in the current episode of depression, assessed using the MGH-ATRQ and confirmed by documented records (eg, medical/pharmacy/prescription records/ or a letter from a treating physician, etc.). <b>In addition, the subject must be taking one of the different oral antidepressant treatment(s) with nonresponse that is documented (on the MGH-ATRQ) for at least the previous 2 weeks (ie, this oral antidepressant treatment must have been taken for at least 6 weeks at or above the minimal therapeutic dose with a lack of clinically meaningful improvement) at the start of the screening/prospective observational phase.</b></p> <ul style="list-style-type: none"> <li>- For specific tricyclic antidepressants which are <b>ongoing and</b> 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.</li> <li>- Subjects must <del>have been</del> <b>be</b> adherent to the continued oral antidepressant treatment medication(s) <del>(without adjustment in dosage)</del> through the screening/prospective observational phase, as documented on the PAQ. Missing <math>\geq 4</math> days of antidepressant medication in the prior 2-week period will be considered as inadequate adherence.</li> <li>- Subjects who are non-responders to their current oral antidepressant medication(s) from the screening/prospective observational phase (as assessed by independent, remote raters) may be eligible for randomization if all other entry criteria are met. Non-response at the end of the screening/prospective observational phase is defined as <math>\leq 25\%</math> improvement in the MADRS total score <del>for 2 consecutive visits</del> <b>from Week 1 to Week 4</b> and a MADRS total score of <math>\geq 28</math> <del>for 2 consecutive visits</del> <b>on Week 2 and Week 4.</b></li> </ul> <p>Synopsis, Overview of Study Design; Synopsis, Dosage and Administration; 3.1.1. Study Phases; 3.2.2. Study Phases</p> <p>Deleted text stating that the antidepressant treatment will continue unchanged at the same dosage during the screening/prospective observational phase.</p>
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Applicable Section(s)	Description of Change(s)
Synopsis, Subject Population; Synopsis, Dosage and Administration; 3.1.1. Study Phases; 3.2.1. Study Population; 6.2.1. Screening/Prospective Observational Phase; 9.1.2. Screening/Prospective Observational Phase	Text regarding antidepressant treatment during the screening/prospective observational phase was revised as follows (bold text added; strikethrough text deleted):  <p><b>In addition, the subject is taking one of the different oral antidepressant treatment(s) with non-response (<math>\leq 25\%</math> improvement) that will be documented (on the MGH ATRQ) for at least the previous 2 weeks (ie, this oral antidepressant treatment must have been taken for at least 6 weeks at or above the minimum therapeutic dose with a lack of clinically meaningful improvement).</b> This antidepressant treatment, as well as any other ongoing medications being taken for depression (including adjunctive/augmentation therapies), will continue <del>unchanged, at the same dosage,</del> from the start of Week 1 through the end of Week 4 of the screening/prospective observational phase to confirm non-response prospectively. <b>Dose adjustment is permitted per clinical judgment, but the oral antidepressant treatment is to remain at or above the minimum therapeutic dose (per the MGH-ATRQ) through the end of Week 4.</b></p>
Synopsis, Subject Population; 3.1.1; Study Phases; 3.2.1. Study Population; 9.1.2. Screening/Prospective Observational Phase	Criteria for the minimum number of oral antidepressant treatments in the current episode of depression with non-response at the start of the screening/prospective observational phase was revised from $\geq 2$ to $\geq 1$ .
Synopsis, Overview of Study Design; Synopsis, Subject Population; 3.1. Overview of Study Design; 3.2.1. Study Population; 3.2.2. Study Phases; 6.2.1. Screening/Prospective Observational Phase; 9.1.2. Screening/Prospective Observational Phase	Criteria for non-response at the end of the screening/prospective observational phase was revised as follows (bold text added; strikethrough text deleted):  <p>Non-response at the end of the screening/prospective observational phase is defined as <math>\leq 25\%</math> improvement in the MADRS total score <b>for 2 consecutive visits from Week 1 to Week 4</b> and a MADRS total score of <math>\geq 28</math> <del>for 2 consecutive visits on Week 2 and Week 4.</del></p>
16.1. Study-specific Design Considerations	Text was revised as follows (bold text added; strikethrough text deleted):  <p>For eligibility, subjects must have <b>had non-response to at least 1 prior antidepressant treatment and TRD and be currently taking non-responders to their current an</b> antidepressant treatment <del>with non-response being observed with</del> <b>at the start of the screening/prospective observational phase that will be continued as</b> prospective treatment in the screening/prospective observational phase. Only subjects with non-response to their current antidepressant treatment after 4 weeks of prospectively observed treatment (for a total duration of antidepressant treatment of at least <del>4</del> <b>6</b> weeks by the end of the screening/prospective observational phase), will be eligible to proceed to the double-blind induction phase, <del>when</del> <b>re</b> all subjects will receive a new oral antidepressant in addition to intranasal esketamine or placebo.</p>

Applicable Section(s)	Description of Change(s)
<b>Rationale:</b>	Inclusion criterion no. 11.1 was revised to specify the same requirements for contraception for female partners of male subjects as specified for female subjects.
4.1.1. Direct-entry Subjects	<p>The text of inclusion criterion no. 11.1 has been changed as follows (bold text added; strikethrough text deleted):</p> <p>During the study (ie, from Day 1 of the double-blind induction phase, prior to randomization) and for a minimum of 1 spermatogenesis cycle (defined as approximately 90 days) after receiving the last dose of intranasal study medication, <del>in addition to the user independent highly effective method of contraception,</del> a man <b>who is sexually active with a woman of childbearing potential</b></p> <ul style="list-style-type: none"> <li>- <b>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).</b> <del>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).</del></li> <li>- <del>who is sexually active with a woman who is pregnant</del> must use a <b>condom if his partner is pregnant.</b></li> <li>- must agree not to donate sperm.</li> </ul> <p><del>12. Alternatively female partners of childbearing potential may be practicing a highly effective method of birth control, eg, established use of oral, injected, or implanted hormonal methods of contraception; placement of an intrauterine device (IUD) or intrauterine system (IUS); or male partner sterilization. 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.</del></p>
<b>Rationale:</b>	Exclusion criterion no. 11.1 was revised to delete the exclusion for first degree atrioventricular (AV) block, as the analyses of PR intervals from subjects in Phase 1 and Phase 2 esketamine studies showed no impact of esketamine on PR interval.
4.2.1. Direct-entry Subjects	<p>Exclusion criterion no. 11.1 revised as follows (bold text added; strikethrough text deleted):</p> <p>Subject has clinically significant ECG abnormalities at the start of the screening/prospective observational phase or on Day 1 of the open-label induction phase prior to randomization, defined as:</p> <ul style="list-style-type: none"> <li>- During screening, a QT interval corrected according to Fridericia's formula (QTcF): <math>\geq 450</math> msec; if the QTcF is prolonged on the initial ECG, the average QTcF of three ECG's, recorded 4 minutes apart, must not be <math>\geq 450</math> msec.</li> <li>- On Day 1 (predose), a QT interval corrected according to Fridericia's formula (QTcF): <math>\geq 450</math> 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 <math>\geq 450</math> msec.</li> <li>- Evidence of 2<sup>nd</sup> and 3<sup>rd</sup> degree AV block, <del>or 1st degree AV block with PR interval <math>&gt; 200</math> msec (may repeat ECG once, and use average of both readings, if the initial PR interval is <math>&lt; 240</math> msec),</del> complete left bundle branch block (LBBB), or complete right bundle branch block (RBBB).</li> <li>- Features of new ischemia.</li> </ul> <p>Arrhythmia (except premature atrial contractions [PACs] and premature ventricular contractions [PVCs]).</p>



Applicable Section(s)	Description of Change(s)
<b>Rationale:</b>	Exclusion criterion no. 14.1 was revised to allow prescription use of psychostimulants with dosing restrictions on intranasal treatment session days to allow subjects to safely use at other permitted times during study participation.
4.2.1. Direct-entry Subjects	<p>Text in exclusion criterion no. 14.1 revised as follows (bold text added; strikethrough text deleted):</p> <p>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/prospective observational phase or Day 1 of the double-blind induction phase prior to randomization.</p> <ul style="list-style-type: none"> <li>- <b>Subjects who have a positive test result at screening due to prescribed psychostimulants (eg, amphetamine, methylphenidate, etc.) taken for an indication other than MDD are permitted to continue to take this medication during the study in accordance with Attachment 1.</b></li> <li>- <del>Otherwise, Subjects</del> <b>subjects</b> who have a positive test result at screening due to prescribed/over-the-counter opiates, <del>or</del> barbiturates, <del>or</del> <del>amphetamines</del> may be permitted to continue in the screening/prospective observational phase if the medication is discontinued at least 1 week or 5 half-lives, whichever is longer, before Day 1 of the double-blind induction phase (prior to randomization) in accordance with Attachment 1 restrictions. The result of the Day 1 (prior to randomization) test for drugs of abuse must be negative for the subject to be randomized. <ul style="list-style-type: none"> <li>o Retesting is not permitted for positive test result(s), except for reasons stated above.</li> </ul> </li> </ul>
<b>Rationale:</b>	Clarifications made regarding the usage of antidepressant treatments for indications other than depression during the screening/prospective observational phase, and the use of corticosteroids, psychostimulants, and ADHD medications.
8. Prestudy and Concomitant Therapy	<p>The following text was added:</p> <p>Any medication that is listed on the MGH-ATRQ and is being taken at the start of the screening/prospective observational phase for an indication other than depression (eg, insomnia) should be continued during the screening/prospective observational phase but must be discontinued before the start of the double-blind induction phase.</p>
Attachment 1	<p>For antidepressants, changed 3<sup>rd</sup> bullet to read “Even if used <b>for indications other than MDD (eg, trazodone primarily for sleep), <del>trazodone</del> the use of any medication listed on the ATRQ</b> is not permitted during the treatment 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, allowed continuous use (previously prohibited); added that 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.</p> <p>For ADHD medications, allowed continuous use (previously prohibited); added that these 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.</p>

Applicable Section(s)	Description of Change(s)
	<p><b>Rationale:</b> 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.</p>
4.1.1. Direct-entry Subjects	<p>The bullets in inclusion criterion no. 7 were revised as follows (bold text added; strikethrough text deleted):</p> <ul style="list-style-type: none"> <li>- Subjects with a pre-existing history of thyroid disease/disorder who are treated with thyroid hormones must be on a stable dosage for 3 months prior to the start of the screening/prospective observational phase <del>and must have thyroid-stimulating hormone (TSH) within normal range in the screening/prospective observational phase.</del></li> <li>- For any subject (regardless of thyroid history), if the <b>thyroid-stimulating hormone (TSH)</b> value is out of range, a free thyroxine (FT4) will be conducted. <del>If the FT4 is normal, the subject can be enrolled.</del> If the FT4 value is <b>abnormal and considered to be clinically significant (after discussion with the medical monitor) out of range</b>, the subject is not eligible.</li> </ul>
	<p><b>Rationale:</b> Based on feedback from the sites to allow subjects to proceed to the end of the optimization phase unless not clinically appropriate, the criterion specifying withdrawal of subjects with MADRS total score <math>\geq 22</math> for 2 consecutive assessments during the optimization phase has been removed.</p>
Synopsis, Dosage and Administration; 6.1.2.3. Intranasal Treatment Session Frequency (All Subjects); 9.1.4. Optimization Phase; 10.2. Withdrawal From the Study	<p>The following withdrawal criterion for the optimization phase and any text referring to this criterion have been deleted:</p> <p>Any subject who has a MADRS total score <math>\geq 22</math> for 2 consecutive assessments separated by 5 to 15 days will be discontinued from the optimization phase.</p>
	<p><b>Rationale:</b> Definition of stable response during the optimization phase adjusted to be less rigid as this subgroup is an exploratory patient population in the maintenance phase. The duration of the response has been changed from the last 4 weeks of the optimization phase to the last 2 weeks of optimization.</p>
Synopsis, Overview of Study Design; 3.1.2. Definitions of Terms	<p>Stable response redefined as <math>\geq 50\%</math> reduction in the MADRS total score from baseline in each of the last 2 weeks of the optimization phase, with at least 1 MADRS total score of <math>&gt;12</math> in these 2 weeks.</p>
	<p><b>Rationale:</b> Provide clarification regarding missed MADRS assessments. With the revision of the definition of stable response, stable responders are no longer required not to have missed the MADRS in all of the last 4 weeks of optimization.</p>
Synopsis, Dosage and Administration; 6.1.2.3. Intranasal Treatment Session Frequency (All Subjects) 9.1.4. Optimization Phase	<p>The following text regarding missed MADRS assessments was deleted:</p> <p>A subject that misses a MADRS assessment during the last 4 weeks of this phase (Week 13 to Week 16) is not eligible to participate in the maintenance phase because eligibility criteria for stable remission or stable response cannot be confirmed. These subjects will be permitted to complete the optimization phase, if desired.</p> <p>The following bullet was deleted from the list of criteria for why a subject would not be eligible to proceed into the maintenance phase:</p> <p>Misses a MADRS assessment in Weeks 13 to 16</p>

Applicable Section(s)	Description of Change(s)
10.2. Withdrawal From the Study	Text regarding missed MADRS assessments was revised as follows (strikethrough text deleted):  Missed MADRS assessments: Subject misses $\geq 3$ assessments in the first 8 weeks (Weeks 5 to 12) <del>or misses a MADRS assessment in Weeks 13 to 16.</del>
11.2. Sample Size Determination	Text was revised as follows (bold text added; strikethrough text deleted):  The actual number of subjects randomized ( <b>which includes</b> both those in stable remission <b>and</b> those with stable response <del>[but who are not in stable remission]) will depend on the time it takes to obtain the necessary number of relapses.</del>
<b>Rationale:</b> Provide clarification regarding when follow-up visits will be performed.	
Synopsis, Overview of Study Design; Time and Events Schedule, Follow-up Phase; 3.1.1. Study Phases; 9.1.7. Follow-up Phase	Specified that follow-up visits will be performed at 1 and 2 weeks after the last clinic visit (instead of after the last dose of intranasal study drug).
<b>Rationale:</b> Provide clarification regarding when the PWC-20 assessment will be administered.	
9.4. Safety Evaluations	Text was revised as follows (bold text added; strikethrough text deleted):  For those subjects who proceed to the optimization and maintenance phases, the PWC-20 is conducted <del>on the last day of intranasal dosing</del> <b>at the End of Study Visit. If subjects withdraw early from the study during any phase, the PWC-20 will be conducted at the Early Withdrawal Visit.</b>
<b>Rationale:</b> Provide clarification in the footnotes regarding antidepressant treatment in the screening/prospective observational phase and guidance on repetition of the MADRS assessment.	
Time and Events Schedule, Screening and Induction Phase	Text was revised as follows (bold text added; strikethrough text deleted):  Footnote “a” revised to state: Subjects who do not require a taper and are thus eligible to immediately proceed to the open-label induction phase <del>can</del> <b>will have Visit 1.3 and Visit 2.1 occurring on the same day or within 1 week of each other (if not occurring the same day, the antidepressant treatment regimen should be continued and discontinued prior to Visit 2.1).</b>  Deleted “only” from footnote “k”.  Footnote “q” revised to state: The MADRS should be administered no more than 2 days prior to the subject’s <del>scheduled</del> <b>targeted (not actual) clinic visit date (except Visit 2.9, which is within 1 day prior)</b> . If performed on the day of the scheduled clinic visit for an intranasal treatment session, the MADRS must be performed prior to the intranasal treatment session.
<b>Rationale:</b> Revise the visit window for Day 28 of the open-label induction phase to allow more flexibility for conducting the visit.	
Time and Events Schedule, Open-label Induction Phase	For Visit 2.9 during the induction phase, the visit window was revised to $\pm 1$ day (rather than -1 day).

Applicable Section(s)	Description of Change(s)
<b>Rationale:</b> To obtain AE and concomitant therapy data in between clinic visits.	
Time and Events Schedule, Follow-up Phase	The following statement was added as footnote “P” to the remote assessment during the follow-up phase:  At the “Remote Assessment ” visit, site staff will contact the subject by telephone to obtain information regarding adverse events and concomitant therapies
<b>Rationale:</b> To add drug accountability for the intranasal study medication to the list of procedures during the Optimization Phase.	
Time and Events Schedule, Optimization Phase	Added a row in the Time and Events Schedule (under the subheading Study Drug) showing drug accountability for the intranasal study medication.  Added a footnote “r” stating: Drug accountability for intranasal study medication should be performed weekly during Weeks 5 through 8 (inclusive) and then weekly or every other week from Weeks 9 through 15 (inclusive).
<b>Rationale:</b> Add information about 54135419TRD3008, an open-label safety extension study, that may be available for eligible subjects participating in ESKETINTRD3003.	
Synopsis, Overview of Study Design; 3.1.1. Study Phases; 9.1.7. Follow-up Phase	The following text was added:  An open-label safety extension study, 54135419TRD3008, may be available (pending country and site approval) for eligible subjects participating in the ESKETINTRD3003 study. Please refer to the 54135419TRD3008 protocol for full details when available.
<b>Rationale:</b> Removal of requirement to report arterial oxygen saturation <93% and any treatment-emergent change in the nasal examination as adverse events because adverse event reporting in these instances should be at the discretion of the PI.	
9.4. Safety Evaluations	Text was revised as follows (bold text added; strikethrough text deleted):  Any arterial oxygen saturation (SpO <sub>2</sub> ) <93% <del>should be and lasting for more than 2 minutes, and</del> confirmed by an additional measurement on another part of the body, <del>will be reported as an adverse event.</del>  The following statement was deleted from the description of nasal examinations: Any treatment-emergent change or worsening from the baseline examination will be recorded as an adverse event.
<b>Rationale:</b> The maximum sertraline dose was changed from 150 mg/day to 200 mg/day as the maximum dose allowed by product labelling is 200 mg/day.	
1.2.1.2. Sertraline; Attachment 3	Maximum dose of sertraline changed from 150 mg/day to 200 mg/day. Titration schedule adjusted accordingly.
<b>Rationale:</b> Revise text regarding uptitration of duloxetine dose, which referred to an incorrect phase of the study.	
1.2.2.1. Duloxetine	Text revised to state that certain subjects may be started on a 30 mg dose of duloxetine and up-titrated to the therapeutic range of 60 mg by the start of Week 2 of the open-label induction phase (not the screening/prospective observational phase).
<b>Rationale:</b> Removal of LSD and MDMA from urine drug screen results that will lead to discontinuation as LSD is not measured in the current urine drug screen and prescribed psychostimulants are now permitted.	
4.3. Prohibitions and Restrictions	Lysergic acid diethylamide (LSD) and MDMA were deleted from the list of drugs that will lead to discontinuation if detected in the urine drug screen during the study.

Applicable Section(s)	Description of Change(s)
<b>Rationale:</b> Clarification of procedure to follow if subjects wish to withdraw from the study.	
10.2 Withdrawal from the Study	Under “Withdrawal of Consent”, the following text was revised to state (bold text added):  Subjects who wish to withdraw from the study should be asked if they are agreeable to <b>continue to an Early Withdrawal Visit (if withdrawing from the induction, optimization or maintenance phase) and the follow up phase, or to</b> be contacted to collect follow-up information.
<b>Rationale:</b> Added definition of treatment-resistant depression (TRD) to the synopsis.	
Synopsis, Subject Population	The following definition of TRD from Section 3.2.1 was added to the synopsis under Subject Population:  Treatment-resistant depression is defined as a lack of clinically meaningful improvement after treatment with at least 2 different antidepressant agents prescribed in adequate doses for adequate duration.
<b>Rationale:</b> 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. All Adverse Events	Text revised as follows (bold text added; strikethrough text deleted):  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), <b>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)</b> . Serious adverse events, including those spontaneously reported to the investigator, <del>within 30 days after the last dose of study drug,</del> 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.
<b>Rationale:</b> Minor changes were made throughout the protocol for compliance with updated protocol template text.	
Cover page	Updated Sponsor Statement to remove Janssen Infectious Diseases BVBA.
4.1.1. Direct-entry Subjects	The following text was added to inclusion criterion no. 9.1:  Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.
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 60.
Attachment 3	Added the following text for footnote “a” as this was inadvertently omitted from the table in Amendment 1:  Subjects should be initiated with 60 mg/day. Subjects that have in the past shown increased sensitivity towards serotonin reuptake inhibitors (SSRI) /norepinephrine reuptake inhibitors (SNRI) can, at the discretion of the treating physician, be started on a 30 mg dose and up-titrated into the therapeutic range of 60 mg by the start of Week 2
Investigator Agreement Page	Removed the “LAST PAGE” designation.

**Amendment 2** (13 January 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:** This amendment updates and clarifies the protocol based on ongoing feedback received during study initiation activities.

Applicable Section(s)	Description of Change(s)
<b>Rationale:</b> Clarification was needed that criteria are the same for transferred-entry subjects as for direct-entry subjects at the beginning of the optimization phase.	
4.1.2. Inclusion Criteria, Transferred-entry Subjects;	The new Inclusion Criterion 15 and Exclusion Criterion 32 were added to clarify that transferred-entry subjects must meet the same criteria at the point of entry to this study as the direct-entry subjects at the same time point (ie, beginning of optimization phase).
4.1.3. Inclusion Criteria, Direct-entry Subjects and Transferred-entry Subjects;	
4.2.2. Exclusion Criteria, Transferred-entry Subjects	
<b>Rationale:</b> The effect of impaired renal clearance on the pharmacokinetic profile of intranasal esketamine is not fully known, and subjects with renal impairment may be more vulnerable to blood pressure increases; therefore, as an added safety precaution, subjects with severe renal impairment will be excluded from the study.	
4.2.1. Exclusion Criteria, Direct-entry Subjects;	The new Exclusion Criterion 31 was added, to exclude subjects with severe renal impairment (creatinine clearance <30 mL/min).
4.2.2. Exclusion Criteria, Transferred-entry Subjects	
9.4. Safety Evaluations	Calculation of creatinine clearance was added.
<b>Rationale:</b> Eligibility criteria and definitions related to previous oral antidepressants (and nonresponse to them) needed to be expanded and clarified.	
Synopsis, Overview of Study Design, Subject Population, Dosage and Administration;	<ul style="list-style-type: none"> <li>• Definitions for nonresponse in the screening/prospective observational phase were clarified, as follows: <ul style="list-style-type: none"> <li>– For nonresponse at the beginning of the phase (for eligibility to enter into the study), Inclusion Criterion 3 and corresponding text (where relevant) now define nonresponse as <math>\leq 25\%</math> improvement per Massachusetts General Hospital - Antidepressant Treatment Response Questionnaire (MGH-ATRQ), which specifies at least 6 weeks of treatment at a minimum therapeutic dose.</li> <li>– For nonresponse at the end of the phase (for eligibility to continue into the optimization phase), the definition is no longer blinded to investigators and is now stated as <math>\leq 25\%</math> improvement in the Montgomery-Asberg Depression Rating Scale (MADRS) total score for 2 consecutive visits and a MADRS total score of <math>\geq 28</math> for 2 consecutive visits.</li> </ul> </li> <li>• For the <math>\geq 2</math> but <math>\leq 5</math> oral antidepressant treatments relevant to Inclusion Criterion 3 and associated descriptions, text was added to specify that the upper limit of <math>\leq 5</math> antidepressants was only applicable to the past 2 years of a current episode of depression in cases where the current episode is <math>&gt; 2</math> years.</li> </ul>
3.2.1. Study Population;	
4.1.1. Inclusion Criteria, Direct-entry Subjects;	
6.2.1. Screening/ Prospective Observational Phase (Direct-entry Subjects Only);	
9.1.2. Screening/ Prospective Observational Phase	

Applicable Section(s)	Description of Change(s)
4.1.1. Inclusion Criteria, Direct-entry Subjects; 9.1.1. Overview	<ul style="list-style-type: none"> <li>For the documentation to confirm nonresponse for Inclusion Criterion 3 and associated descriptions, acceptable sources were updated to add a letter from the subject's treating physician, etc.</li> <li>In Inclusion Criterion 3 and associated descriptions, clarification was added about the requirement for a subject to be taking one of the aforementioned oral antidepressant treatment(s) with nonresponse that is documented on the MGH-ATRQ (ie, this oral antidepressant treatment must have been taken for at least 6 weeks at the minimal therapeutic dose with a lack of clinically meaningful improvement) at the start of the screening/prospective observational phase.</li> </ul> <p>Inclusion Criterion 3 and related assessments were modified as follows:</p> <ul style="list-style-type: none"> <li>Eligibility was modified for tricyclic antidepressant dose ingested versus therapeutic blood level attained (ie, if a subject is taking a specific tricyclic antidepressant at a dose below the MGH-ATRQ minimum therapeutic dose, then a blood level that is within the therapeutic [antidepressant] range is acceptable to establish the adequacy of the antidepressant treatment).</li> <li>The table describing the volume of blood to be collected from each subject was updated to reflect this change.</li> </ul>
<b>Rationale:</b> The scope of the Site Independent Qualification Assessment needed clarification.	
Synopsis, Subject Population; 3.2.1. Study Population; 4.1.1. Inclusion Criteria, Direct-entry Subjects; 9.1.2. Screening/Prospective Observational Phase; 9.6. Other Evaluations	Inclusion Criterion 5 and other associated text about the Site Independent Qualification Assessment were edited to specify that this assessment confirms not only the subject's current major depressive episode and antidepressant treatment response in the current depressive episode, but also the severity of depression (required at Week 1 to be MADRS total score $\geq 28$ ).
<b>Rationale:</b> Assessments and eligibility relevant to thyroid health needed to be expanded and clarified.	
4.1.1. Inclusion Criteria, Direct-entry Subjects	In Inclusion Criterion 7, new parameters were added for all subjects (regardless of thyroid history). If the thyroid-stimulating hormone (TSH) value is outside the normal reference range, then the free thyroxine (FT4) level will be assessed. If the FT4 level is normal, then the subject can be enrolled. If the FT4 level is outside the normal reference range, then the subject is not eligible.
9.1.1. Overview; 9.4. Safety Assessments	The analysis of FT4 was added for cases where the TSH is outside of the normal reference range.
Attachment 1	Comments about thyroid hormone supplements were deleted, to harmonize this attachment with the associated Inclusion Criterion 7.
<b>Rationale:</b> Eligibility parameters and assessments related to childbearing potential and contraception needed to be clarified and strengthened. Many of these issues were related to changes in the sponsor's protocol template (ie, some of these issues may be generally applicable to all similar studies and may not be specific to this study).	
4.1.1. Inclusion Criteria, Direct-entry Subjects	Inclusion Criterion 9 was strengthened in its definitions of women who are not of childbearing potential and in its requirements for highly effective methods of contraception.

Applicable Section(s)	Description of Change(s)
4.1.1. Inclusion Criteria, Direct-entry Subjects; 9.1.1. Overview	Inclusion Criterion 10 was edited to state that the serum test for $\beta$ -human chorionic gonadotropin ( $\beta$ -hCG) must be highly sensitive, and to clarify the serum versus urine tests. The table that describes the volume of blood to be collected from each subject now specifies the highly sensitive nature of the $\beta$ -hCG test.
4.1.1. Inclusion Criteria, Direct-entry Subjects	Inclusion Criterion 11 was strengthened in its requirements for men whose sperm could have come in contact with a woman via sexual activity or donation; requirements are specified both for male study subjects and for their female partners.
Time and Events Schedules (All Phases); 9.6. Other Evaluations	Footnotes and text were added to clarify menstrual cycle tracking (the start date of the last menstrual period prior to the study visit). This tracking is captured as part of Module I of the Massachusetts General Hospital - Female Reproductive Lifecycle and Hormones Questionnaire (MGH-FRLHQ) at Week 1 of the screening/prospective observational phase, and then is tracked separately thereafter only for women with a menstrual cycle. The redundant tracking was removed at Week 1 in the Time and Events Schedule of the screening/prospective observational phase, leaving only the MGH-FRLHQ at that first time point.
<b>Rationale:</b> The description of the studies that could precede this study needed to be corrected.	
4.1.2. Inclusion Criteria, Transferred-entry Subjects	In Inclusion Criterion 12, the induction phase of the ESKETINTRD3001 and ESKETINTRD3002 studies was revised from the incorrect open-label description to the correct double-blind description.
<b>Rationale:</b> Eligibility criteria and definitions related to previous procedural interventions for depression needed to be expanded and clarified.	
Synopsis, Subject Population; 4.2.1. Exclusion Criteria, Direct-entry Subjects	In the exclusion criteria about antidepressant procedures and the related synopsis section, <ul style="list-style-type: none"> <li>Exclusion Criterion 1 was modified so it is clearer that nonresponse to electroconvulsive therapy (ECT) may be either unilateral or bilateral ECT.</li> <li>Exclusion Criterion 2 was modified to emphasize the stimulation of the vagal nerve rather than the method of stimulation; ie, the mention of the implant was deleted.</li> </ul>
<b>Rationale:</b> The exclusionary features associated with (comorbid to) major depressive disorder (MDD) needed to be clarified and expanded.	
Synopsis, Subject Population; 4.2.1. Exclusion Criteria, Direct-entry Subjects	In Exclusion Criterion 3 and in the corresponding synopsis text. <ul style="list-style-type: none"> <li>Obsessive-compulsive disorder was clarified as being exclusionary only when current, not when prior.</li> <li>The diagnostic codes for the exclusion related to intellectual disability were broadened from the previous 319 only to also include 317, 318.0, 318.1, 318.2, 315.8, or 319.</li> <li>Autism spectrum disorder was added as exclusionary.</li> <li>The terminology of "MDD with psychosis" was harmonized with terminology that already appeared elsewhere in the protocol, to read "MDD with psychotic features."</li> </ul>



Applicable Section(s)	Description of Change(s)
<b>Rationale:</b> The exclusions and prohibitions related to cardiovascular health and medications needed clarification and modification.	
4.2.1. Exclusion Criteria, Direct-entry Subjects	<ul style="list-style-type: none"> <li>Exclusion Criterion 8 was modified to allow entry of patients who had revascularization procedures performed &gt;12 months prior to screening and are now clinically stable and symptom-free in the investigator's clinical judgment.</li> <li>In Exclusion Criterion 9, the term "antihypertensive medication regimen" was changed to "antihypertensive medication(s)."</li> <li>In Exclusion Criterion 11, <ul style="list-style-type: none"> <li>For QT interval corrected (QTc) according to Fridericia's formula (QTcF), text was clarified that the exclusionary abnormal result of <math>\geq 450</math> msec during screening or on Day 1 should be based on a repeated demonstration (ie, average of 3 electrocardiograms [ECGs] with QTcF of <math>\geq 450</math> msec, recorded 4 minutes apart).</li> <li>For left or right bundle branch blocks, text was clarified that only "complete" block was exclusionary.</li> <li>For exclusionary first-degree atrioventricular block with PR interval &gt;200 msec, text was modified to state that retesting was permitted if the initial PR interval was &lt;240 msec, and that the average of both readings should then be used.</li> </ul> </li> <li>In Exclusion Criterion 12, the use of concomitant medications that prolong the QT/QTc interval was deleted (no longer excluding such subjects from study enrollment).</li> </ul>
<b>Rationale:</b> Flexibility was needed for retesting of potentially transient abnormal alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values, in case of collection/laboratory errors or other transient factors.	
4.2.1. Exclusion Criteria, Direct-entry Subjects	Exclusion Criterion 13 was modified to allow one repeat of a screening test for abnormal ALT and AST during the screening period, per investigator discretion and provided there is an alternative explanation for the out of range value.
<b>Rationale:</b> Testing time points versus exclusion for cannabinoids needed clarification and harmonization.	
4.2.1. Exclusion Criteria, Direct-entry Subjects; 9.4. Safety Evaluations	Exclusion Criterion 14 and related text were modified to clarify that testing for cannabinoids is to be conducted both during screening and at predose on Day 1; however, a positive result is not exclusionary during screening (as long as the subject does not meet the criteria for substance use disorder) but is exclusionary at predose on Day 1.
<b>Rationale:</b> Exclusions related to diabetes needed clarification.	
4.2.1. Exclusion Criteria, Direct-entry Subjects	In Exclusion Criterion 15, the redundant term "secondary diabetes" was removed, since the criterion had already stated that any uncontrolled diabetes mellitus was exclusionary.
<b>Rationale:</b> Exclusions due to anatomical or medical conditions that could impede delivery or absorption of intranasal study drug needed modification.	
4.2.1. Exclusion Criteria, Direct-entry Subjects	In Exclusion Criterion 17, text was added to clarify that the exclusion would be determined by the investigator's clinical judgment based on assessment. Examples of such conditions (eg, significant structural or functional abnormalities of the nose) were deleted. The now-redundant Exclusion Criterion 18, which had described exclusionary conditions related to nasal septa, was similarly deleted.
<b>Rationale:</b> Eligibility related to sleep apnea needed to be clarified.	
4.2.1. Exclusion Criteria, Direct-entry Subjects	In Exclusion Criterion 23, the parameter for effective treatment was clarified as reaching the previously stated apnea-hypopnea index (AHI) threshold of <30 (events per hour of sleep).

Applicable Section(s)	Description of Change(s)
<b>Rationale:</b> Exclusions relevant to current or previous participation in other studies needed clarification.	
4.2.1. Exclusion Criteria, Direct-entry Subjects	In Exclusion Criterion 24, text was clarified that previous participation in 2 or more studies of MDD must involve different investigational medications to be exclusionary, and that current enrollment in an investigational study must be interventional to be exclusionary.
<b>Rationale:</b> Details about limitations on prior and concomitant therapies and interacting substances needed modifications and clarifications.	
4.3. Prohibitions and Restrictions	Lysergic acid diethylamide (LSD) was added to the list of positive urine drug screen results that would lead to discontinuation during any treatment phase (open-label induction, optimization, or maintenance phases).
4.3. Prohibitions and Restrictions	The restriction was removed about ingesting grapefruit juice, Seville oranges, or quinine for 24 hours before an intranasal dose of study medication.
4.3. Prohibitions and Restrictions; 8. Prestudy and Concomitant Therapy	<ul style="list-style-type: none"> <li>• <u>Cognitive behavioral therapy (CBT)</u>: Where the protocol previously had stated that subjects receiving CBT must have had it stable in terms of frequency for the last 6 months, this parameter was made less stringent, to now read that CBT must have been ongoing for the last 3 months. The protocol now clarifies that new CBT is prohibited.</li> <li>• <u>Non-CBT psychotherapy</u>: Where the protocol previously had stated that subjects receiving psychotherapy must have had it stable in terms of frequency for the last 6 months, this parameter was made less stringent, removing the time restriction and stating that subjects receiving psychotherapy can continue receiving psychotherapy, and that new non-CBT psychotherapy is allowed during the study.</li> <li>• <u>For any kind of therapy</u>: The protocol now clarifies that any change in existing therapy or any new therapy must be documented on the concomitant therapies form.</li> </ul>
6.2.1. Screening/ Prospective Observational Phase (Direct-entry Subjects Only); 4.3. Prohibitions and Restrictions; 8. Prestudy and Concomitant Therapy	<p>Restrictions on the use of benzodiazepines and non-benzodiazepine sleeping medications were clarified, to state the following:</p> <ul style="list-style-type: none"> <li>• 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/prospective observational phase can continue these medications.</li> <li>• No dose increases beyond the equivalent of 6 mg/day of lorazepam or new benzodiazepine medications are permitted during the induction phase, with the exception of the use of permitted benzodiazepine rescue medication.</li> <li>• 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.</li> </ul>
8. Prestudy and Concomitant Therapy	A previously included phrase was revised for clarity, to state that if a subject routinely takes his or her oral antihypertensive medication(s) in the morning, then the usual morning dose(s) should be taken prior to intranasal dosing.
8. Prestudy and Concomitant Therapy	A sentence was added to clarify that even 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 at the start of the screening/prospective observational phase.

Applicable Section(s)	Description of Change(s)
Attachment 1	<ul style="list-style-type: none"> <li>• Additional examples were provided for existing classes of medications.</li> <li>• Prohibitions were deleted for cytochrome P450 subtype 3A4 (CYP3A4) inhibitors.</li> <li>• Prohibitions were added for pseudoephedrine-containing products in the 12 hours prior to an intranasal treatment session, for nonstimulant attention-deficit/hyperactivity disorder medications, and for non-vitamin K antagonist oral anticoagulation agents.</li> <li>• Prohibitions were clarified. In the section about antidepressants, clarification was added that trazodone is not permitted during study phases that include intranasal treatment, even if used primarily for sleep. In the section about benzodiazepines and nonbenzodiazepine sleeping medication, the allowable dosage was clarified (equal to or less than the equivalent of 6 mg/day lorazepam) and comments were consolidated.</li> <li>• Comments about thyroid hormone supplements were deleted, to harmonize this attachment with the associated inclusion criterion, as described above.</li> </ul>
<p><b>Rationale:</b> Clarification was needed about how a subject's medications for depression must be maintained unchanged and then fully discontinued at the end of the screening/prospective observational phase for subjects eligible to enter the open-label induction phase.</p>	
Synopsis, Overview of Study Design and Dosage and Administration; 3.1.1. Study Phases; 3.2.2. Study Phases; 6.2.1. Screening/ Prospective Observational Phase (Direct-entry Subjects Only); 9.1.2. Screening/ Prospective Observational Phase	Text was added and harmonized to clarify that all medication(s) being used for depression, including adjunctive/augmentation therapies and any other prohibited psychotropic medications, will be discontinued at the end of the screening/prospective observational phase for subjects eligible to enter the open-label induction phase.
Attachment 1	The following details were added: If a medication is part of the antidepressant treatment regimen being taken at the time of signing the informed consent form (ie, start of screening/prospective observational phase), then it must be continued unchanged until the end of Week 4 of the screening/prospective observational phase; therefore, the prohibition terms are not applicable to those medications during that period. In such cases the investigator may choose to taper the relevant medication during the optional taper period of up to 3 weeks that may follow the screening/prospective observational phase, based on clinical judgment.
<p><b>Rationale:</b> The titration schedule with the oral antidepressant medication in the open-label induction phase needed to be clarified for all antidepressants and modified for duloxetine.</p>	
Synopsis, Dosage and Administration; 3.2.4.2. Oral Antidepressant; 6.2.2. Open-label Induction Phase (Direct-entry Subjects Only)	For the lower limit, the time point for the minimum therapeutic dose was specified as the end of the induction phase. For the upper limit, the text was clarified that doses are not to exceed the maximum dose defined in the titration schedule. Statements were added to clarify that use of the titration schedule in Attachment 3 is mandatory.

Applicable Section(s)	Description of Change(s)
1.2.2.1. Duloxetine; Attachment 3	For the duloxetine starting dose of 60 mg/day, this amendment adds flexibility for subjects who have in the past shown increased sensitivity towards selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs). Those subjects can, at the discretion of the treating physician, now be started on a 30-mg dose and then up-titrated into the therapeutic range of 60 mg by the start of Week 2 of the open-label induction phase.
<b>Rationale:</b> The oral antidepressant was not scheduled to be dispensed frequently enough to ensure continuous coverage. (One dispensation had been omitted in error.)	
Time and Events Schedule (Maintenance Phase)	In the row entitled "Dispensing oral antidepressant (open-label)," an X was added to the column at Week 16.
<b>Rationale:</b> Clarification was needed about the order of administering intranasal devices.	
6.1.2.3. [Optimization Phase], Intranasal Treatment Session Frequency (All Subjects) 6.1.3. Maintenance Phase	Footnotes were added to the tables that describe intranasal treatment sessions, clarifying that the intranasal devices for each intranasal treatment session should be administered in the medication kit order provided by the Interactive Web Response System (IWRS).
<b>Rationale:</b> The guidance for discontinuing any subjects who may develop ulcerative cystitis needed to be strengthened.	
3.2.6. Safety Evaluations	The previous text stating that "if cystitis is considered to be associated with esketamine, subjects will be discontinued" was strengthened to state that if a subject is determined to have a diagnosis of ulcerative cystitis, the subject must be discontinued.
9.4. Safety Evaluations	Under the subheading for Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS), a new criterion for discontinuation was added: if a subject is determined to have a diagnosis of ulcerative cystitis, then the subject must be discontinued from the study and followed up with appropriate medical care.
<b>Rationale:</b> A guidance for discontinuing subjects who may develop abnormal ECG readings needed to be added.	
9.4. Safety Evaluations; 10.2. Withdrawal From the Study	Text was added to specify that a subject must be discontinued at any time point after baseline (Day 1, predose), if either of the following criteria are met: <ul style="list-style-type: none"> <li>• QTcF change from baseline is <math>\geq 60</math> msec and QTcF <math>&gt; 480</math> msec, or</li> <li>• QTcF <math>&gt; 500</math> msec.</li> </ul>
<b>Rationale:</b> Clarification was needed regarding training requirements for site staff who will be present with the subject during the intranasal treatment session and the postdose observation period.	
Synopsis, Dosage and Administration; 6.1. Intranasal Study Drug	Previous text that stated a physician, nurse, or other appropriate member of the site staff with recent (ie, within 1 year) training for cardiopulmonary resuscitation now states a site staff member with training in cardiopulmonary resuscitation (eg, a basic life support course or equivalent course) that is up to date per local regulations.

Applicable Section(s)	Description of Change(s)
<b>Rationale:</b> The guidance for blood pressure monitoring on intranasal treatment session days needed to be more conservative, comprehensive, and clear.	
6.1. Intranasal Study Drug	<ul style="list-style-type: none"> <li>• <u>Regarding predose monitoring.</u> <ul style="list-style-type: none"> <li>- Values that should prompt retesting (for a single observation), or postponing the dose (for same-day values), or referral for consultation (if persistent to the next visit) were made more conservative. The systolic blood pressure (SBP) alert parameter was lowered from <math>\geq 160</math> to <math>&gt;140</math> mm Hg and the diastolic blood pressure (DBP) alert parameter was lowered from <math>\geq 100</math> to <math>&gt;90</math> mm Hg, making these parameters consistent with those already stated in Exclusion Criterion 9.</li> <li>- Text was added to clarify that the predose blood pressure requirements were also applicable to all intranasal treatment session days after Day 1.</li> <li>- The period of rest between retesting was changed from a 10-minute period to an open-ended period.</li> </ul> </li> <li>• <u>Regarding both predose and postdose monitoring.</u> "other specialist" was added as an option (along with cardiologist and primary care physician) to whom subjects should be referred if alert parameters were met.</li> <li>• <u>Regarding postdose monitoring.</u> <ul style="list-style-type: none"> <li>- For subjects with SBP <math>\geq 160</math> mm Hg and/or DBP <math>\geq 100</math> mm Hg at 1.5 hours postdose, the handling options for the 30-minute assessments thereafter were updated.</li> <li>- For subjects with SBP <math>\geq 180</math> mm Hg and/or DBP <math>\geq 110</math> mm Hg at 2 hours after dosing, a new parameter was added, stating that these subjects should be referred for immediate medical treatment.</li> <li>- For subjects with SBP <math>\geq 180</math> but <math>&lt;200</math> mm Hg and/or DBP <math>\geq 110</math> but <math>&lt;120</math> mm Hg, conditions for continuing with intranasal dosing (after referral for assessment) were changed from "given approval" to if recommended by the referring doctor and considered appropriate according to clinical judgment.</li> <li>- For subjects with SBP <math>\geq 200</math> mm Hg and/or DBP <math>\geq 120</math> mm Hg at any postdose time point, the handling was strengthened from should discontinue from further dosing to must discontinue from further dosing.</li> </ul> </li> </ul>
<b>Rationale:</b> Flexibility was needed for methods to measure blood pressure and pulse/heart rate.	
9.4. Safety Evaluations	The emphasis on the completely automated device was decreased and the allowance for manual techniques was made broader.
<b>Rationale:</b> Cognition testing needed clarification.	
Time and Events Schedule (Screening/Prospective Observational Phase); 9.4. Safety Evaluations	The table and text were clarified to state that a practice session will be conducted only for the computerized cognitive battery, while the Hopkins Verbal Learning Test - Revised (HVLTR) has no practice session.
9.4. Safety Evaluations	The description of the HVLTR was clarified and was revised to describe administration by a person rather than a computer.
<b>Rationale:</b> The University of Pennsylvania Smell Identification Test (UPSIT) and the Smell Threshold Test needed to be administered more frequently and more flexibly.	
Time and Events Schedule (All Phases); 9.4. Safety Evaluations	Footnotes and text were added to indicate that if a subject has significant nasal congestion on the day of a scheduled assessment of sense of smell, then the site should consider postponing the UPSIT, Smell Threshold Test, or both (as applicable) to the next scheduled clinic visit.

Applicable Section(s)	Description of Change(s)
Time and Events Schedule (Maintenance Phase)	An additional UPSIT assessment was added to Week 20 (Visit 4.5).
<b>Rationale:</b> Flexibility was needed for decongestants versus delay for a subject with congestion on an intranasal dosing day.	
6.1. Intranasal Study Drug	For subjects with nasal congestion on a dosing day, the text was changed from "it is recommended that the dosing day be delayed" to "an intranasal decongestant can be used to reduce congestion or the dosing day can be delayed." This section had already stated that if an intranasal decongestant is used to reduce congestion, it cannot be used within 1 hour prior to intranasal study drug dosing.
<b>Rationale:</b> Clarification was needed about repetition of safety assessments if a subject starts a scheduled clinic visit in which an intranasal treatment session is planned, but then a predose observation prompts the site staff to postpone the intranasal treatment session within the visit window.	
Time and Event Schedules (Open-label Induction Phase, Optimization Phase, Maintenance Phase); 9.4. Safety Evaluations	A paragraph and footnotes were added to describe which assessments must be repeated on the actual intranasal treatment session day after a postponement.
<b>Rationale:</b> The volume of blood to be collected needed to be updated.	
9.1.1. Overview; 16.1. Study-specific Design Considerations	After adding conditional assessments as already described above in this section (for FT4 and for tricyclic antidepressant level), and then reducing the volume of blood to be collected for biomarkers, the total volume of blood to be collected needed to be updated. It previously was stated as up to 210 or 231 mL, but now is stated as up to 189 mL.
<b>Rationale:</b> During the open-label induction phase, the Sheehan Disability Scale (SDS) was administered too infrequently to track the time course of improvement.	
Time and Events Schedule, Open-label Induction Phase	An additional SDS assessment was added to Study Day 15.
<b>Rationale:</b> The windows and methods for remote MADRS assessment needed modification and clarification.	
Time and Events Schedules (Screening/Prospective Observational Phase and Open-label Induction Phase)	The guidance about the window for remote MADRS monitoring was moved out of a table header row and into a footnote (associated with the MADRS row) providing similar guidance.
9.2.1.1. Primary Efficacy Evaluation: Montgomery-Asberg Depression Rating Scale (MADRS); References	Information was added to clarify that the independent remote raters will be using the Structured Interview Guide for the MADRS. A reference was added to describe this guide.

Applicable Section(s)	Description of Change(s)
<b>Rationale:</b> The definition of relapse updated to include completed suicide.	
Synopsis, Overview of Study Design; 3.1.2. Definitions of Terms	The definition was updated to state that relapse was hospitalization for worsening depression or any other clinically relevant event determined per clinical judgment to be suggestive of a relapse of depressive illness such as suicide attempt, completed suicide, or hospitalization for suicide prevention. If hospitalized for any of these events, the start date of hospitalization will be used for the date of relapse. Otherwise the date of the event will be used if the subject is not hospitalized.
<b>Rationale:</b> Some template-based text that can be applicable to all of the sponsor's studies needed to be made more specific to the latest details about this study.	
9.3. Medical Resource Utilization	The description of data to be collected was simplified and reduced.
12.3.2. Serious Adverse Events	In the list of hospitalizations that do not meet criteria for serious adverse events, hospitalizations for convenience "for the duration of the treatment period" were edited to read "at times during the treatment period."
15. Study-Specific Materials	The list of materials supplied to the investigator was updated to include the MGH-ATRQ guidance document.
17.4. Source Documentation	Text was deleted about parameters that would be recorded directly and considered to be source data.
<b>Rationale:</b> The protocol needed to be updated for better alignment with recent changes to one or more of the sponsor's general practices for all studies: an initiative to prevent missing data, the template for protocols, or other policies and procedures. (The underlying issues may be applicable to all of the sponsor's studies and are not necessarily specific to this study.)	
4. Subject Population	The previous statement about "should consult the appropriate sponsor representative" was strengthened to "must consult," and the qualifier "and resolve any issues" was added. A statement was added that waivers are not allowed.
10.2. Withdrawal From the Study	This section was updated to include methods to prevent loss to follow-up and withdrawal of consent, and for documentation and notification of withdrawn consent.
10.3. Withdrawal From the Use of Samples in Future Research; 16.2.5. Long-term Retention of Samples for Additional Future Research	The section that was previously a subheading ("Withdrawal From the Use of Samples for Future Research") under Section 10.2 was promoted to its own section. A cross-reference to this section from elsewhere in the protocol (ie, from Section 16.2.5) was updated.
12.3.1. All Adverse Events	This section was updated to describe how the sponsor will report suspected unexpected serious adverse reactions (SUSARs).
14.5. Drug Accountability	The "drug return form" was replaced with the "investigational product destruction form."
16.2.2. Independent Ethics Committee or Institutional Review Board	For the statement about annual review and reapproval of this study, the qualifier "where required" was added.
17.4. Source Documentation	The information was reorganized and expanded to include review of methods for source data collection with the investigator.

Applicable Section(s)	Description of Change(s)
17.5. Case Report Form Completion	Roles and options were updated for handling corrections to an electronic case report form (eCRF) after the initial entry into the eCRF, and other clarifications were made.
<b>Rationale:</b> Minor errors were noted and clarifications were needed.	
Time and Events Schedules (Screening/Prospective Observational Phase and Open-label Induction Phase)	For ECGs, the footnote was revised from expressing a range of visits ("Visits 2.3 to 2.8," which could have been incorrectly interpreted as intending every visit within that range) to instead match the specific visits already marked in the table: "Visits 2.3, 2.5, and 2.8."
Time and Events Schedule (Screening/Prospective Observational Phase)	A footnote was added to Visit 2.1 C-SSRS (Since Last Visit) assessment, to indicate that it is only performed for subjects who do not have Visit 1.3 and 2.1 occur on the same day.
Time and Events Schedules (Maintenance Phase)	In the header and associated footnote, "From Week 21" was changed to "From Week 20."
1.1.1. Summary of Nonclinical Findings	Regarding the studies in dogs, one of the duplicative but inconsistent sections was modified. Both sections now state that the results are about ECGs, where previously one section indicated that the results were about EEGs (electroencephalograms).
2.1. Objectives	Medical resource utilization had previously been stated as an exploratory objective in the protocol synopsis but a secondary objective in the protocol body. The protocol body now has been updated to correctly state the exploratory nature.
9.4. Safety Evaluations	In the section about pulse oximetry, one instance of " $\leq 93\%$ " was changed to " $< 93\%$ " in the description of arterial oxygen saturation, and the section was revised for better clarity. (Another instance in this section had already stated the correct $< 93\%$ .)
16.1. Study-specific Design Considerations	A sentence was revised from previous internal inconsistency ("had response . . . lack of response") to be internally consistent ("had nonresponse . . . lack of response").
Attachment 3	Country-specific titration schedules were removed for countries where no sites are participating in the study.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.



**Amendment INT-1** (21 April 2015)

This amendment is considered to be nonsubstantial 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, in that it does not significantly impact the safety or physical/mental integrity of subjects, nor the scientific value of the study.

**The overall reason for the amendment:** The overall reason for the amendment is to correct an error in the Time and Events Schedule that is required for the Interactive Web Response System (IWRS) setup.

Applicable Section(s)	Description of Change(s)
<b>Rationale:</b> Corrections made to the Time and Events Schedule to specify assessments for the Week 20 visit, and to clarify dosing instructions in case of a missed dose during the induction phase.	
Synopsis, Maintenance Phase; Time and Events Schedule (Optimization Phase, Maintenance Phase); 6.1.3. Maintenance Phase; Table 5.	Collection of biomarkers was deleted at Visit 3.1 (Week 4, Day 28 ) of the optimization phase as it would have been collected twice at the same visit (is still being collected at Day 28 but as part of the induction phase Visit 2.9). Blood volume table (Table 5) was adjusted to reflect the lower volume of blood collected due to deletion of the duplicate collection.  During maintenance phase, a column which was missing in the table was added for Week 20, Visit 4.5 (Day 137). Timing of various procedures and assessments were revised accordingly to be performed at Week 20 visit. Subsequent visits now start with Visit 4.6 (Week 21).  Text was adjusted where applicable.
Synopsis, Dosage and Administration; 6.1.1. Open-label Induction Phase	Sentence was added to clarify in case of a missed dose during the induction phase: If there is no intranasal treatment session on Day 15 (eg, visit is missed), a dose reduction from 84 mg to 56 mg is permitted on Day 18 if required for tolerability; no dose increase is permitted.
<b>Rationale:</b> Changes were made to simplify the algorithm and facilitate implementation by only allowing subjects to switch dosing frequency at fixed time points.	
Synopsis, Optimization Phase; 6.1.2.3. Intranasal Treatment Session Frequency	Clarified that the 2 fixed time points where adjustments to dosing frequency can be made are Week 8 and 12. The algorithms used to determine whether a frequency adjustment could be made (based on MADRS total score at Week 8 and Week 12) were clarified. Added guidance on how to determine if a change in dosing frequency is indicated in case of a missing MADRS assessment.
Synopsis, Maintenance Phase; Time and Events Schedule (Maintenance Phase); 6.1.3 Maintenance Phase	Clarified the guidance for dosing frequency adjustments at Week 16 and Week 20 and every 4 weeks until the end of the phase. Added guidance on how to determine if a change in dosing frequency is indicated in case of a missing MADRS assessment.
<b>Rationale:</b> For consistency with other Phase 3 protocols, added language to specify that direct entry subjects requiring lower doses of the oral antidepressant than those prescribed in the protocol are allowed to complete the induction phase but not eligible to participate in the optimization phase.	
Synopsis, Oral Antidepressants; 3.2.4.2. Oral Antidepressant; 6.2.2. Open-label Induction Phase	Added the sentence “While subjects requiring lower doses can continue in the study and complete the induction phase, such subjects will not be eligible to participate in the optimization phase and will proceed to the follow-up phase after completion of the induction phase.”

Applicable Section(s)	Description of Change(s)
<b>Rationale:</b> To add / revise information for dispensing, review, and collection of subject diaries for oral antidepressant	
Time and Events Schedule, all phases; 6.2 Oral Antidepressants; 7. Treatment Compliance; 15. Study-Specific Materials	Rows / timepoints / text added for subject diaries for oral antidepressants.
<b>Rationale:</b> To revise the amount of oral antidepressant dispensed at the End of Study visit from a 4 week supply to 2 week supply, in order to comply with company regulations that drug accountability must be performed for all dispensed study medication.	
Synopsis, Follow Up Phase, Oral Antidepressant; Time and Events Schedule (Induction, Optimization and Maintenance Phases); 3.1.1. Study Phases; 6.2.4. Follow-up Phase; 9.1.7 Follow-up Phase; 16.1 Study Specific Design Considerations.	Revised (or added where it wasn't present) text to indicate that subjects will be provided with an additional 2-week supply (rather than 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.
<b>Rationale:</b> To clarify scoring of the PAQ assessment	
9.6. Other Evaluations	Text describing scoring of the PAQ was revised to indicate it is based on Question 1 (not 1c through 1f).
<b>Rationale:</b> Corrections made to the diagram of the study design, Safety Analyses section, and reference list.	
Figure 1.	Relapse prevention phase replaced with maintenance phase for consistency with protocol text terminology.
11.6. Safety Analyses.	Deletion of sentences that defined baseline values for subsections on clinical laboratory tests, electrocardiograms, vital signs, nasal examination and nasal symptom questionnaire, and other safety and tolerability questionnaires and assessments. Details about relevant baseline will be provided within the Statistical Analysis Plan (SAP).
References.	Reference number 139 corrected (for PHQ-9).

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## SYNOPSIS

### **A Randomized, Double-blind, Multicenter, Active-controlled Study of Intranasal Esketamine Plus an Oral Antidepressant for Relapse Prevention in Treatment-resistant Depression**

EudraCT Number: 2014-004586-24

## INTRODUCTION

Major depressive disorder (MDD) is a serious, recurrent, and disabling psychiatric illness, is the second leading cause of years lost to disability worldwide, and is associated with excess mortality (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 esketamine for antidepressant therapy. The higher NMDA receptor affinity of esketamine versus ketamine allows a lower volume of medication to be administered via the noninvasive and rapidly absorbed intranasal route.

This study will investigate whether repeated use of intranasal esketamine plus an oral antidepressant can sustain the antidepressant effects of an induction course of intranasal esketamine plus an oral antidepressant in subjects with TRD, or whether the oral antidepressant alone is sufficient to maintain the antidepressant effect.

## OBJECTIVES AND HYPOTHESIS

### **Primary Objective**

The primary objective of this study is to assess the efficacy of intranasal esketamine plus an oral antidepressant compared with an oral antidepressant (active comparator) plus intranasal placebo in delaying relapse of depressive symptoms in subjects with TRD who are in stable remission (see Definitions of Terms below) after an induction and optimization course of intranasal esketamine plus an oral antidepressant.

### **Secondary Objectives**

- To assess the efficacy of intranasal esketamine plus an oral antidepressant compared with an oral antidepressant (active comparator) plus intranasal placebo in delaying relapse of depressive symptoms in subjects with TRD with stable response (but who are not in stable remission) (see Definitions of Terms below) after an induction and optimization course of intranasal esketamine plus an oral antidepressant
- To assess the effect of intranasal esketamine plus an oral antidepressant compared with an oral antidepressant (active comparator) plus intranasal placebo on:
  - Depressive symptoms
  - Overall severity of depressive illness

- 
- Functional impairment and associated disability
  - Anxiety symptoms
  - Health-related quality of life and health status
  - To investigate the safety and tolerability of intranasal esketamine plus an oral antidepressant compared with an oral antidepressant (active comparator) plus intranasal placebo in subjects with TRD, with special attention to the following:
    - Treatment-emergent adverse events (TEAEs), including AEs of special interest
    - Local nasal tolerability
    - Effects on heart rate, blood pressure, respiratory rate, and blood oxygen saturation
    - Effects on alertness and sedation
    - Potential psychosis-like symptoms
    - Dissociative symptoms
    - Potential effects on cognitive function
    - Potential effects on suicidal ideation/behavior
    - Potential treatment-emergent symptoms of cystitis and/or lower urinary tract symptoms
    - Potential withdrawal and/or rebound symptoms following cessation of intranasal esketamine treatment
    - Potential effects on sense of smell

### **Exploratory Objectives**

- To assess the potential relationship of biomarkers with response/non-response to intranasal esketamine plus an oral antidepressant or to an oral antidepressant plus intranasal placebo in adult subjects with TRD
- To assess medical resource utilization

### **Hypothesis**

The hypothesis for this study is that intranasal esketamine plus an oral antidepressant is more effective than treatment with an oral antidepressant plus intranasal placebo in delaying relapse of depressive symptoms in subjects with TRD in stable remission.

### **OVERVIEW OF STUDY DESIGN**

This is a randomized, double-blind, parallel-group, active-controlled, multicenter study to evaluate the efficacy, safety, and tolerability of intranasal esketamine plus an oral antidepressant compared with an oral antidepressant (active comparator) plus intranasal placebo in delaying relapse of depressive symptoms in adult men and women with TRD who are in stable remission after an induction and optimization course with intranasal esketamine plus an oral antidepressant.

Approximately 211 subjects in stable remission (see Definition of Terms below) at the end of the optimization phase will be randomized in a 1:1 ratio to either continue intranasal esketamine (same dose) or be switched to intranasal placebo; all subjects will continue the same oral antidepressant at the same dose.

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

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 (ESKETINTRD3001 or ESKETINTRD3002) (referred to as transferred-entry subjects).

The study has 5 phases:

- A 4-week screening/prospective observational phase, with an optional taper of up to 3 weeks for oral antidepressant medication(s) (direct-entry subjects only)
- A 4-week open-label induction phase (direct-entry subjects only)
- A 12-week optimization phase (open-label for direct-entry subjects and double-blind for transferred-entry subjects)
- A maintenance phase (variable duration)
- A 2-week follow-up phase

The maximum duration of a subject's participation will be variable, depending on whether he or she enters the study directly or is transferred from one of the double-blind short-term studies, and whether he or she meets phase-specific criteria (eg, meets criteria for response at the end of the induction phase, is in stable remission/response at the end of the optimization phase, and when and if he or she relapses in the maintenance phase). Direct-entry subjects may participate in up to 5 phases and transferred-entry subjects may participate in up to 3 phases.

The study will be stopped once 84 relapses (in the subjects with stable remission) occur during the maintenance phase, or earlier based on the results of the interim analysis for efficacy. At the time the study is stopped, subjects in the induction phase will be able to complete the Induction phase. Those subjects who are responders, after completing an Early Withdrawal Visit may proceed to the 54135419TRD3008 study without completing the follow-up phase. Those who are not responders will have an Early Withdrawal Visit and proceed directly to the follow-up phase. Subjects who are in the optimization or maintenance phase at the time the study is terminated will have an Early Withdrawal Visit/End of Maintenance Visit conducted and proceed directly to the follow-up phase.

### **Definitions of Terms:**

- Open-label Induction Phase
  - Response:  $\geq 50\%$  reduction in the MADRS total score from baseline (Day 1 prior to the first intranasal dose) to the end of the 4-week open-label induction phase.
- Optimization Phase
  - Stable remission:
    - MADRS total score  $\leq 12$  for at least 3 of the last 4 weeks of the optimization phase, but one excursion of a MADRS total score  $> 12$  or one missing MADRS assessment is permitted at Optimization week 13 or 14 only. The MADRS total score at weeks 15 and 16 must be  $\leq 12$ .
  - Stable response:  $\geq 50\%$  reduction in the MADRS total score from baseline (Day 1 of induction phase; pre-randomization/prior to the first intranasal dose) in each of the last 2 weeks of the optimization phase, but does not meet criteria for stable remission. Note: For transferred-entry subjects, Day 1 of the open-label induction phase will take place in ESKETINTRD3001 or ESKETINTRD3002.
- Maintenance Phase: Relapse is defined as any of the following:
  - MADRS total score  $\geq 22$  for 2 consecutive assessments separated by 5 to 15 days. The date of the second MADRS assessment will be used for the date of relapse.

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

**Screening/Prospective Observational Phase:**

Direct-entry subjects will participate in this 4-week phase to prospectively assess treatment response to the subject's current oral antidepressant treatment regimen. After 4 weeks of continuing the same treatment regimen, subjects who are non-responders to their current oral antidepressant treatment (as assessed by independent, remote raters) may be eligible to proceed to the open-label induction phase if they have  $\leq 25\%$  improvement in the MADRS total score from Week 1 to Week 4 and a MADRS total score of  $\geq 28$  on Week 2 and Week 4.

Eligible subjects who are entering the open-label induction phase will discontinue their current oral antidepressant medication(s). If clinically indicated, a subject's current antidepressant medication(s) may be tapered over an additional, optional period of up to 3 weeks per the local prescribing information or clinical judgment.

As a new oral antidepressant will be initiated on Day 1 of the open-label induction phase, eligible subjects who do not require a tapered discontinuation of their antidepressant medication(s) can immediately proceed into the open-label induction phase.

**Open-label Induction Phase:**

Eligible direct-entry subjects will receive intranasal esketamine (flexible dose: 56 mg or 84 mg) treatment sessions twice weekly for 4 weeks. In addition, all subjects will initiate a new, open-label oral antidepressant on Day 1 that will be taken daily for the duration of the induction phase. The assigned oral antidepressant will be 1 of 4 oral antidepressant medications (duloxetine, escitalopram, sertraline, or venlafaxine extended release [XR]), that the subject has not previously had a non-response to in the current depressive episode, has not been previously intolerant to (lifetime), and is available in the participating country.

At the end of the induction phase, subjects who are responders (defined as  $\geq 50\%$  reduction in the MADRS total score from baseline [Day 1 prior to the first intranasal dose] to the end of the 4-week open-label induction phase) may be eligible to proceed to the optimization phase. All subjects who do not proceed to the optimization phase will have an Early Withdrawal Visit conducted and proceed to the follow-up phase.

At the time the study is stopped, subjects in the induction phase will be able to complete the phase. Those who are responders, after completing an Early Withdrawal Visit, may proceed to the 54135419TRD3008 study without completing the follow-up phase. Those who are not responders will have an Early Withdrawal Visit conducted and proceed directly to the follow-up phase.

**Optimization Phase:**

Eligible direct-entry subjects from the open-label induction phase and transferred-entry subjects from the 2 double-blind short-term studies (ESKETINTRD3001 and ESKETINTRD3002) will participate in this 12-week phase.

The intranasal treatment session frequency will be reduced from that in the induction phase (twice weekly) to weekly for the first 4 weeks of this phase. After the first 4 weeks, the frequency of intranasal

treatment sessions will be individualized to either once weekly or once every other week based on the severity of depressive symptoms, as assessed by the MADRS total score. The dose of intranasal esketamine will remain unchanged from the dose at the end of the induction phase. All subjects will continue taking the same oral antidepressant treatment (at the same dosage) that was initiated during the induction phase.

At the end of the optimization phase, subjects in stable remission and those with stable response (but who are not in stable remission) may be eligible to continue into the maintenance phase; all other subjects will have an Early Withdrawal Visit conducted and proceed to the follow-up phase.

For subjects in stable remission and those with stable response at the end of this phase, the last visit of the optimization phase (Visit 3.13; Week 16) also serves as the baseline visit (Visit 4.1; Week 16) of the maintenance phase. Subjects eligible for the maintenance phase will be randomized and receive their first double-blind intranasal treatment session of the maintenance phase at this visit.

At the time the study is stopped, subjects in the optimization phase will have an Early Withdrawal Visit conducted and proceed directly to the follow-up phase.

### **Maintenance Phase:**

On Day 1 of this phase:

- Approximately 211 subjects in stable remission at the end of the optimization phase (after treatment with intranasal esketamine plus an oral antidepressant) will be randomized in a 1:1 ratio to either continue with intranasal esketamine (same dose) and the same oral antidepressant or to continue with the same oral antidepressant (active comparator) but switch to intranasal placebo. The primary efficacy analysis will be performed for these subjects only.
- Additionally, subjects with stable response (but who are not in stable remission) at the end of the optimization phase (after treatment with intranasal esketamine plus an oral antidepressant) will be randomized in a 1:1 ratio (using a separate randomization list) to either continue with intranasal esketamine (same dose) and the same oral antidepressant or to continue with the same oral antidepressant (active comparator) but switch to intranasal placebo (for a secondary efficacy analysis only).
- Transferred-entry subjects who achieve stable remission or stable response at the end of the optimization phase after treatment with an oral antidepressant plus intranasal placebo will continue to receive the same treatment in order to maintain the blinding for the ongoing short-term studies. These subjects will not be included in the efficacy analyses, but will be included in safety analyses.

The frequency of intranasal treatment sessions will be further individualized during the maintenance phase to once weekly or once every other week based on the severity of depressive symptoms, as assessed by the MADRS total score. Subjects will only be permitted to switch from weekly to every other weekly dosing a total of 3 times. After this time, if a given subject is unable to sustain improvement on every other week dosing they will remain on a weekly dosing regimen for the duration of this phase.

This phase will have a variable duration, continuing until 84 relapses occur in the subjects with stable remission, or earlier based on interim analysis results.

Subjects who meet the relapse criteria and subjects who remain relapse-free at study termination will have an End of Maintenance Phase Visit conducted and may proceed to the follow-up phase. If clinically indicated, subjects who have met relapse criteria after completing the end of maintenance visit may proceed to the open-label safety extension study, 54135419TRD3008, without completing the follow up phase. Subjects who are participating in the maintenance phase at the time the study is stopped will have an Early Withdrawal Visit conducted and proceed directly to 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. For those subjects who relapse in the Maintenance phase, if clinically indicated based on investigator's judgment, after completing the end of maintenance visit, the subject may proceed to the open-label safety extension study, 54135419TRD3008, without completing the follow-up phase. Similarly, when the study is stopped, subjects in the Induction phase who are responders, after completing the early withdrawal visit, may proceed to the 54135419TRD3008 study, without completing the follow up phase.

Follow-up visits will be performed at 1 and 2 weeks after the last clinic visit.

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 treatment administered during this phase. Subjects will be provided with an additional 2-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, the oral antidepressant should be continued during the 2-week 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 ESKETINTRD3003 study. Please refer to the 54135419TRD3008 protocol for full details of potential pathways for entry.

**SUBJECT POPULATION*****Direct-entry Subjects***

The study population will include adult men and women, 18 (or older if the minimum legal age of consent in the country in which the study is taking place is >18) to 64 years of age (inclusive), who meet the Diagnostic and Statistical Manual of Mental Disorders (5th Edition; DSM-5) diagnostic criteria for recurrent MDD or single-episode MDD (if a single episode, the duration of episode must be  $\geq 2$  years), without psychotic features, based upon clinical assessment, and confirmed by the Mini International Neuropsychiatric Interview. The subject must have an Inventory of Depressive Symptomatology-Clinician rated, 30-item (IDS-C<sub>30</sub>) total score of  $\geq 34$ , which corresponds to moderate to severe depression.

At the start of the screening/prospective observational phase, subjects must have had non-response (ie, lack of clinically meaningful improvement, defined as  $\leq 25\%$  improvement) to  $\geq 1$  but  $\leq 5$  (if current episode is >2 years, upper limit is applicable to only the last 2 years) different oral antidepressant treatments taken at adequate dosage and for adequate duration, as assessed on the Massachusetts General Hospital – Antidepressant Treatment Response Questionnaire (MGH-ATRQ) and documented by medical/pharmacy/prescription records or a letter from a treating physician, etc. for the current episode of depression. In addition, the subject is taking a different oral antidepressant treatment (on the MGH-ATRQ) for at least the previous 2 weeks at or above the minimum therapeutic dose.

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

The subject's current major depressive episode and treatment response to antidepressant treatments used in the current episode (retrospectively assessed) must be deemed valid for participation in a clinical study based on the Site Independent Qualification Assessment. The Site Independent Qualification Assessment is a tool to facilitate subject selection for MDD clinical studies, with a goal to ensure enrollment of subjects who have symptoms that reflect the current state of illness, that these symptoms can be reliably



measured with appropriate measurement tools, and that the severity of depression is appropriate (required at Week 1 to be MADRS total score  $\geq 28$ ).

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

### ***Transferred-entry Subjects***

Subjects who enter this study after participation in 1 of the short-term studies (ESKETINTRD3001 or ESKETINTRD3002) must have completed the double-blind induction phase in the short-term study and must have demonstrated response at the end of that phase ( $\geq 50\%$  reduction in the MADRS total score from baseline [Day 1 pre-randomization] at the end of the 4-week double-blind induction phase).

## **DOSAGE AND ADMINISTRATION**

### **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 course) that is up to date per local regulations must be present with the subject during the intranasal treatment session and the postdose observation period. In addition, equipment for supportive ventilation and resuscitation needs to be present.

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.

On all intranasal dosing days, subjects must remain at the site until study procedures have been completed and the subject is ready for discharge. Subjects should be accompanied by a responsible adult when released from the clinical site. Subjects must not drive a car or work with machines for 24 hours after receiving intranasal 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 intranasally) a demonstration intranasal device that is filled with a placebo solution.

### ***Open-label Induction Phase***

This phase is for direct-entry subjects only. All subjects will self-administer intranasal esketamine twice a week for 4 weeks at the study site. The first treatment session will be on Day 1.

On Day 1, subjects will start with a dose of 56 mg. On Day 4, the dose may be increased to 84 mg or remain at 56 mg, as determined by the investigator based on efficacy and tolerability. On Day 8, the dose

may be increased to 84 mg (if Day 4 dose was 56 mg), remain the same, or be reduced to 56 mg (if Day 4 dose was 84 mg), as determined by the investigator based on efficacy and tolerability. Similarly, on Days 11, 15, 18, and 22, the dose may be increased to 84 mg, remain the same, or be reduced to 56 mg, if applicable as determined by the investigator based on efficacy and tolerability. On Day 25, a dose reduction from 84 mg to 56 mg is permitted if required for tolerability; no dose increase is permitted.

### ***Optimization Phase***

*Transferred-entry subjects:* In this phase, subjects will continue the same double-blind intranasal study drug (same dose) from the double-blind induction phase of ESKETINTRD3001 or ESKETINTRD3002.

*Direct-entry subjects:* In the optimization phase, subjects will continue the same open-label intranasal esketamine treatment (same dose) from the open-label induction phase.

All subjects will continue their oral antidepressant medication (at the same dosage) during this phase.

#### *Intranasal Treatment Session Frequency:*

During this phase, the MADRS will be performed weekly by an independent, remote rater, and changes to the intranasal treatment session frequency will be based on the MADRS total score, if applicable (see below).

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 phase (Week 5 to Week 8).

During this phase, there are two fixed time points (Week 8 and Week 12) in which an adjustment to the frequency will be made if applicable.

#### Week 8:

- Subjects with a MADRS total score  $>12$  at Week 8 visit will continue to receive weekly intranasal treatment sessions for the remainder of the optimization phase. No further change to the treatment session frequency is permitted for the remainder of the optimization phase (through Week 16).
- If the MADRS total score is  $\leq 12$  at Week 8, 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).
  - This is the only time during the optimization phase that a subject will be permitted to change to a frequency of every other week.
- If the MADRS assessment is missed at Week 8, 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  $\leq 12$ , 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 for the remainder of the optimization phase. No further change to the treatment session frequency is permitted for the remainder of the optimization phase (through Week 16).

Week 12 (only for those on an every other week treatment session frequency):

- If the MADRS total score is  $>12$  at Week 12, the frequency of intranasal treatment sessions will be increased to weekly for the remainder of the optimization phase; no further change to the treatment session frequency is permitted for the remainder of the optimization phase (through Week 16).
- If the MADRS total score is  $\leq 12$  at Week 12, the subject will remain on the treatment session frequency of every other week for the next 4 weeks (ie, through to Week 16).
- If the MADRS is missed at Week 12, the last MADRS total score available prior to Week 12 will be used to determine if a change in treatment session frequency is indicated at Week 12. In this case:
  - If MADRS total score is  $\leq 12$ , the subject will remain on the treatment session frequency of every other week for the next 4 weeks (ie, through to Week 16).
  - If the MADRS total score  $>12$  at that week, the frequency of intranasal treatment sessions will be increased to weekly for the remainder of the optimization phase; no further change to the treatment session frequency is permitted for the remainder of the optimization phase (through Week 16).

### ***Maintenance Phase***

All subjects will receive double-blind intranasal study medication in this phase, as described above (see Overview of Study Design, Maintenance Phase).

During this phase, the MADRS will continue to be assessed weekly by an independent, remote rater, and changes to the intranasal treatment session frequency will occur at 4-week intervals, if applicable, and be based on the MADRS total score (see below).

At the start of this phase (Visit 4.1; Week 16):

- Subjects who currently receive intranasal treatment sessions on a weekly basis will stay at the same weekly intranasal treatment session frequency for the first 4 weeks of this phase.
- For those on an every other week frequency:
  - If the MADRS total score is  $>12$  at Week 16, the frequency of intranasal treatment sessions will be increased to weekly for the next 4 weeks.
  - If the MADRS total score is  $\leq 12$  at Week 16, the subject will stay at the same every other week intranasal treatment session frequency for the next 4 weeks.

After the first 4 weeks of this phase (ie, starting from Week 20), the intranasal treatment session frequency will be adjusted (if applicable) at fixed, 4-week intervals (eg, Week 20, 24, 28, 32, 36, 40, 44 and every 4 weeks until the end of the phase), based on the guidance below:

- If the MADRS total score is  $\leq 12$  at that week:
  - If the frequency is weekly, the frequency will be changed to every other week.
  - If the frequency is every other week, there will be no change in frequency.
- If the MADRS total score  $>12$  at that week:
  - If frequency is weekly, there will be no change in frequency.
  - If 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. In this case:
  - If the MADRS total score is  $\leq 12$ , and the frequency is every other week, there will be no change in frequency.

- If the MADRS total score is  $\leq 12$ , and the frequency is weekly, the frequency will be changed to every other week.
- If the MADRS total score is  $>12$ , and the frequency is weekly, there will be no change in frequency.
- If the MADRS total score is  $>12$ , and the 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 maintenance phase. After this time, if a given subject is unable to sustain improvement on every other week dosing they will remain on a weekly dosing regimen for the duration of this 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 the oral antidepressant treatment not be taken until at least 3 hours after the treatment session.

### ***Screening/Prospective Observational Phase (Direct-entry Subjects Only)***

During this phase, direct-entry subjects will continue taking their current oral antidepressant treatment regimen for the duration of the 4-week phase for prospective observation of response or non-response. The regimen must include a different oral antidepressant treatment (on the MGH-ATRQ) for at least the previous 2 weeks at or above the minimum therapeutic dose. This antidepressant treatment, as well as any other medication(s) being used for depression (including adjunctive/augmentation therapies), will continue from the start of Week 1 through the end of Week 4 of this phase. Dose adjustment is permitted per clinical judgment, but the oral antidepressant treatment is to remain at or above the minimum therapeutic dose (per the MGH-ATRQ) through the end of Week 4.

The sponsor will not supply these oral antidepressants. Antidepressant treatment adherence will be assessed during this phase using the Patient Adherence Questionnaire (PAQ). For subjects who are eligible to enter the open-label induction phase, after the completion of 4 weeks of prospective antidepressant treatment and confirmation of the antidepressant treatment non-response, all medication(s) being used for depression will be discontinued, including adjunctive/augmentation therapies. If clinically indicated (eg, antidepressant treatments with short half-lives, such as paroxetine and venlafaxine XR), the medication(s) being used for depression may be tapered off and discontinued over a period of up to 3 weeks per the local prescribing information or clinical judgment. Eligible subjects who do not require a taper of their medication(s) being used for depression can immediately proceed into the open-label induction phase.

### ***Open-label Induction Phase (Direct-entry Subjects Only)***

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

Dosing of the oral antidepressant will begin on Day 1. A mandatory titration schedule is provided in the protocol. Doses are not to exceed the maximum dose defined in the titration schedule. If higher doses are not tolerated, a down-titration is permitted based on clinical judgment. However, the subject's dose

should not be lower than the following minimum therapeutic doses at the end of the induction phase: sertraline (50 mg/day), venlafaxine XR (150 mg/day), escitalopram (10 mg/day), and duloxetine (60 mg/day). While subjects requiring lower doses can continue in the study and complete the induction phase, such subjects will not be eligible to participate in the optimization phase and will proceed to the follow-up phase after completion of the induction phase.

### ***Optimization and Maintenance Phases (Direct-entry and Transferred-entry Subjects)***

For all subjects, the same oral antidepressant treatment (duloxetine, escitalopram, sertraline, or venlafaxine XR) started on Day 1 of the induction phase will be continued through the optimization and maintenance phases. The oral antidepressant dosage at the end of the induction phase will remain unchanged through the maintenance phase.

Subjects who miss  $\geq 21$  days of the oral antidepressant doses (total daily dose) in the optimization phase will not be eligible to continue into the maintenance phase.

### ***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 study medication will be administered during this phase.

The decision to continue the oral antidepressant medication in this phase will be at the discretion of the investigator; however, in order to better assess potential withdrawal symptoms from the intranasal study medication, the oral antidepressant medication should be continued during the 2-week follow-up phase, unless determined as not clinically appropriate.

All subjects will be provided with an additional 2-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.

## **EFFICACY EVALUATIONS/ENDPOINTS**

### **Primary Efficacy Evaluation/Endpoint**

The primary efficacy evaluation will include the MADRS total score as it pertains to relapses.

The primary efficacy endpoint includes only subjects who are in stable remission at the end of the optimization phase after treatment with intranasal esketamine plus an oral antidepressant, and is defined as the time between subject randomization and the first documentation (earliest date) of a relapse in the maintenance phase.

### **Secondary Efficacy Evaluations/Endpoints**

Secondary efficacy evaluations/endpoints include the following:

- The time between subject randomization and the first documentation (earliest date) of a relapse in the maintenance phase for subjects with stable response (not in remission) at the end of the optimization phase after treatment with intranasal esketamine plus an oral antidepressant.
- The change from baseline (of maintenance phase) to endpoint in:
  - Depressive symptoms, using the MADRS and the self-reported Patient Health Questionnaire 9-item (PHQ-9) scale
  - Overall severity of illness, using the Clinical Global Impression - Severity (CGI-S)
  - Symptoms of anxiety, using the Generalized Anxiety Disorder, 7-item (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)

### **BIOMARKER, PHARMACOGENOMIC (DNA), AND EXPRESSION (RNA) EVALUATIONS**

Assessment of biomarkers (protein and RNA) and their potential relationship to the different treatment groups and to maintenance/stabilization of response, non-response, and relapse will be explored. Blood samples will be collected to measure genetic and epigenetic markers (including but not limited to brain derived neurotrophic factor [BDNF] allelic variants) and protein markers (including but not limited to growth factors, inflammation, endocrine, or metabolic markers). Samples of DNA and biomarkers 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 healthcare encounters, will be collected using the Healthcare Resource Use Questionnaire (HRUQ) during the optimization, maintenance, and follow-up phases. The HRUQ includes information regarding utilization of healthcare services (including the duration and type of services), enabling changes in level and quantity of services to be considered as a variable in economic models.

### **SAFETY EVALUATIONS**

Safety evaluations will include:

- Monitoring of TEAEs, including TEAEs of special interest; clinical laboratory tests (including hematology, serum chemistry, and urinalysis), pregnancy testing (for women of childbearing potential), urine drug screen, 12-lead electrocardiogram, vital signs, pulse oximetry, physical examination, and body weight measurements
- Nasal examinations and nasal symptom questionnaire
- Columbia Suicide Severity Rating Scale (C-SSRS), to assess potential suicidal ideation and behavior
- Clinician Administered Dissociative States Scale (CADSS), to assess treatment-emergent dissociative symptoms
- Four-item positive symptom subscale of the Brief Psychiatric Rating Scale (BPRS+), to assess potential 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 and is the clinician's assessment of the readiness to be discharged from the study site
- Physician Withdrawal Checklist (PWC-20) includes 20 items to assess potential withdrawal symptoms following cessation of intranasal esketamine treatment
- Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS), to monitor subjects for potential symptoms of cystitis, bladder pain, and interstitial cystitis
- Computerized cognitive battery and Hopkins Verbal Learning Test-Revised (HVLT-R), to assess the effect of intranasal esketamine on cognition
- University of Pennsylvania Smell Identification Test (UPSIT) and Smell Threshold Test, to assess any potential treatment-emergent effects on the sense of smell

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## STATISTICAL METHODS

### Subject Information

The full analysis sets for the primary efficacy evaluation are defined as follows:

- At Interim Analysis: All subjects who are in stable remission at the end of the optimization phase and who receive at least 1 dose of intranasal study drug and 1 dose of oral antidepressant during the maintenance phase at the time of the interim analysis data cutoff
- At Final Analysis: All subjects who are in stable remission at the end of the optimization phase and who receive at least 1 dose of intranasal study drug and 1 dose of oral antidepressant during the maintenance phase

The safety analysis set for each phase is defined as all subjects who receive at least 1 dose of intranasal study drug or 1 dose of oral antidepressant during that phase.

Transferred-entry subjects who continue to receive an oral antidepressant plus intranasal placebo will be summarized separately in both optimization and maintenance phases.

### Sample Size Determination

The maximum number of relapses (in the subjects with stable remission) required by this study is 84, which provides 90% power to detect a hazard ratio of 0.493 at the 1-sided significance level of 0.025 for a fixed-sample design to detect superiority of esketamine plus oral antidepressant over antidepressant alone in delaying relapse of depressive symptoms in subjects with stable remission. The calculation of sample size assumed that the time to the first relapse follows an exponential distribution, with a median time of 6 months for oral antidepressant alone and 12.17 months for intranasal esketamine plus oral antidepressant (hazard ratio = 0.493). The corresponding 6-month relapse rates are 50% for oral antidepressant alone and 28.95% for oral antidepressant plus intranasal esketamine.

Assumptions were made for accrual period and rate, maximum study duration, and dropout rate. Based on such assumptions, calculations indicated that a total of approximately 211 subjects in stable remission need to be randomized (in a 1:1 ratio) in order to obtain 84 relapses.

### Interim Analysis

To evaluate the assumptions used in sample size calculation, relapse rates will be monitored sequentially during the maintenance phase. In particular, a 2-stage group-sequential design will be adopted, with 1 interim analysis to be performed when a total of 30 relapses are observed. Early termination of the maintenance phase for efficacy will be based on interim analysis results. If the interim analysis results show that the study should proceed to the second stage (ie, continue to record more relapses after the interim cutoff), sample size re-estimation will be performed based on the interim analysis results to determine how many additional relapses should be obtained. The study team will not know the adjustments that will be made to the sample size; however, the clinical supplies group will be informed of the decision made at the interim analysis so that only the required amount of study medication will be packaged.

### Efficacy Analyses

The primary efficacy endpoint will be the time between subject randomization into the maintenance phase and the first documentation of a relapse event. Subjects with stable remission who meet at least 1 of the relapse criteria for the primary analysis while receiving treatment in the maintenance phase at the time that the study is stopped are considered to have had a relapse. All other randomized subjects with stable remission who had entered the maintenance phase but do not have a relapse by the time that the study is stopped will be considered censored.

The cumulative distribution function of the time to relapse will be estimated by the Kaplan-Meier method. Time to relapse will be summarized (number of relapses, number of censored subjects, median, 25th and 75th percentile of time to relapse, if estimable) by treatment group. Treatment differences will be compared using a 2-sided log-rank test as the primary analysis. The estimate of the hazards ratio and its 95% confidence interval will be based on the Cox proportional hazards model with treatment as a factor.

Treatment comparison between intranasal esketamine plus oral antidepressant and oral antidepressant (active comparator) plus intranasal placebo in the changes from baseline to endpoint of MADRS total score, PHQ-9, CGI-S, SDS, and GAD-7 during the maintenance phase will be performed using an analysis of covariance model with treatment and country as factors and baseline (maintenance phase) value as a covariate. Least-squares estimates of the treatment differences and 95% confidence intervals will be presented. Dimension scores of EQ-5D-5L data, health status index, and the overall health status score will be summarized over time. These analyses will be provided separately for stable remitters and stable responders (not in remission).

Additionally, the time between the randomization of a subject with stable response (but who are not in stable remission) and the first documentation of a relapse for that subject in the maintenance phase will be analyzed using the log-rank test as described above for the primary efficacy endpoint.

### **Biomarker, Pharmacogenomic (DNA), and Expression (RNA) Analyses**

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 comparison of biomarker measures between the treatment groups and correlation with baseline and change from baseline biomarker values in the efficacy and other measures. Additional exploratory analyses may also include relationship of baseline and change from baseline in biomarker measures to clinical response, maintenance/stabilization of response, relapse, and non-response.

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

### **Medical Resource Utilization Analysis**

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

### **Safety Analyses**

All safety data will be analyzed separately for each phase.

For each adverse event, the percentage of subjects who experience at least 1 occurrence of any given adverse event will be summarized by treatment group. Data from clinical laboratory tests, electrocardiograms, and vital signs will be provided as descriptive statistics and frequency tabulations. Nasal examination results will be provided as a shift table for changes from baseline, while nasal tolerability questionnaire results will be summarized descriptively. The C-SSRS results will be summarized in incidence and shift tables. The BPIC-SS, BPRS+, CADSS, CGADR, computerized cognitive battery, HVLT-R, MOAA/S, Smell Threshold Test, PWC-20, and UPSIT results will be provided as descriptive statistics of scores and their changes (and/or percent changes) from predose or baseline, as appropriate per assessment.



**TIME AND EVENTS SCHEDULE (Screening/Prospective Observational Phase and Open-label Induction Phase)**

Visit number	Screening/Prospective Observational Phase			Open-label Induction Phase								
	1.1	1.2	1.3 <sup>a</sup>	2.1 <sup>a</sup>	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9 <sup>b</sup>
Week	Week 1	End of Week 2	End of Week 4	1		2		3		4		
Study day	—	—	—	1 (baseline)	4	8	11	15	18	22	25	28
Clinic visit window (in days)	—	±2	±2	—	±1	±1	±1	±1	±1	±1	±1	±1
Clinic visit (C) or remote MADRS interview only (RM)	C	C	C	C	C	C	C	C	C	C	C	C
<b>Screening/Administrative</b>												
Informed consent (ICF)	X											
Medical history, psychiatric history, demographics, employment status	X											
MINI	X											
MGH-ATRQ	X											
Site Independent Qualification Assessment	X											
Height	X											
Inclusion/exclusion criteria	X			X								
Prestudy therapy	X											
Preplanned surgery/procedures	X											
STOP-Bang questionnaire (including assessment of BMI and neck circumference)	X											
MGH-Female RLHQ: Module I	X											
IDS-C <sub>30</sub>	X											
<b>Study Drug</b>												
Dispensing of new oral antidepressant (duloxetine, escitalopram, sertraline, or venlafaxine XR)				X								X <sup>m</sup>
Practice session for use of intranasal device				X <sup>c</sup>								
Intranasal esketamine				X	X	X	X	X	X	X	X	
Drug accountability (intranasal study medication)				X	X	X	X	X	X	X	X	
Drug accountability (oral antidepressant study medication)				X								X
Dispense subject diary for oral antidepressant				X								
Review subject diary and update (if applicable)					X	X	X	X	X	X	X	X

Visit number	Screening/Prospective Observational Phase			Open-label Induction Phase								
	1.1	1.2	1.3 <sup>a</sup>	2.1 <sup>a</sup>	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9 <sup>b</sup>
Week	Week 1	End of Week 2	End of Week 4	1		2		3		4		
Study day	—	—	—	1 (baseline)	4	8	11	15	18	22	25	28
Clinic visit window (in days)	—	±2	±2	—	±1	±1	±1	±1	±1	±1	±1	±1
Clinic visit (C) or remote MADRS interview only (RM)	C	C	C	C	C	C	C	C	C	C	C	C
Oral antidepressant compliance check						X		X		X		X
Collect/return of subject diary												X
<b>Safety Assessments (Site-completed)</b>												
Physical examination	X			X								X
Nasal examination <sup>c</sup>	X			X								X
Vital signs: blood pressure, pulse, respiratory rate, temperature <sup>c,p</sup>	X			X	X	X	X	X	X	X	X	
Vital signs (postdose): blood pressure, pulse, respiratory rate <sup>d</sup>				X	X	X	X	X	X	X	X	
Weight	X			X								X
12-lead ECG <sup>e,p</sup>	X			X		X		X			X	
C-SSRS: Baseline/Screening version	X											
C-SSRS: Since last visit version <sup>p</sup>		X	X	X <sup>t</sup>	X	X	X	X	X	X	X	X
MOAA/S and pulse oximetry <sup>f,p</sup>	X			X	X	X	X	X	X	X	X	
BPRS+ <sup>g,p</sup>				X	X	X	X	X	X	X	X	
CADSS <sup>g,p</sup>				X	X	X	X	X	X	X	X	
CGADR <sup>h</sup>				X	X	X	X	X	X	X	X	
PWC-20 <sup>i</sup>											X	
<b>Safety Assessments (Subject-completed)</b>												
Nasal symptom questionnaire <sup>j</sup>				X	X		X		X		X	
BPIC-SS <sup>c</sup>				X				X				X
<b>Assessment of Sense of Smell</b>												
UPSIT <sup>c,o</sup>		X						X				X
Smell Threshold Test <sup>c,o</sup>		X										X
<b>Efficacy Assessments (Clinician)</b>												
MADRS (7-day recall; performed by independent, remote raters)	X	X <sup>q</sup>	X <sup>q</sup>	X <sup>k,q</sup>		X <sup>c,q</sup>		X <sup>c,q</sup>		X <sup>c,q</sup>		X <sup>c,q</sup>
CGI-S <sup>c</sup>	X			X	X	X	X	X		X		X

Visit number	Screening/Prospective Observational Phase			Open-label Induction Phase								
	1.1	1.2	1.3 <sup>a</sup>	2.1 <sup>a</sup>	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9 <sup>b</sup>
Week	Week 1	End of Week 2	End of Week 4	1		2		3		4		
Study day	—	—	—	1 (baseline)	4	8	11	15	18	22	25	28
Clinic visit window (in days)	—	±2	±2	—	±1	±1	±1	±1	±1	±1	±1	±1
Clinic visit (C) or remote MADRS interview only (RM)	C	C	C	C	C	C	C	C	C	C	C	C
<b>Subject-completed Assessments</b>												
PAQ	X	X	X									
PHQ-9 <sup>c</sup>	X			X				X				X
SDS <sup>c</sup>	X			X				X				X
GAD-7 <sup>c</sup>	X			X								X
EQ-5D-5L <sup>c</sup>	X			X				X				X
<b>Cognition Testing</b>												
Practice session for computerized cognitive battery		X										
Computerized cognitive battery and HVL-T-R				X								X
<b>Clinical Laboratory Assessments</b>												
TSH, HbA1c	X											
Lipid panel (fasting)		X										
Hematology, chemistry <sup>c</sup>	X			X								X
Urine drug screen <sup>c</sup>	X			X				X			X	
Alcohol breath test	X			X								
Urinalysis <sup>c</sup>	X			X				X				X
Serum pregnancy test	X											
Urine pregnancy test <sup>c</sup>				X				X				X
<b>Biomarkers</b>												
Blood sample collection (protein) <sup>c,1</sup>	X			X		X						X
Blood sample collection (RNA) <sup>c,1</sup>	X			X		X						X
Blood sample collection (DNA) <sup>c,1</sup>	X											X
<b>Ongoing Subject Review</b>												
Concomitant therapy	<i>Ongoing</i>											
Adverse events	<i>Ongoing</i>											
<b>Other</b>												
Menstrual cycle tracking (start date of last menstrual period prior to study visit) <sup>a</sup>				X								X

Footnotes:

Abbreviations: BMI = body mass index; BPIC-SS = Bladder Pain/Interstitial Cystitis Symptom Score; BPRS+ = 4-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; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EQ-5D-5L = EuroQol-5 dimension = 5-level; EW = early withdrawal; GAD-7 = Generalized Anxiety Disorder = 7-item scale; HbA1c = glycated hemoglobin test; HRUQ = Healthcare Resource Use Questionnaire; HVLTR = Hopkins Verbal Learning Test-Revised; IDS-C<sub>30</sub> = Inventory of Depressive Symptomatology Clinician-rated, 30-item scale; MADRS = Montgomery-Asberg Depression Rating Scale; MGH-ATRQ = Massachusetts General Hospital Antidepressant Treatment History Questionnaire; MGH Female RLHQ = Massachusetts General Hospital Female Reproductive Lifecycle and Hormones Questionnaire; MINI = Mini International Neuropsychiatric Interview; MOAA/S = Modified Observer's Assessment of Alertness/Sedation; PAQ = Patient Adherence Questionnaire; PHQ-9 = Patient Health Questionnaire – 9; PWC-20 = Physician Withdrawal Checklist, 20 item scale; RNA = ribonucleic acid; 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; UPSIT = University of Pennsylvania Smell Identification Test.

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) An additional, optional period of up to 3 weeks is permitted to taper and discontinue all current medication(s) being used for depression after completion of the Week 4 (Visit 1.3) assessments, per the local prescribing information or clinical judgment. Subjects who do not require a taper and are thus eligible to immediately proceed to the open-label induction phase can have Visit 1.3 and Visit 2.1 occur on the same day or within 1 week of each other (if not occurring the same day, the antidepressant treatment regimen should be continued and discontinued prior to Visit 2.1).
- b) If a subject withdraws before the end of the open-label induction phase (ie, before completing Visit 2.9/Day 28) for reasons other than withdrawal of consent, an Early Withdrawal Visit (refer to Time and Events Schedule: Early Withdrawal/End of Maintenance Phase Visit and Follow-up 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.
- c) Predose (if/when performed on intranasal dosing days). Predose subject-reported outcome assessments should be administered before all other study-related procedures during a clinic visit.
- d) Postdose vital signs will be performed at 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.
- e) Twelve-lead ECG will be performed predose and at t = 1 hour postdose at Visit 2.1. Thereafter, 12-lead ECG will be performed at t = 1 hour postdose only (ie, no predose ECG is required) at Visits 2.3, 2.5, and 2.8. A time window of ±15 minutes will be permitted.
- f) The MOAA/S will not be performed at Visit 1.1 (pulse oximetry only). The MOAA/S will be performed every 15 minutes from predose to t = +1.5 hours postdose (please refer to Section 9.4 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 9.4 for further guidance on timing of pulse oximetry assessments).
- g) The BPRS+ and CADSS will be performed predose and at 40 minutes and 1.5 hours postdose.
- h) CGADR will be performed at 1 hour and 1.5 hours 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 prior to the 1.5 hour time point.
- i) PWC-20 will be performed only if the subject is not continuing into the optimization phase.
- j) Nasal symptom questionnaire will be performed predose and at 1 hour postdose.
- k) Performed for subjects requiring a taper period during the screening/prospective observational phase; the result will be considered as the subject’s baseline MADRS for the open-label induction phase. For all other subjects, the baseline MADRS for the open-label induction phase will be the MADRS performed at the end of Week 4 of the screening/prospective observational phase.
- l) 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.
- m) Additional 2-week supply of the oral antidepressant medication only for subjects entering the follow-up phase.
- n) At Week 1 of the screening/prospective observational phase, the start date of the last menstrual period prior to study visit is captured as part of the MGH-FRLHQ: Module 1. Thereafter, menstrual cycle tracking is only applicable to women with a menstrual cycle and is documented separately.
- o) If the subject has significant nasal congestion on the day of a scheduled assessment of sense of smell, then the site should consider postponing the UPSIT, Smell Threshold Test, or both (as applicable) to the next scheduled clinic visit.
- p) If a subject has started a scheduled clinic visit in which an intranasal treatment session is planned, but then a predose observation (eg, blood pressure results) prompts the site staff to postpone the intranasal treatment session within the visit window, then all time points (including predose) of the footnoted assessments must be repeated on the actual intranasal treatment session day, as follows: 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.
- q) The MADRS should be administered no more than 2 days prior to the subject’s targeted (not actual) clinic visit date (except Visit 2.9, which is within 1 day prior). If performed on the day of the scheduled clinic visit for an intranasal treatment session, the MADRS must be performed prior to the intranasal treatment session.
- r) Performed only if Visit 1.3 and Visit 2.1 do not occur on the same day.

**TIME AND EVENTS SCHEDULE (Optimization Phase)**

Phase	Optimization Phase <sup>a</sup>												
Visit Number	3.1 <sup>b</sup>	3.2	3.3	3.4	3.5	3.6	3.7	3.8	3.9	3.10	3.11	3.12	3.13 <sup>c</sup>
Week	4	5	6	7	8	9	10	11	12	13	14	15	16
Day	28	32	39	46	53	60	67	74	81	88	95	102	109
Clinic (C) or remote MADRS only (RM) visit <sup>d</sup>	C	C	C	C	C	C or RM	C	C or RM	C	C or RM	C	C or RM	C
<b>Study Procedures</b>													
<b>Administrative</b>													
ICF (transferred-entry subjects only)	X												
Inclusion/exclusion criteria (transferred-entry subjects only)	X												
<b>Efficacy Assessments (Clinician)</b>													
MADRS (7-day recall): independent remote rater Permitted window: -3 days		X	X	X	X	X	X	X	X	X	X	X	X
CGI-S		X	X	X	X	X <sup>e</sup>	X	X <sup>e</sup>	X	X <sup>e</sup>	X	X <sup>e</sup>	X
<b>Subject-completed Assessments</b>													
PHQ-9 <sup>f</sup>			X		X		X		X		X		X
SDS <sup>f</sup>					X				X				X
GAD-7 <sup>f</sup>					X		X		X				X
EQ-5D-5L <sup>f</sup>			X		X		X		X		X		X
<b>Study Drug</b>													
Intranasal treatment session		X	X	X	X	X <sup>e</sup>	X	X <sup>e</sup>	X	X <sup>e</sup>	X	X <sup>e</sup>	
Adjustment of intranasal treatment session frequency (if applicable)					X				X				
Dispensing oral antidepressant (open-label)	X				X				X				X <sup>n</sup>
Dispense subject diary for oral antidepressant	X												
Oral antidepressant compliance check, including review of subject diary		X	X	X	X		X		X		X		X
Collect/return of subject diary													X
Drug accountability (intranasal study medication) <sup>f</sup>		X	X	X	X	X	X	X	X	X	X	X	
Drug accountability (oral antidepressant)					X				X				X
<b>Safety Assessments (Site-completed)</b>													
Physical examination, nasal examination, weight					X				X				X
Vital signs (predose): blood pressure, pulse, respiratory rate, and temperature <sup>f,q</sup>		X	X	X	X	X <sup>e</sup>	X	X <sup>e</sup>	X	X <sup>e</sup>	X	X <sup>e</sup>	X

Phase	Optimization Phase <sup>a</sup>												
Visit Number	3.1 <sup>b</sup>	3.2	3.3	3.4	3.5	3.6	3.7	3.8	3.9	3.10	3.11	3.12	3.13 <sup>c</sup>
Week	4	5	6	7	8	9	10	11	12	13	14	15	16
Day	28	32	39	46	53	60	67	74	81	88	95	102	109
Clinic (C) or remote MADRS only (RM) visit <sup>d</sup>	C	C	C	C	C	C or RM	C	C or RM	C	C or RM	C	C or RM	C
<b>Study Procedures</b>													
Vital signs (postdose): blood pressure, pulse, and respiratory rate only <sup>g</sup>		X	X	X	X	X <sup>e</sup>	X	X <sup>e</sup>	X	X <sup>e</sup>	X	X <sup>e</sup>	
12-lead ECG <sup>h,q</sup>		X			X	X <sup>e</sup>		X <sup>e</sup>	X	X <sup>e</sup>		X <sup>e</sup>	
C-SSRS (since last visit version) <sup>q</sup>		X	X	X	X	X <sup>e</sup>	X	X <sup>e</sup>	X	X <sup>e</sup>	X	X <sup>e</sup>	
MOAA/S and pulse oximetry <sup>i,q</sup>		X	X	X	X	X <sup>e</sup>	X	X <sup>e</sup>	X	X <sup>e</sup>	X	X <sup>e</sup>	
BPRS+ and CADSS <sup>j,q</sup>		X	X	X	X	X <sup>e</sup>	X	X <sup>e</sup>	X	X <sup>e</sup>	X	X <sup>e</sup>	
CGADR <sup>k</sup>		X	X	X	X	X <sup>e</sup>	X	X <sup>e</sup>	X	X <sup>e</sup>	X	X <sup>e</sup>	
PWC-20 (only for subjects not entering maintenance phase)													X
<b>Safety Assessments (Subject)</b>													
Nasal symptom questionnaire <sup>l</sup>		X	X	X	X	X <sup>e</sup>	X	X <sup>e</sup>	X	X <sup>e</sup>	X	X <sup>e</sup>	
BPIC-SS		X			X				X				X
<b>Assessment of Sense of Smell</b>													
UPSIT <sup>l,p</sup>									X				
Smell Threshold Test <sup>p</sup>													X
<b>Cognitive Testing</b>													
Computerized cognitive battery and HVL-T-R <sup>f</sup>													X
<b>Clinical Laboratory Tests <sup>f</sup></b>													
Hematology and chemistry					X				X				X
Urinalysis					X				X				X
Urine drug screen					X				X				X
Alcohol breath test					X				X				X
Urine pregnancy test					X				X				X
<b>Medical Resource Utilization</b>													
HRUQ			X		X		X		X		X		X
<b>Biomarkers</b>													
Blood sample collection (protein) <sup>l,m</sup>					X								X
Blood sample collection (RNA) <sup>l,m</sup>					X								X
Blood sample collection (DNA) <sup>l,m</sup>					X								X

Phase	Optimization Phase <sup>a</sup>												
Visit Number	3.1 <sup>b</sup>	3.2	3.3	3.4	3.5	3.6	3.7	3.8	3.9	3.10	3.11	3.12	3.13 <sup>c</sup>
Week	4	5	6	7	8	9	10	11	12	13	14	15	16
Day	28	32	39	46	53	60	67	74	81	88	95	102	109
Clinic (C) or remote MADRS only (RM) visit <sup>d</sup>	C	C	C	C	C	C or RM	C	C or RM	C	C or RM	C	C or RM	C
<b>Study Procedures</b>													
<b>Ongoing Subject Review and Other</b>													
Menstrual cycle tracking (start date of last menstrual period prior to study visit) <sup>o</sup>					X				X				X
Concomitant therapy	Ongoing												
Adverse events	Ongoing												

**Footnotes:**

Abbreviations: 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 = European Quality of Life (EuroQol) Group, 5-Dimension, 5-Level; GAD-7 = Generalized Anxiety Disorder, 7-item; 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; RM = Remote MADRS; SDS = Sheehan Disability Scale; UPSIT = University of Pennsylvania Smell Identification Test.

Note: On intranasal dosing days, time 0 is defined as the time of the first intranasal spray.

- a) If a subject withdraws before the end of the optimization phase for reasons other than withdrawal of consent, or is not eligible to continue into the maintenance phase, an Early Withdrawal Visit (Refer to Time and Events Schedule: Early Withdrawal/End of Maintenance Phase Visit and follow up phase) should be conducted. If the Early Withdrawal Visit is conducted on the same day as a scheduled visit, duplicate assessments are not required.
- b) Results for all assessments performed on Day 28 of the induction phase for direct-entry subjects (Visit 2.9) and transferred-entry subjects (Visit 2.10 of Study ESKETINTRD3001 or ESKETINTRD3002) will serve as the baseline values for the optimization phase and will not be repeated as part of Visit 3.1. The Day 28 visit should coincide with Day 28 (Visit 3.1) for this study. All transferred-entry subjects must meet all of the transferred-entry subject-specific inclusion criteria and none of the exclusion criteria in order to be enrolled.
- c) Visit 3.13 (Week 16) serves as the last visit for the optimization phase and will also be the first visit (Visit 4.1; Week 16) of the maintenance phase for subjects who qualify to continue. Results for all assessments performed at this visit will also serve as baseline for the maintenance phase and will be completed before randomization to double-blind intranasal study drug.
- d) Clinic visits (visit window ±3 days) will be conducted for all intranasal treatment sessions (weekly or every other week); otherwise only a remote MADRS (visit window: -3 days) will be conducted.
- e) Performed only at clinic visits for intranasal treatment sessions (omitted if remote MADRS only).
- f) Predose (if/when performed on intranasal dosing days). Predose subject-reported outcome assessments should be administered before all other study-related procedures during a clinic visit.
- 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) The 12-lead electrocardiogram 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 9.4 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 9.4 for further guidance on timing of pulse oximetry assessments).
- j) The BPRS+ and CADSS will be performed predose and at 40 minutes and 1.5 hours postdose.
- k) 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.

- l) The nasal symptom questionnaire will be performed predose and at 1 hour postdose.
- m) 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.
- n) Additional 2-week supply of the oral antidepressant medication only for subjects entering the follow-up phase.
- o) Only applicable to women with a menstrual cycle.
- p) If the subject has significant nasal congestion on the day of a scheduled assessment of sense of smell, then the site should consider postponing the UPSIT or Smell Threshold Test (as applicable) to the next scheduled clinic visit.
- q) If a subject has started a scheduled clinic visit in which an intranasal treatment session is planned, but then a predose observation (eg, blood pressure results) prompts the site staff to postpone the intranasal treatment session within the visit window, then all time points (including predose) of the footnoted assessments must be repeated on the actual intranasal treatment session day, as follows: 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.
- r) Drug accountability for intranasal study medication should be performed weekly during Weeks 5 through 8 (inclusive) and then weekly or every other week from Weeks 9 through 15 (inclusive).



**TIME AND EVENTS SCHEDULE (Maintenance Phase)**

Phase	Maintenance Phase									
	4.1 <sup>c</sup>	4.2	4.3	4.4	4.5	4.6 to 4.X				
Visit Number <sup>a,b</sup>						Study Procedure Frequency From Week 20 Through End of Phase				
Week	16	17	18	19	20	Every week	Every 2 weeks	Every 4 weeks	Every 8 weeks	Every 12 weeks
Day	109	116	123	130	137	Every 7 days	Every 14 days	Every 28 days	Every 56 days	Every 84 days
Clinic (C) or Remote MADRS only (RM) visit <sup>d</sup>	C	C/RM	C	C/RM	C	C/RM	C	C	C	C
Study Procedures										
Study Drug <sup>d</sup>										
Randomization: Primary (subjects in stable remission after treatment with intranasal esketamine and an oral antidepressant)	X <sup>e</sup>									
Randomization: Secondary (subjects with stable response after treatment with intranasal esketamine and an oral antidepressant)	X <sup>e</sup>									
Intranasal treatment session (esketamine or placebo)	X	X <sup>f</sup>	X	X <sup>f</sup>	X	X <sup>f</sup>	X <sup>f</sup>			
Adjustment of intranasal treatment session frequency (if applicable)	X				X			X		
Dispensing oral antidepressant (open-label)	X				X			X		
Dispense subject diary for oral antidepressant	X									
Oral antidepressant compliance check, including review of subject diary	X		X		X		X			
Drug accountability for intranasal study medication	X	X <sup>f</sup>	X	X <sup>f</sup>	X	X <sup>f</sup>				
Drug accountability for oral antidepressant					X			X		
Efficacy Assessments (Clinician)										
MADRS (7-day recall) <sup>h</sup> – independent, remote rater		X	X	X	X	X				
CGI-S			X		X	X <sup>f</sup>				
Subject-completed Assessments										
PHQ-9 <sup>i</sup>			X		X		X			
SDS <sup>i</sup>					X			X		
GAD-7 <sup>i</sup>					X			X		
EQ-5D-5L <sup>i</sup>			X		X		X			

Phase	Maintenance Phase									
	4.1 <sup>c</sup>	4.2	4.3	4.4	4.5	4.6 to 4.X				
Visit Number <sup>a,b</sup>						Study Procedure Frequency From Week 20 Through End of Phase				
Week	16	17	18	19	20	Every week	Every 2 weeks	Every 4 weeks	Every 8 weeks	Every 12 weeks
Day	109	116	123	130	137	Every 7 days	Every 14 days	Every 28 days	Every 56 days	Every 84 days
Clinic (C) or Remote MADRS only (RM) visit <sup>a</sup>	C	C/RM	C	C/RM	C	C/RM	C	C	C	C
<b>Safety Assessments (Site-completed)</b>										
Physical examination, nasal examination, and weight					X			X		
Vital signs (predose): blood pressure, pulse, respiratory rate, and temperature <sup>s</sup>		X <sup>f</sup>	X	X <sup>f</sup>	X	X <sup>f</sup>				
Vital signs (postdose): blood pressure, pulse, and respiratory rate only <sup>j</sup>	X	X <sup>f</sup>	X	X <sup>f</sup>	X	X <sup>f</sup>				
12-lead ECG <sup>k,s</sup>	X		X					X		
C-SSRS (since last visit version) <sup>s</sup>		X <sup>f</sup>	X	X <sup>f</sup>	X	X <sup>f</sup>				
MOAA/S and pulse oximetry <sup>ls</sup>	X	X <sup>f</sup>	X	X <sup>f</sup>	X	X <sup>f</sup>				
BPRS+ and CADSS <sup>ms</sup>	X	X <sup>f</sup>	X	X <sup>f</sup>	X	X <sup>f</sup>				
CGADR <sup>n</sup>	X	X <sup>f</sup>	X	X <sup>f</sup>	X	X <sup>f</sup>				
PWC-20 (performed at last clinic visit of this phase)										
<b>Safety Assessments (Subject)</b>										
Nasal symptom questionnaire <sup>o</sup>	X		X		X			X		
BPIC-SS					X			X		
<b>Clinical Laboratory Tests<sup>i</sup></b>										
Hematology and chemistry					X			X		
Urinalysis (to be performed at same visit as BPIC-SS)					X			X		
Urine drug screen					X			X		
Alcohol breath test					X			X		
Urine pregnancy test					X			X		
<b>Assessment of Sense of Smell</b>										
UPSIT <sup>f</sup>					X				X	
Smell Threshold Test <sup>f</sup>										X
<b>Cognition Testing<sup>e</sup></b>										
Computerized cognitive battery and HVLIT-R										X

Phase	Maintenance Phase									
Visit Number <sup>a,b</sup>	4.1 <sup>c</sup>	4.2	4.3	4.4	4.5	4.6 to 4.X				
						Study Procedure Frequency From Week 20 Through End of Phase				
Week	16	17	18	19	20	Every week	Every 2 weeks	Every 4 weeks	Every 8 weeks	Every 12 weeks
Day	109	116	123	130	137	Every 7 days	Every 14 days	Every 28 days	Every 56 days	Every 84 days
Clinic (C) or Remote MADRS only (RM) visit <sup>a</sup>	C	C/RM	C	C/RM	C	C/RM	C	C	C	C
<b>Medical Resource Utilization</b>										
HRUQ			X		X		X			
<b>Biomarkers</b>										
Blood sample collection (protein) <sup>1p</sup>					X					
Blood sample collection (RNA) <sup>1p</sup>					X					
Blood sample collection (DNA) <sup>1p</sup>					X					
<b>Ongoing Subject Review and Other</b>										
Menstrual cycle tracking (start date of last menstrual period prior to study visit) <sup>11</sup>					X			X		
Concomitant therapy	<i>Ongoing</i>									
Adverse events	<i>Ongoing</i>									

**Footnotes:**

Abbreviations: BPIC-SS = Bladder Pain/Interstitial Cystitis Symptom Score. BPRS+ = Brief Psychiatric Rating Scale, positive symptom subscale; 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; EQ-5D-5L = European Quality of Life (EuroQol) Group, 5-Dimension, 5-Level; GAD-7 = Generalized Anxiety Disorder, 7-item; HRUQ= Healthcare Resource Use Questionnaire; HVL-T-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; UPSIT = University of Pennsylvania Smell Identification Test.

Note: On intranasal dosing days, time 0 is defined as the time of the first intranasal spray.

- a) Visits (clinic or remote contacts) will be conducted weekly during the maintenance phase. Clinic visits (visit window: ±3 days) will be conducted for all intranasal treatment sessions (weekly or every other week); otherwise only a remote visit for MADRS (visit window: -3 days) will be conducted. Due to the variable duration of this phase, following Visit 4.5 visit numbers will continue sequentially (eg, 4.6, 4.7, etc) until the subject completes the phase. The frequency of study procedures from Week 20 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) If a subject withdraws before the end of the maintenance phase for reasons other than withdrawal of consent, an Early Withdrawal Visit should be conducted. A subject meeting relapse criteria is not considered to be an early withdrawal subject; for relapse subjects, and those subjects remaining relapse-free at the time of study termination, an End of Maintenance Phase Visit should be conducted. If the End of Maintenance Visit is conducted on the same day as a scheduled visit, duplicate assessments are not required. Refer to the Time and Events Schedule: Early Withdrawal/End of Maintenance Phase Visit and Follow-up Phase.

- c) Visit 3.13 (Week 16) serves as the last visit for the optimization phase and will also be the first visit (Visit 4.1; Week 16) of the maintenance phase for subjects who qualify to continue. Results for all assessments performed at this Visit 3.13 of the optimization phase will also serve as baseline for the maintenance phase and will be completed before randomization to double-blind intranasal study drug. Duplicate assessments are not required.
- d) Transferred-entry subjects who achieve stable remission or stable response in the optimization phase after treatment with an oral antidepressant plus intranasal placebo will continue to receive the same treatment in order to maintain the blinding for the ongoing short-term studies.
- e) Performed prior to intranasal dose administration.
- f) Performed only at clinic visits for intranasal treatment sessions (omit if remote contact visit).
- g) At the last clinic visit of this phase, an additional 2-week supply of the oral antidepressant medication is provided only for subjects entering the follow-up phase.
- h) The last MADRS assessment performed prior to the first intranasal treatment session of the maintenance phase will be the baseline value for this phase.
- i) Predose (if/when performed on intranasal dosing days). Predose subject-reported outcome assessments should be administered before all other study-related procedures during a clinic visit.
- j) 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.
- k) At clinic visits for intranasal treatment sessions, the 12-lead electrocardiogram will be performed at 1 hour postdose. A time window of  $\pm 15$  minutes is permitted.
- l) The MOAA/S will be performed every 15 minutes from predose to  $t = 1.5$  hours postdose (please refer to Section 9.4 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 9.4 for further guidance on timing of pulse oximetry assessments).
- m) The BPRS+ and CADSS will be performed predose and at 40 minutes and 1.5 hours postdose.
- n) 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.
- o) At clinic visits for intranasal treatment sessions, the nasal symptom questionnaire will be performed predose and at 1 hour postdose.
- p) 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.
- q) Only applicable to women with a menstrual cycle.
- r) If the subject has significant nasal congestion on the day of a scheduled assessment of sense of smell, then the site should consider postponing the UPSIT or Smell Threshold Test (as applicable) to the next scheduled clinic visit.
- s) If a subject has started a scheduled clinic visit in which an intranasal treatment session is planned, but then a predose observation (eg, blood pressure results) prompts the site staff to postpone the intranasal treatment session within the visit window, then all time points (including predose) of the footnoted assessments must be repeated on the actual intranasal treatment session day, as follows: 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.

**TIME AND EVENTS SCHEDULE (Early Withdrawal/End of Maintenance Phase Visit and Follow-up Phase)**

Phase	Early Withdrawal//End of Maintenance Phase <sup>a</sup>	Follow-up Phase <sup>b</sup>	
	EW/EMP	5.1	5.2
<b>Visit Number</b>	-	1	2
<b>Weeks After Last Clinic Visit</b>	-	1	2
<b>Clinic (C) or Remote Assessments Only (RA) Visit</b>	C	RA <sup>f</sup>	C
<b>Study Procedures</b>			
<b>Study Drug</b>			
Drug accountability (oral antidepressant study medication)	X		X
Dispensing of additional supply of new oral antidepressant (duloxetine, escitalopram, sertraline, or venlafaxine XR)	X		
Oral antidepressant compliance check	X		X
Collect/return of subject diary	X		
<b>Safety Assessments (Site-Completed)</b>			
Physical examination	X		X
Nasal examination	X		X
Vital signs: blood pressure, pulse, respiratory rate, temperature	X		X
12-lead electrocardiogram	X		X
C-SSRS: Since last visit version	X		X
PWC-20	X	X	X
<b>Safety Assessments (Subject-Completed) <sup>e</sup></b>			
BPIC-SS	X		X
<b>Efficacy Assessments (Clinician-Completed)</b>			
MADRS (independent, remote blinded rater)	X	X	X
CGI-S	X		X
<b>Efficacy Assessments (Subject-Completed) <sup>e</sup></b>			
PHQ-9	X		X
SDS	X		X
GAD-7	X		X
EQ-5D-5L	X		X
<b>Assessment of Sense of Smell</b>			
UPSIT <sup>e</sup>	X		
Smell Threshold Test <sup>e</sup>	X		
<b>Cognition testing</b>			
Computerized cognitive battery and HVLT-R	X		X

Phase	Early Withdrawal/End of Maintenance Phase <sup>a</sup>	Follow-up Phase <sup>b</sup>	
		5.1	5.2
Visit Number	EW/EMP	1	2
Weeks After Last Clinic Visit	-	1	2
Clinic (C) or Remote Assessments Only (RA) Visit	C	RA <sup>f</sup>	C
<b>Medical Resource Utilization</b>			
HRUQ	X		X
<b>Clinical Laboratory Assessments</b>			
Hematology and chemistry	X		X
Urinalysis	X		X
Serum pregnancy test	X		X
<b>Biomarkers</b>			
Blood sample collection (protein)	X		X
Blood sample collection (RNA)	X		X
Blood sample collection (DNA)	X		
<b>Other Assessments</b>			
Menstrual cycle tracking (start date of last menstrual period prior to study visit) <sup>d</sup>			X
Concomitant therapy	X	<i>Ongoing</i>	
Adverse events	X	<i>Ongoing</i>	

**Footnotes:**

Abbreviations: 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 Use Questionnaire; HVLT-R = Hopkins Verbal Learning Test - Revised; MADRS = Montgomery-Asberg Depression Rating Scale; PHQ-9 = Patient Health Questionnaire, 9-item; PWC-20 = Physician Withdrawal Checklist, 20-item; RA = remote assessment only; SDS = Sheehan Disability Scale.

- a) If a subject withdraws before the end of the induction, optimization, or maintenance phase for reasons other than withdrawal of consent, or has completed the induction or optimization phase but is not eligible to continue to the next treatment phase, an Early Withdrawal Visit 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. A subject meeting relapse criteria is not considered to be an early withdrawal subject; for these subjects, and subjects currently in the maintenance phase at the time the study is terminated, will conduct an End of Maintenance Phase Visit. For those subjects who relapse in the Maintenance phase, if clinically indicated based on investigator’s judgment, after completing the end of maintenance visit, the subject may proceed to the open-label safety extension study, 54135419TRD3008, without completing the follow up phase. Similarly, when the study is stopped, subjects in the Induction phase who are responders, after completing the early withdrawal visit, if clinically indicated based on the investigator’s judgment, may proceed to the 54135419TRD3008 study, without completing the follow up phase.
- b) Visit window will be ±3 days.
- c) Subject-reported outcome assessments should be administered before all other study-related procedures during a clinic visit.
- d) Only applicable to women with a menstrual cycle.
- e) If the subject has significant nasal congestion on the day of a scheduled assessment of sense of smell, then the site should consider postponing the UPSIT and Smell Threshold Test to the next scheduled clinic visit.
- f) At the “Remote Assessment” visit, site staff will contact the subject by telephone to obtain information regarding adverse events and concomitant therapies.

## ABBREVIATIONS

AHI	apnea-hypopnea index
ASA	American Society of Anesthesiologists
AUC	area under the plasma concentration-time curve
BDNF	brain-derived neurotrophic factor
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
CADSS	Clinician-Administered Dissociative States Scale
CGADR	Clinical Global Assessment of Discharge Readiness
CGI-S	Clinical Global Impression - Severity
C <sub>max</sub>	maximum plasma concentration
CRF	case report form
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	cytochrome P450, with any appended letters (2B6, 3A4, etc) indicating subtypes
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, fourth edition
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
FT4	free thyroxine
GAD-7	Generalized Anxiety Disorder, 7-item (scale)
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
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 <sub>30</sub>	Inventory of Depressive Symptomatology - Clinician-rated, 30 item
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
IWRS	interactive web response system
MADRS	Montgomery-Asberg Depression Rating Scale
MAOI	monoamine oxidase inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview
MMRM	mixed-effects model for repeated measures
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
PAQ	Patient Adherence (to Antidepressant Medication) Questionnaire
PCP	phencyclidine
PHQ-9	Patient Health Questionnaire, 9-item
PQC	product quality complaint
PWC-20	Physician Withdrawal Checklist, 20-item
QTc	QT interval corrected
QTcB	QT interval corrected according to Bazett's formula
QTcF	QT interval corrected according to Fridericia's formula

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SAP	statistical analysis plan
SD	standard deviation
SDS	Sheehan Disability Scale
SE	standard error
SmPC	Summary of Product Characteristics
SNRI	serotonin-norepinephrine reuptake inhibitor
SpO <sub>2</sub>	saturation of peripheral blood oxygen
SSRI	selective serotonin reuptake inhibitors
STOP-Bang	<u>S</u> noring, <u>T</u> iredness, <u>O</u> bserved Apnea, High 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
TRD	treatment-resistant depression
UPSIT	University of Pennsylvania Smell Identification Test
US	United States
XR	extended-release



## 1. INTRODUCTION

Major depressive disorder (MDD) is a serious, recurrent, and disabling psychiatric illness; is the second leading cause of years lost to disability worldwide; and is associated with excess mortality (the estimated median years of potential life lost is 10 years).<sup>134,135,140</sup> About 30% of patients fail to achieve remission despite treatment with multiple antidepressant medications, and are considered to have treatment-resistant depression (TRD).<sup>44,113</sup> 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.<sup>113,118</sup> 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.<sup>26,33</sup>

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.<sup>65</sup> The desired analgesic-anesthetic effects of ketamine and esketamine are attributed to the blockade of ionotropic N-methyl-D-aspartate (NMDA) glutamate receptors.<sup>82,101,145</sup>

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.<sup>33</sup> In contrast, the mechanism of action of ketamine and esketamine is distinct from conventional antidepressants because both ketamine and esketamine profoundly affect fast excitatory glutamate transmission, increase BDNF release, and stimulate synaptogenesis.<sup>33</sup>

Most literature reports of the antidepressant effects of ketamine describe studies using IV administration of the racemate, with a few exceptions.<sup>71</sup> Janssen Research & Development (JRD) is developing intranasal esketamine as an antidepressant therapy because it has higher NMDA receptor affinity, which allows a lower volume to be administered via the intranasal route.<sup>80,95,103</sup>

For the most comprehensive nonclinical and clinical information regarding esketamine (JNJ-54135419), please refer to the latest edition of the Investigator's Brochure.<sup>60</sup>

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<sup>®</sup> (ketamine hydrochloride injection)<sup>65</sup>:

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  $\alpha$ -adrenergic blockade), by  $\beta$ -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.<sup>60</sup>

#### 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 ECG changes were noted up 72 mg/day. Heart rate was slightly increased.

Further details can be found in the Investigator's Brochure.<sup>60</sup>

##### *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.<sup>60</sup>

### *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.<sup>60</sup>

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***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.<sup>60</sup>

***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.<sup>60</sup>

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.<sup>39</sup> 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<sup>®</sup> (ketamine hydrochloride [HCl] for injection) provides the following guidance.

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

The dog would be considered the most predictive species in terms of ketamine's cardiovascular effects in humans, but the antidepressant effects of ketamine were studied only in rodent models. The myocardial contractility effects and blood pressure responses to ketamine vary between species.<sup>60</sup> 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.<sup>60</sup>

### **1.1.2. Clinical Studies**

#### **1.1.2.1. Pharmacokinetics and Product Metabolism**

##### **Metabolism**



##### **Excretion**



##### **Intravenous Esketamine**



[Redacted]

**Intranasal Esketamine**

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

**1.1.2.2. Pharmacodynamics and Efficacy**

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### **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.<sup>51,66,108,125</sup>



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

According to the SmPC for esketamine,<sup>66</sup> 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.<sup>64</sup>

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 ( $\geq 65$  years of age, with 3 subjects  $\geq 75$  years of age) and 20 healthy younger adult subjects (18 to 55 years of age, inclusive).<sup>15</sup> 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).

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.<sup>116</sup> 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 the double-blind or open-label phases of ESKETINTRD2003. 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 received no further study medication. The event resolved on the same day and 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. Study medication was stopped following 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 (84 mg/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 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.<sup>116</sup>

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 (SD) peak systolic blood pressure after the first administration in each dose group was:
  - Placebo: 124.2 (11.51) mm Hg (mean [SD] increase of 5.4 [7.84] mm Hg)
  - 28 mg: 131.8 (15.49) mm Hg (mean [SD] increase of 10.4 [10.44] mm Hg)
  - 56 mg: 130.4 (18.64) mm Hg (mean [SD] increase of 11.2 [15.01] mm Hg)
  - 84 mg: 146.1 (19.9) mm Hg (mean [SD] increase of 17.1 [15.5] mm Hg)
- Mean (SD) peak diastolic blood pressure after the first administration in each dose group was:
  - Placebo: 81.2 (8.36) mm Hg (mean [SD] increase of 3.8 [7.99] mm Hg)
  - 28 mg: 85.7 (9.16) mm Hg (mean [SD] increase of 6.5 [7.00] mm Hg)
  - 56 mg: 86.5 (11.34) mm Hg (mean [SD] increase of 7.2 [9.67] mm Hg)
  - 84 mg: 87.8 (10.62) mm Hg (mean [SD] increase of 8.1 [9.12] mm Hg)

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.<sup>88</sup> Eighty percent of the participants were retested at the end of 1 year. Cognitive deficits (including impairment in spatial working memory, pattern recognition memory, and category fluency) were mainly observed in frequent users and not with the infrequent users. Short-lasting, dose-dependent effects of psychosis were associated with ketamine users. There was no increase in symptoms over time, and symptoms were completely reversible upon stopping use of ketamine. As noted, these data should be interpreted with caution, as baseline data predating drug use were not available. Furthermore, in their recent review, Morgan and Curran report that

there is little evidence of any link between chronic, heavy use of ketamine and diagnosis of a psychotic disorder.<sup>86</sup>

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.<sup>22,85,87,93</sup> Overall, infrequent or recreational ketamine use does not appear to be associated with long-term cognitive impairment.<sup>93</sup> The most robust findings are that frequent ketamine users (more than 5 times a week) exhibit impairments in both short- and long-term memory.<sup>87</sup> 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.<sup>88</sup>

Ketamine-induced ulcerative cystitis is a recently identified complication.<sup>86</sup> The most common symptoms are frequency and urgency of urination, dysuria, urge incontinence, and occasionally painful hematuria (blood in urine). Computerized tomography scans of these subjects revealed a marked thickening of the bladder wall, a small bladder capacity, and perivesicular stranding consistent with severe inflammation. At cystoscopy, all patients had severe ulcerative cystitis. Biopsies in 4 of these cases found denuded urothelial mucosa with thin layers of reactive and regenerating epithelial cells, and ulcerations with vascular granulation tissue and scattered inflammatory cells. Cessation of ketamine use provided some relief of symptoms. Most of the described cases are in near-daily users of ketamine for recreational purposes. The prevalence is difficult to determine, as it is seen in recreational users who often do not seek help.

The majority of cases resolve after stopping ketamine use, one-third remaining static.

### **Abuse Liability, Dependence, and Withdrawal**

There are a number of reports of ketamine dependence in the literature,<sup>56,61,84,99</sup> but no large-scale studies, and so the incidence of ketamine dependence is largely unknown.<sup>86</sup> 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.<sup>89</sup> 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.<sup>123</sup> There is conflicting evidence of the existence of a "withdrawal syndrome" after cessation of ketamine use.<sup>86</sup> 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.<sup>86</sup> 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.<sup>20,76</sup> However, a specific ketamine withdrawal syndrome has not yet been described.<sup>86</sup>

Please refer to the Investigator's Brochure for a summary of the adverse events reported in ketamine and esketamine studies.<sup>60</sup>

### **1.1.3. Marketing Experience**

No intranasal formulation of esketamine is currently marketed.

## **1.2. Active Comparators**

Subjects will be assigned to receive 1 of 4 commercially available oral antidepressant medications from 2 different classes of antidepressant medications, selective serotonin reuptake inhibitors (SSRIs: escitalopram or sertraline), or serotonin and norepinephrine reuptake inhibitors (SNRIs: duloxetine or venlafaxine extended release [XR]). The oral antidepressant medication will be started on Day 1 of the open-label induction phase and continued in the optimization, maintenance, and follow-up (if clinically indicated) phases.

The indications and safety information provided below for each oral antidepressant are from the United States (US) prescribing information.<sup>32,32,75,132</sup> For further information, please refer to the appropriate package insert applicable to the local country in which the study is being conducted.

In the US, all 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.

### **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.

The starting dosage for MDD in the US prescribing information 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 20 mg/day dose.

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

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

of stopping escitalopram]); concomitant use with pimozide; and known hypersensitivity to escitalopram or citalopram or any of the inactive ingredients.

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

### **1.2.1.2. Sertraline**

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

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

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

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

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

## **1.2.2. Serotonin and Norepinephrine Reuptake Inhibitors**

### **1.2.2.1. Duloxetine**

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

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

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

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

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

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

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

#### **1.2.2.2. Venlafaxine Extended-release**

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

The starting dosage for MDD in US prescribing information is 75 mg/day (in some patients, 37.5 mg/day for 4 to 7 days), with a dosage increase by 75 mg/day at intervals of 4 days or longer, and a maximum dosage of 225 mg/day. Dosage reductions are recommended for hepatic impairment (including mild) and renal impairment.

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

In adult subjects with MDD, adverse events in short-term studies that occurred in at least 5% of the subjects receiving venlafaxine 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  $\geq 15$ -mm Hg increase in supine diastolic blood pressure, with blood pressure  $\geq 105$  mm Hg, compared with 0.9% of subjects in the placebo groups. Similarly, 1% of subjects in the venlafaxine XR-treated groups experienced a  $\geq 20$ -mm Hg increase in supine systolic blood pressure, with blood pressure  $\geq 180$  mm Hg, 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 how to sustain the antidepressant effect over the long term. No systematic studies have yet described sustaining the response to ketamine. The only available 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.<sup>7</sup> On average, the duration of response from a single IV dose of ketamine is approximately 5 to 7 days.<sup>146</sup> 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)<sup>90</sup> or a mean of 16 days (range, 7 to 28 days).<sup>122</sup>

In the abovementioned Study KETIVTRD2002, in the group that received IV ketamine twice per week for 4 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.<sup>18,19</sup>

A number of studies have assessed maintenance of the benefit from ECT with continuation of pharmacotherapy. The relapse rates in these studies are typically around 50% within 6 months, despite vigorous use of pharmacotherapy.<sup>62</sup> The relapse rates correlate with the degree of treatment resistance. Patients with TRD are less likely to achieve remission and, when they do, are much more prone to relapse.<sup>45</sup> Relapse rates with placebo after ECT are extremely high: remission may be lost as early as the first few weeks after the acute course,<sup>63</sup> ~65% in 3 months,<sup>73</sup> and 84% at 6 months.<sup>114</sup> Relapse rates after ECT are reduced with pharmacotherapy

alone: 60% at 6 months on nortriptyline alone and 39% at 6 months on nortriptyline plus lithium.<sup>114</sup> Most relapses occurred within 5 weeks of completion of ECT.<sup>114</sup> The role of pharmacotherapy in more treatment resistant subjects is also questioned.<sup>115</sup> Consequently, clinicians have adopted maintenance ECT to prolong remission. Recent studies have demonstrated that pharmacotherapy plus continued maintenance ECT is significantly more effective at preventing relapse than pharmacotherapy alone following induction of antidepressant response with a course of ECT.<sup>94,143</sup> The frequency of maintenance ECT is challenging to determine. A fixed schedule is considered suboptimal due to the large inter-patient variability. Therefore, one study developed a strategy based on symptom severity to guide the frequency of ECT treatment, aiming to reduce the number of relapses within 1 month after completion of ECT.<sup>77</sup> Back-testing of this algorithm would have prevented nearly 100% of the subjects from relapsing.<sup>77</sup>

This study is modeled after the ECT literature to investigate whether repeated use of intranasal esketamine plus an oral antidepressant can sustain the antidepressant effects of an induction course of intranasal esketamine plus an oral antidepressant in subjects with TRD, or whether the oral antidepressant alone is sufficient to maintain the antidepressant effect. As outlined below, the sponsor designed this study using an individualized approach, with the frequency of intranasal esketamine treatment sessions driven by the severity of depressive symptoms.

## **2. OBJECTIVES AND HYPOTHESIS**

### **2.1. Objectives**

#### **Primary Objective**

The primary objective of this study is to assess the efficacy of intranasal esketamine plus an oral antidepressant compared with an oral antidepressant (active comparator) plus intranasal placebo in delaying relapse of depressive symptoms in subjects with TRD who are in stable remission (see Section 3.1.2, Definitions of Terms) after an induction and optimization course of intranasal esketamine plus an oral antidepressant.

#### **Secondary Objectives**

- To assess the efficacy of intranasal esketamine plus an oral antidepressant compared with an oral antidepressant (active comparator) plus intranasal placebo in delaying relapse of depressive symptoms in subjects with TRD with stable response (but who are not in stable remission) (see Section 3.1.2, Definitions of Terms) after an induction and optimization course of intranasal esketamine plus an oral antidepressant
- To assess the effect of intranasal esketamine plus an oral antidepressant compared with an oral antidepressant (active comparator) plus intranasal placebo on:
  - Depressive symptoms
  - Overall severity of depressive illness
  - Functional impairment and associated disability
  - Anxiety symptoms



- Health-related quality of life and health status
- To investigate the safety and tolerability of intranasal esketamine plus an oral antidepressant compared with an oral antidepressant (active comparator) plus intranasal placebo in subjects with TRD, with special attention to the following:
  - Treatment-emergent adverse events (TEAEs), including AEs of special interest
  - Local nasal tolerability
  - Effects on heart rate, blood pressure, respiratory rate, and blood oxygen saturation
  - Effects on alertness and sedation
  - Potential psychosis-like symptoms
  - Dissociative symptoms
  - Potential effects on cognitive function
  - Potential effects on suicidal ideation/behavior
  - Potential treatment-emergent symptoms of cystitis and/or lower urinary tract symptoms
  - Potential withdrawal and/or rebound symptoms following cessation of intranasal esketamine treatment
  - Potential effects on sense of smell

### **Exploratory Objective**

- To assess the potential relationship of biomarkers with response/non-response to intranasal esketamine plus an oral antidepressant or to an oral antidepressant plus intranasal placebo in adult subjects with TRD.
- To assess medical resource utilization.

## **2.2. Hypothesis**

The hypothesis for this study is that intranasal esketamine plus an oral antidepressant is more effective than treatment with an oral antidepressant plus intranasal placebo in delaying relapse of depressive symptoms in subjects with TRD in stable remission.

## **3. STUDY DESIGN AND RATIONALE**

### **3.1. Overview of Study Design**

This is a randomized, double-blind, parallel-group, active-controlled, multicenter study to evaluate the efficacy, safety, and tolerability of intranasal esketamine plus an oral antidepressant compared with an oral antidepressant (active comparator) plus intranasal placebo in delaying relapse of depressive symptoms in adult men and women with TRD who are in stable remission after an induction and optimization course with intranasal esketamine plus an oral antidepressant.

Approximately 211 subjects in stable remission (see Section 3.1.2, Definition of Terms) at the end of the optimization after treatment with intranasal esketamine plus an oral antidepressant will be randomized in a 1:1 ratio to either continue intranasal esketamine (same dose) or be

switched to intranasal placebo; all subjects will continue the same oral antidepressant, at the same dose.

An Independent Data Monitoring Committee (IDMC) will be commissioned for this study (see Section 11.8).

### **3.1.1. Study Phases**

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 (ESKETINTRD3001 or ESKETINTRD3002) (referred to as transferred-entry subjects).

The study has 5 phases:

- A 4-week screening/prospective observational phase, with an optional taper of up to 3 weeks for oral antidepressant medication(s) (direct-entry subjects only)
- A 4-week open-label induction phase (direct-entry subjects only)
- A 12-week optimization phase (open-label for direct-entry subjects and double-blind for transferred-entry subjects)
- A maintenance phase (variable duration)
- A 2-week follow-up phase

The maximum duration of a subject's participation will be variable, depending on whether he or she enters the study directly or is transferred from one of the double-blind short-term studies, and whether he or she meets phase-specific criteria (eg, meets criteria for response at the end of the induction phase, is in stable remission/response at the end of the optimization phase, and when and if he or she relapses in the maintenance phase). Direct-entry subjects may participate in up to 5 phases and transferred-entry subjects may participate in up to 3 phases.

The study will be stopped once 84 relapses (in the subjects with stable remission) occur during the maintenance phase, or earlier based on the results of the interim analysis for efficacy. At the time the study is stopped, subjects in the induction phase will be able to complete the Induction phase. Those subjects who are responders after completing an Early Withdrawal Visit may proceed to the 54135419TRD3008 study without completing the follow up phase. Those who are not responders will have an Early Withdrawal Visit and proceed directly to the follow-up phase. Subjects who are in the optimization or maintenance phase at the time the study is terminated will have an Early Withdrawal Visit/End of Maintenance Visit conducted and proceed directly to the follow-up phase.

#### **Screening/Prospective Observational Phase**

Direct-entry subjects will participate in this phase, which prospectively assesses treatment response to the subject's current oral antidepressant treatment regimen.

At the start of the screening/prospective observational phase, the subject must have had documented non-response to at least 1 antidepressant treatment (based on MGH-ATRQ) in the

current episode of depression, and the subject is taking a different oral antidepressant treatment (listed on the MGH-ATRQ) for at least the previous 2 weeks at or above the minimum therapeutic dose. This antidepressant treatment, as well as any other ongoing medications being taken for depression at screening (including adjunctive/augmentation therapies), will continue from the start of Week 1 through the end of Week 4 of the screening/prospective observational phase. Dose adjustment is permitted per clinical judgment, but the oral antidepressant treatment is to remain at or above the minimum therapeutic dose (per the MGH-ATRQ) through the end of Week 4.

After 4 weeks, subjects who are non-responders to their current oral antidepressant treatment may be eligible to proceed to the open-label induction phase. Non-response at the end of the screening/prospective observational phase is defined as  $\leq 25\%$  improvement in the MADRS total score from Week 1 to Week 4 and a MADRS total score of  $\geq 28$  on Week 2 and Week 4.

Eligible subjects who are entering the open-label induction phase will discontinue all of their current antidepressant treatment(s), including adjunctive/augmentation therapies. Of note, subjects taking benzodiazepines (at dosages equal to or less than the equivalent of 6 mg/day of lorazepam) and/or permitted non-benzodiazepine sleep medications (eg, zolpidem, zaleplon) during the screening/prospective observational phase can continue these medications. No dose increases beyond the equivalent of 6 mg/day lorazepam, or new benzodiazepine are permitted during the screening/prospective observational phase. If clinically indicated, a subject's current antidepressant treatment(s) may be tapered and discontinued over an additional, optional period of up to 3 weeks per the local prescribing information or clinical judgment.

### **Open-label Induction Phase**

Eligible direct-entry subjects will receive intranasal esketamine (flexible dose: 56 mg or 84 mg) treatment sessions twice weekly for 4 weeks. In addition, all subjects will initiate a new, open-label oral antidepressant on Day 1 that will be taken daily for the duration of the induction phase. The assigned oral antidepressant will be 1 of 4 oral antidepressant medications (duloxetine, escitalopram, sertraline, or venlafaxine extended release [XR]), that the subject has not previously had a non-response to in the current depressive episode, has not been previously intolerant to (lifetime), and is available in the participating country.

Subjects 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/prospective observational phase can continue these medications during the induction phase. No dose increases beyond the equivalent of 6 mg/day of lorazepam, or new benzodiazepine medications are permitted during the induction phase, with the exception of the use of permitted benzodiazepine rescue medication (post-dose on the dosing day only).

Subjects will self-administer (under clinical supervision) open-label intranasal esketamine during a scheduled treatment session twice a week for 4 weeks, with titration to a dose individualized per efficacy and tolerability (either 56 or 84 mg). At the end of the induction phase, subjects who are responders (defined as  $\geq 50\%$  reduction in the MADRS total score from baseline [Day 1 prior to the first intranasal dose] to the end of the 4-week open-label induction phase) may be eligible to proceed to the optimization phase. All subjects who do not proceed to the optimization phase

will have an Early Withdrawal Visit conducted and proceed to the follow-up phase (see Section 3.1.2).

At the time the study is stopped, subjects in the induction phase will be able to complete the phase. Those who are responders, after completing an Early Withdrawal Visit, may proceed to the 54135419TRD3008 study without completing the follow up phase. Those who are not responders will have an Early Withdrawal Visit conducted and proceed directly to the follow-up phase.

### **Optimization Phase**

Eligible direct-entry subjects from the open-label induction phase and transferred-entry subjects from the 2 double-blind short-term studies (ESKETINTRD3001 and ESKETINTRD3002) will participate in this 12-week phase.

The intranasal treatment session frequency will be reduced from that in the induction phase (twice weekly) to weekly for the first 4 weeks of this phase. After the first 4 weeks, the frequency of intranasal treatment sessions will be individualized to either once weekly or once every other week based on the severity of depressive symptoms, as assessed by the MADRS total score. The dose of intranasal esketamine will remain unchanged from the dose at the end of the induction phase. All subjects will continue taking the same oral antidepressant treatment (at the same dosage) that was initiated during the induction phase.

At the end of the optimization phase, subjects in stable remission and those with stable response (but who are not in stable remission) may be eligible to continue into the maintenance phase; all other subjects will have an Early Withdrawal Visit conducted and proceed to the follow-up phase.

For subjects in stable remission and those with stable response at the end of this phase, the last visit of the optimization phase (Visit 3.13; Week 16) also serves as the baseline visit (Visit 4.1; Week 16) of the maintenance phase. Subjects eligible for the maintenance phase will be randomized and receive their first double-blind intranasal treatment session of the maintenance phase at this visit.

At the time the study is stopped, subjects in the optimization phase will have an Early Withdrawal Visit conducted and proceed directly to the follow-up phase.

### **Maintenance Phase**

On Day 1 of this phase:

- Approximately 211 subjects in stable remission at the end of the optimization phase (after treatment with intranasal esketamine plus an oral antidepressant) will be randomized in a 1:1 ratio to either continue with intranasal esketamine (same dose) and the same oral antidepressant or to continue with the same oral antidepressant (active comparator) but switch to intranasal placebo. The primary efficacy analysis will be performed for these subjects only.

- Additionally, subjects with stable response (but who are not in stable remission) at the end of the optimization phase (after treatment with intranasal esketamine plus an oral antidepressant) will be randomized in a 1:1 ratio (using a separate randomization list) to either continue with intranasal esketamine (same dose) and the same oral antidepressant or to continue with the same oral antidepressant (active comparator) but switch to intranasal placebo (for a secondary efficacy analysis only).
- Transferred-entry subjects who achieve stable remission or stable response at the end of the optimization phase after treatment with an oral antidepressant plus intranasal placebo will continue to receive the same treatment in order to maintain the blinding for the ongoing short-term studies. These subjects will not be included in the efficacy analyses, but will be included in safety analyses.

The frequency of intranasal treatment sessions will be further individualized during the maintenance phase to once weekly or once every other week based on the severity of depressive symptoms, as assessed by the MADRS total score. Subjects will only be permitted to switch from weekly to every other weekly dosing a total of 3 times. After this time, if a given subject is unable to sustain improvement on every other week dosing they will remain on a weekly dosing regimen for the duration of this phase.

This phase will have a variable duration, continuing until 84 relapses occur in the subjects with stable remission, or earlier based on interim analysis results.

Subjects who meet the relapse criteria and subjects who remain relapse-free at study termination will have an End of Maintenance Phase Visit conducted and may proceed to the follow-up phase. If clinically indicated, subjects who have met relapse criteria after completing the end of maintenance visit may proceed to the open-label safety extension study, 54135419TRD3008, without completing the follow up phase. Subjects who are participating in the maintenance phase at the time the study is stopped will have an Early Withdrawal Visit conducted and proceed directly to 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. For those subjects who relapse in the Maintenance phase, if clinically indicated based on investigator's judgment, after completing the end of maintenance visit, the subject may proceed to the open-label safety extension study, 54135419TRD3008, without completing the follow up phase. Similarly, when the study is stopped, subjects in the Induction phase who are responders, after completing the early withdrawal visit, may proceed to the 54135419TRD3008 study, without completing the follow up phase.

Follow-up visits will be performed at 1 and 2 weeks after the last clinic visit.

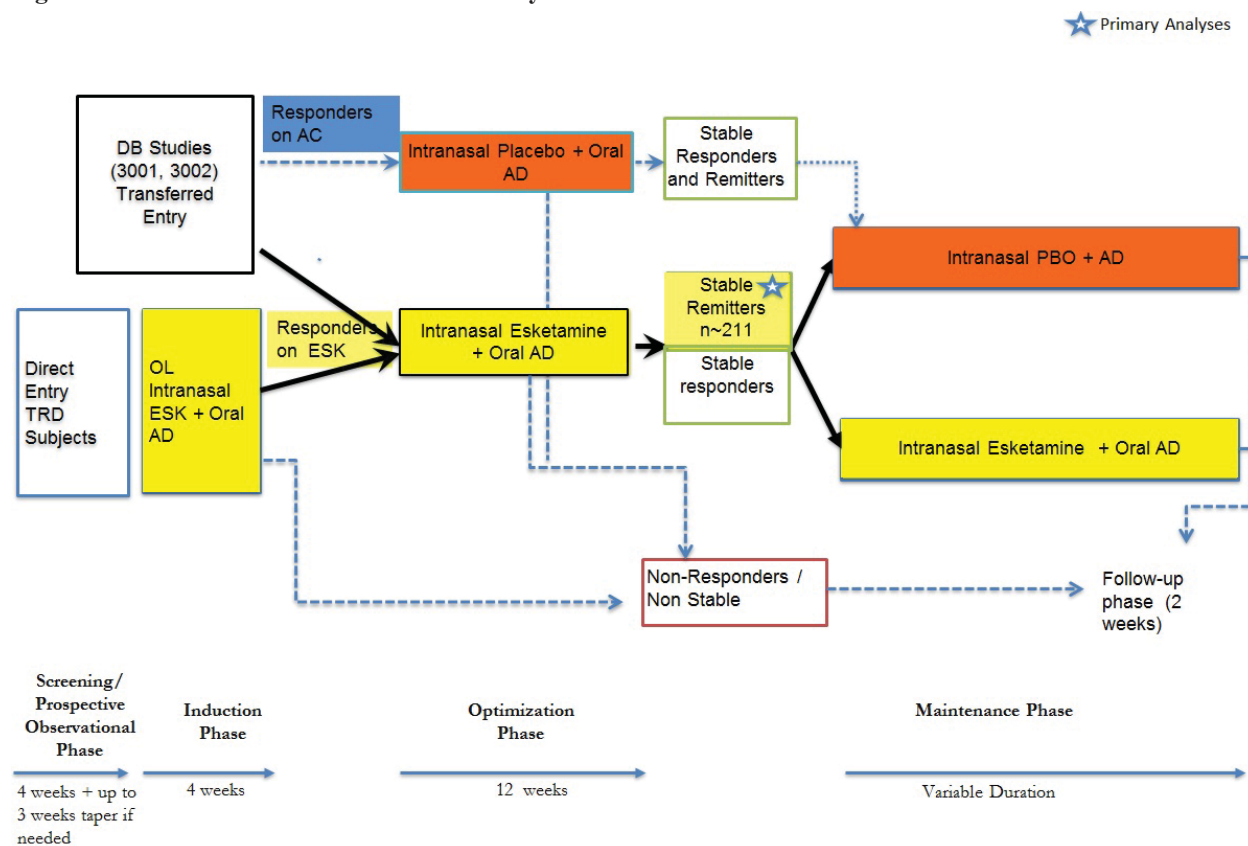
At the start of the follow-up phase, further clinical/standard of care for the treatment of depression will be arranged by the study investigator and/or the subject's treating physician. There will be no intranasal treatment administered during this phase. Subjects will be provided with an additional 2-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, the oral antidepressant should be continued during the 2-week 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 ESKETINTRD3003 study. Please refer to the 54135419TRD3008 protocol for full details of potential pathways for entry.

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

**Figure 1: Schematic Overview of the Study**



AC = active comparator; AD = antidepressant; DB = double-blind; ESK = esketamine; OL = open-label; PBO = placebo. TRD = treatment-resistant depression.

The study will end when 84 relapses are reached. An interim analysis will be performed at 30 relapses.

### 3.1.2. Definitions of Terms

#### Open-label Induction Phase

- Response:  $\geq 50\%$  reduction in the MADRS total score from baseline (Day 1 prior to the first intranasal dose) to the end of the 4-week open-label induction phase

#### Optimization Phase

- Stable remission:

- MADRS total score  $\leq 12$  for at least 3 of the last 4 weeks of the optimization phase, but one excursion of a MADRS total score  $> 12$  or one missing MADRS assessment is permitted at Optimization week 13 or 14 only. The MADRS total score at weeks 15 and 16 must be  $\leq 12$ .
- Stable response:  $\geq 50\%$  reduction in the MADRS total score from baseline (Day 1 of induction phase; pre-randomization/prior to the first intranasal dose) in each of the last 2 weeks of the optimization phase, but does not meet criteria for stable remission. Note: For transferred-entry subjects, Day 1 of the open-label induction phase will take place in ESKETINTRD3001 or ESKETINTRD3002.

### **Maintenance Phase**

Relapse is defined as any of the following:

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

## **3.2. Study Design Rationale**

### **3.2.1. Study Population**

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 (ESKETINTRD3001 or ESKETINTRD3002) (referred to as transferred-entry subjects). Both patient populations are considered similar as both have met the same rigorous criteria for TRD, including prospective confirmation of non-response in the screening/prospective observational phase prior to the 4-week induction phase.

#### **Direct-entry Subjects**

The study population will include adult men and women, therefore the age range of 18 (or older if the minimum legal age of consent in the country in which the study is taking place is  $> 18$ ) to 64 years of age (inclusive) is considered appropriate.

Subjects will meet DSM-5 diagnostic criteria for single-episode MDD (if single episode, duration of episode must be  $\geq 2$  years) or recurrent MDD, without psychotic features, based upon clinical assessment, and confirmed by the Mini. At the start of the screening/prospective observational phase, subjects must have an Inventory of Depressive Symptomatology-Clinician rated, 30-item (IDS-C<sub>30</sub>) total score of  $\geq 34$ , which corresponds to moderate to severe depression.

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

In addition, at the start of the screening/prospective observational phase, the subject is taking a different oral antidepressant treatment (on the MGH-ATRQ) for at least the previous 2 weeks at or above the minimum therapeutic dose. This antidepressant treatment, as well as any other ongoing medications being taken for depression at screening (including adjunctive/ augmentation therapies), will continue from the start of Week 1 through the end of Week 4 of the screening/prospective observational phase. Dose adjustment is permitted per clinical judgment, but the oral antidepressant treatment is to remain at or above the minimum therapeutic dose (per the MGH-ATRQ) through the end of Week 4.

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

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

### **Transferred-entry Subjects**

The same study population (ie, same inclusion and exclusion criteria) will be enrolled into the 2 short-term studies (ESKETINTRD3001 and ESKETINTRD3002). The transferred-entry subjects in this study are subjects who complete the double-blind induction phase and have demonstrated response at the end of this phase in 1 of the short-term studies.



### **3.2.2. Study Phases**

#### **Screening/Prospective Observational Phase**

The 4-week duration of the screening/prospective observational phase for direct-entry subjects will provide adequate time to assess subject eligibility according to the study entry criteria, while also allowing for a prospective confirmation of non-response to the current antidepressant treatment(s) that is continued for the duration of this phase. This method of recruitment allows subjects to enter the study on a variety of different antidepressant medications that they had been taking, which mimics clinical practice and yet allows for prospective demonstration of treatment resistance to the current antidepressant treatment. Even though there is no depression rating score available at the start of the antidepressant treatment, the subjects at screening will have to meet criteria for moderate to severe depression. After 4 weeks of prospective observation of continuation of the current antidepressant treatment and assessment of treatment response, subjects who meet the predefined non-response criteria ( $\leq 25\%$  improvement in the MADRS total score from Week 1 to Week 4 and a MADRS total score of  $\geq 28$  on Week 2 and Week 4) and are eligible to enter the open-label induction phase will discontinue all of the current antidepressant treatments, including adjunctive/augmentation therapies, prior to starting the next phase.

Non-responders that are eligible to enter the open-label induction phase are permitted to have up to 3 additional weeks to taper and discontinue the all current medication(s) being used for depression prior to entry into the open-label induction phase, per the local prescribing information or clinical judgment (eg, tolerability concerns). The duration of up to 3 weeks is expected to provide an adequate amount of time for taper and discontinuation.

#### **Open-label Induction Phase**

The 4-week duration of the open-label induction phase for direct-entry subjects was selected based upon the onset of effect of typical antidepressants, with a 4-week duration considered to be sufficiently long to show the antidepressant effects of the active comparator. Preliminary findings from an analysis of antidepressants were presented recently, as well as a completed analysis of 24 recent MDD studies that compared study durations of 4, 6, and 8 weeks. Exploratory analyses were conducted for each of the study durations using mixed-model repeated measures (MMRM), but excluding data beyond the duration of interest. These preliminary findings suggest that it is plausible to shorten study duration down to 4 weeks.<sup>68,142</sup> Similarly, it has been demonstrated that improvement of  $\geq 25\%$  on the Hamilton Depression Rating Scale on Day 14 was a significant cutoff value to predict response after 5 weeks of treatment, and a lack of improvement (ie,  $< 25\%$ ) by Day 14 predicted poor response after 5 weeks of treatment<sup>96</sup>. All together, these results suggest that a 4-week duration should be adequate to assess antidepressant response.

#### **Optimization Phase**

The fixed duration of 12 weeks for the optimization 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). For the primary analysis, a subject must be in stable remission (see full definition, section 3.1.2) to enter the maintenance phase. This duration of the optimization phase is critical to the time to relapse. Shorter duration of stabilization (referred to as the optimization phase in this study) is associated with faster relapses. A recent meta-analysis showed that beyond 16 weeks, the effects of duration of stabilization did not appear to impact relapses.<sup>3</sup>

Subjects with stable response ( $\geq 50\%$  reduction in the MADRS total score from baseline [Day 1 of induction phase; pre-randomization/prior to the first intranasal dose]) in each of the last 2 weeks of the optimization phase who do not meet criteria for stable remission, will also enter the maintenance phase, but will not be part of the primary analysis. Although not part of the primary analysis, this subject population is of clinical interest. A 2-week duration to confirm stable response is considered appropriate to ascertain the subject's status prior to the next treatment phase.

### **Maintenance Phase**

The duration of the maintenance phase is variable, and the phase will continue until the required number of relapses is achieved or until the study is recommended to be stopped based on the interim analysis results. Assumptions regarding the duration of time to relapse are provided in Section 1.3, Overall Rationale for the Study. While all subjects will enter this phase at the same frequency of intranasal treatment sessions that they had in the optimization phase, the frequency of intranasal treatment sessions will continue to be individualized to once weekly or once every other week based on the severity of depression, as assessed by the MADRS total score, during this phase; however, there will be a limit (ie, no more than 3 times) on the number of times a subject can be switched from weekly to every other week. This is considered a sufficient number of times to evaluate if a subject can sustain antidepressant efficacy with every -other -week dosing.

### **Follow-up Phase**

The 2-week duration of the follow-up phase will allow sufficient time to assess safety and tolerability after cessation of intranasal dosing, including potential withdrawal symptoms. At the start of 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 Randomization**

Blinded intranasal treatment will be used in the optimization phase (for transferred-entry subjects) to avoid unblinding the short-term studies at the individual level, and in the maintenance phase (for all subjects) to reduce potential bias during data collection and evaluation of clinical endpoints.

Randomization will be used in the maintenance phase for subjects in stable remission (primary analysis) and subjects with stable response but who are not in stable remission (secondary analysis) to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of

statistical comparisons across treatment groups. The randomizations will be stratified by country with an allocation ratio of 1:1 to intranasal placebo or intranasal esketamine. The stratification is aimed at balancing treatment groups across country.

Transferred-entry subjects who achieve stable remission or stable response after treatment with intranasal placebo plus an oral antidepressant will continue to receive the same treatment in order to maintain the blinding for the ongoing short-term studies. These subjects will not be randomized during the maintenance phase.

### **3.2.4. Treatment Groups and Dose Selection**

#### **3.2.4.1. Intranasal Study Drug**

##### **Open-label Induction Phase**

All direct-entry subjects will receive intranasal esketamine during this phase. The dose selection (56 mg and 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, and Panel A of Study ESKETINTRD2003, described above in Section 1.1.2.

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

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.

##### **Optimization Phase**

There will be no changes to the intranasal dose permitted during the optimization phase. Subjects will continue to receive the same intranasal treatment (esketamine or placebo) from the induction phase; therefore, direct-entry and transferred-entry subjects will continue to receive open-label and double-blind intranasal treatment, respectively.

The intranasal treatment session frequency will be reduced from that in the induction phase (twice weekly) to weekly for the first 4 weeks of this 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 individualization is intended to allow subjects to sustain the antidepressant response while minimizing the frequency of intranasal treatment sessions required.

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**Maintenance Phase**

Subjects in stable remission after treatment with intranasal esketamine plus an oral antidepressant will be randomized in a 1:1 ratio to either continue with intranasal esketamine (same dose) and the same oral antidepressant or to continue with the same oral antidepressant (active comparator) but switch to intranasal placebo (for the primary efficacy analysis).

Subjects with stable response (but who are not in stable remission) after treatment with intranasal esketamine plus an oral antidepressant will be randomized in a 1:1 ratio (using a separate randomization list) to either continue with intranasal esketamine (same dose) and the same oral antidepressant or to continue with the same oral antidepressant (active comparator) but switch to intranasal placebo (for secondary efficacy analysis only).

Transferred-entry subjects who achieve stable remission or stable response after treatment with intranasal placebo plus an oral antidepressant will continue to receive the same treatment in order to maintain the blinding for the ongoing short-term studies. These subjects will not be included in the efficacy analyses, but will be included in safety analyses.

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. As noted above, however, there will be a limit (ie, no more than 3 times) to the number of times the frequency can be switched from weekly to every other week. This further individualization of treatment session frequency is intended to allow subjects to sustain the antidepressant response while minimizing the frequency of intranasal treatment sessions required.

**3.2.4.2. 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 assigned to receive 1 of 4 oral antidepressant medications from 2 different classes of antidepressant treatments, an SSRI (escitalopram or sertraline) or an SNRI (duloxetine or venlafaxine XR). The assignment of the oral antidepressant will be done by the investigator based on review of the MGH-ATRQ and relevant prior antidepressant medication information.

These 2 classes were selected because they are the most commonly prescribed antidepressant classes in this population and are generally well-tolerated. The oral antidepressant treatment assigned will be one that the subject has not previously had a non-response to in the current episode, has not been previously intolerant to (lifetime), and is available in the participating country. Dosing of the oral antidepressant will begin on Day 1 of the open-label induction phase. A mandatory titration schedule is provided in [Attachment 3](#). Doses are not to exceed the maximum dose defined in the titration schedule, to ensure that the oral antidepressant is taken at an adequate dosage and duration for assessment of potential maintenance of effect. If higher doses are not tolerated, a down-titration is permitted based on clinician's judgment. However, the subject's dose should not be lower than the following minimum therapeutic doses at the end of the induction phase: sertraline (50 mg/day), venlafaxine XR (150 mg/day), escitalopram (10 mg/day), and duloxetine (60 mg/day). While subjects requiring lower doses can continue in the study and complete the induction phase, such subjects will not be eligible to participate in the optimization phase and will proceed to the follow-up phase after completion of the induction phase.

For all subjects, the same oral antidepressant treatment will be continued throughout the optimization, maintenance, and follow-up (if clinically indicated) phases.

The rationale for initiating and continuing an oral antidepressant in combination with intranasal esketamine treatment is provided in [Section 1.3](#), Overall Rationale for the Study.

### **3.2.5. Efficacy Measures**

#### **MADRS**

The 10-item clinician-administered MADRS was designed to be used in subjects with MDD to measure the overall severity of depressive symptoms.<sup>83</sup> The MADRS scale has been selected as an efficacy measure for this study because it is validated, reliable, and acceptable to regulatory health authorities as a primary scale to determine efficacy in major depression.

Response is defined as a  $\geq 50\%$  reduction in the initial symptom score, and remission is defined as a total score of  $\leq 12$ . At the end of the open-label induction phase, subjects who meet this criterion for response (ie,  $\geq 50\%$  reduction in the initial symptom score) will be considered responders and are eligible to continue into the optimization phase.

During the optimization phase, the MADRS will be used to measure severity of depressive symptoms to individualize intranasal treatment session frequency as well as to determine stable remission and response for eligibility to enter the maintenance phase.

During the maintenance phase, the primary efficacy evaluation will include the MADRS total score as it pertains to relapses. A MADRS total score  $\geq 22$  for 2 consecutive assessments separated by 5 to 15 days (the date of the second MADRS assessment in the 2-week period will be used for the date of relapse) is a relapse criteria in this study. In addition, it will continue to be used to measure severity of depressive symptoms to further individualize intranasal treatment session frequency.

**PHQ-9**

- The PHQ-9 will be used as a patient-reported measure of depressive symptomatology.<sup>128</sup> Please refer to Section 9.2.1.3 for additional information regarding PHQ-9.

**SDS**

- The Sheehan Disability Scale (SDS) is patient-reported outcome measure included as an assessment of functional impairment and associated disability.<sup>74,121</sup> Please refer to Section 9.2.1.6 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.<sup>50</sup> Please refer to Section 9.2.1.2 for additional information regarding CGI-S.

**GAD-7**

- The GAD-7 is included as a brief and validated measure of overall anxiety.<sup>127</sup> Please refer to Section 9.2.1.4 for additional information regarding GAD-7.

**EQ-5D-5L**

- The EQ-5D-5L is included as a standardized patient-completed instrument for use as a measure of health-related quality of life and health status.<sup>41,42</sup> Please refer to Section 9.2.1.5 for additional information regarding EQ-5D-5L.

**3.2.6. 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 conducted as per the Time and Event Schedule to assess for any treatment-emergent nasal tolerability symptoms.

The 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.<sup>55</sup> 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 determined to have a diagnosis of ulcerative cystitis, the subject must be discontinued from the study and followed up with appropriate medical care.

The effect of intranasal esketamine on cognition over the 4-week open-label induction phase will be assessed using the computerized cognitive battery and Hopkins Verbal Learning Test-Revised (HVLT-R). The cognitive battery will provide assessment of multiple cognitive domains, including attention, visual learning and memory, and executive function. The HVLT-R is a measure of verbal learning and memory.

The University of Pennsylvania Smell Identification Test (UPSIT) and Smell Threshold Test will be performed to assess any treatment-emergent effects on the sense of smell.

On all intranasal dosing days, subjects must remain at the site until study procedures have been completed and the subject is ready for discharge. Subjects should be accompanied by a responsible adult when released from the clinical site. Subjects must not drive a car or work with machines for 24 hours after receiving intranasal study drug.

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

### **3.2.7. Biomarker, Pharmacogenomic (DNA), and Expression (RNA) Evaluations**

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

Genetic variation can be an important contributory factor to interindividual differences in drug distribution and response and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain interindividual variability in clinical outcomes

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

Protein, metabolite, and RNA biomarkers may aid in the elucidation of the mechanism of action of the different treatment groups 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 the different treatment groups, and aid in evaluating the drug-clinical response relationship.

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

### **3.2.8. Other Assessments**

#### **Patient Adherence Questionnaire**

During the screening/prospective observational phase, the self-reported PAQ will be used to assess how often the subject has taken, and whether he or she has made any changes to, his or her antidepressant treatment regimen in the last 2 weeks. This assessment will provide confirmation of medication compliance when evaluating antidepressant treatment response. Subjects who report missing  $\geq 4$  days of antidepressant medication during a 2-week recall period will be discontinued because of inadequate adherence.

### **3.2.9. Medical Resource Utilization Data Collection**

Delay of relapse and maintenance of response/remission may result in lower utilization of healthcare services (such as outpatient visits, emergency room visits, or hospitalization) associated with relapse of symptoms of depression; therefore, comparison will be done across treatment groups. The Healthcare Resource Use Questionnaire (HRUQ) will be used to assess medical resource utilization. It includes information regarding utilization of healthcare services over the course of the study, including the type and duration of services, enabling changes in level and quantity of services to be considered as a variable in economic models.



## 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.

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

The sponsor will evaluate and approve/reject requests to rescreen an individual 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. At the time of signing the informed consent form (ICF) the subject, a man or woman, must be 18 (or older if the minimum legal age of consent in the country in which the study is taking place is >18) to 64 years of age, inclusive.
2. At the start of the screening/prospective observational phase, each subject must meet Diagnostic and Statistical Manual of Mental Disorders - fifth edition (DSM-5) diagnostic criteria for single-episode MDD (if single-episode MDD, the duration must be  $\geq 2$  years) or recurrent MDD, without psychotic features, based on clinical assessment and confirmed by the Mini International Neuropsychiatric Interview (MINI).
3. Criterion modified per Amendment 2:
  - 3.1. Criterion modified per Amendment 3:
  - 3.2. At the start of the screening/prospective observational phase, subject must have had non-response ( $\leq 25\%$  improvement) to  $\geq 1$  but  $\leq 5$  (if current episode is >2 years, upper limit is applicable to only the last 2 years) oral antidepressant treatments in the current episode of depression, assessed using the MGH-ATRQ and confirmed by documented records (eg, medical/pharmacy/prescription records or a letter from a treating physician, etc.). In addition, the subject is taking a different oral antidepressant treatment (on the MGH-ATRQ) for at least the previous 2 weeks at or above the minimum therapeutic dose.
    - For specific tricyclic antidepressants which are ongoing and being taken at a dose below the MGH-ATRQ minimum therapeutic dose, a blood level that is within the therapeutic (antidepressant) range, is acceptable to establish the adequacy of the antidepressant treatment.
    - Subjects must be adherent to the continued oral antidepressant treatment medication(s) through the screening/prospective observational phase, as documented on the PAQ. Missing  $\geq 4$  days of antidepressant medication in the prior 2-week period will be considered as inadequate adherence.

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- Subjects who are non-responders to their current oral antidepressant medication(s) from the screening/prospective observational phase (as assessed by independent, remote raters) may be eligible to continue to the open-label induction phase. Non-response at the end of the screening/prospective observational phase is defined as  $\leq 25\%$  improvement in the MADRS total score from Week 1 to Week 4 and a MADRS total score of  $\geq 28$  on Week 2 and Week 4.
4. At the start of the screening/prospective observational phase, each subject must have an Inventory of Depressive Symptomatology, Clinician-rated, 30-item (IDS-C<sub>30</sub>) total score of  $\geq 34$ .
  5. Criterion modified per Amendment 2:
    - 5.1. The subject's current major depressive episode, depression symptom severity (Week 1 MADRS total score  $\geq 28$  required), and antidepressant treatment response in the current depressive episode, must be confirmed using the Site Independent Qualification Assessment.
  6. Subject must be medically stable on the basis of physical examination, medical history, vital signs (including blood pressure), pulse oximetry, and 12-lead ECG performed in the screening/prospective observational phase. If there are any abnormalities that are not specified in the inclusion and exclusion criteria, their clinical significance must be determined by the investigator and recorded in the subject's source documents and initialed by the investigator.
  7. Criterion modified per Amendment 2:
    - 7.1. Criterion modified per Amendment 3:
    - 7.2 Subject must be medically stable on the basis of clinical laboratory tests performed in the screening/prospective observational phase. If the results of the serum chemistry panel, hematology, or urinalysis are outside the normal reference ranges, the subject may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for the population under study. This determination must be recorded in the subject's source documents and initialed by the investigator.
      - Subjects with a pre-existing history of thyroid disease/disorder who are treated with thyroid hormones must be on a stable dosage for 3 months prior to the start of the screening/prospective observational phase.
      - For any subject (regardless of thyroid history), if the thyroid-stimulating hormone (TSH) value is out of range, a free thyroxine (FT4) will be conducted. If the FT4 value is abnormal and considered to be clinically significant (after discussion with the medical monitor), the subject is not eligible.
  8. Subject must be comfortable with self-administration of intranasal medication and be able to follow the intranasal administration instructions provided.
  9. Criterion modified per Amendment 2:
    - 9.1. Criterion modified per Amendment 3:
    - 9.2. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

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) will 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, 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.

## 10. Criterion modified per Amendment 2:

10.1. A woman of childbearing potential must have a negative highly sensitive serum ( $\beta$ -human chorionic gonadotropin [ $\beta$ -hCG]) at the start of the screening/prospective observational phase and a negative urine pregnancy test must be obtained before the first dose of study drug on Day 1 of the open-label induction phase prior to randomization.

11. Criterion modified per Amendment 2:

11.1. Criterion modified per Amendment 3:

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

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

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

#### 4.1.2. Transferred-entry Subjects

The following criteria apply to subjects who enter this study after participation in a short-term study (ESKETINTRD3001 or ESKETINTRD3002). Each potential subject must satisfy the following criteria to be enrolled in the study:

12. Criterion modified per Amendment 2:

12.1. The subject must have completed the double-blind induction phase in ESKETINTRD3001 or ESKETINTRD3002 and must have demonstrated response at the end of that phase ( $\geq 50\%$  reduction in the MADRS total score from baseline [Day 1 pre-randomization] at the end of the 4-week double-blind induction phase).

Note that the following criterion is intentionally not numbered sequentially:

15. Criterion added per Amendment 2: Transferred-entry subjects must meet the same criteria at the point of entry to this study as the direct-entry subjects at the same time point (ie, beginning of optimization phase).

#### 4.1.3. Direct-entry Subjects and Transferred-entry Subjects

The following inclusion criteria apply to both groups of subjects; ie, those entering the study directly or those who have completed a short-term study (ESKETINTRD3001 or ESKETINTRD3002):

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

14. Each subject must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and is willing to participate in the study.
15. Criterion added per Amendment 2, in Section 4.1.2.

## 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 2:
  - 1.1. Subject's depressive symptoms have previously not responded to any of the following:
    - Esketamine or ketamine in the current major depressive episode per clinical judgment, or
    - All of the oral antidepressant treatment options available in the respective country for the open-label induction phase (ie, duloxetine, escitalopram, sertraline, and venlafaxine XR) in the current major depressive episode (based on MGH-ATRQ), or
    - An adequate course of treatment with electroconvulsive therapy (ECT) in the current major depressive episode, defined as at least 7 treatments with unilateral/bilateral ECT.
2. Criterion modified per Amendment 2:
  - 2.1. Subject has received vagal nerve stimulation (VNS) or has received deep brain stimulation (DBS) in the current episode of depression.
3. Criterion modified per Amendment 2:
  - 3.1. 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.
4. Subject has homicidal ideation/intent, per the investigator's clinical judgment, or has suicidal ideation with some intent to act within 6 months prior to the start of the screening/prospective observational phase, per the investigator's clinical judgment or based on the C-SSRS, corresponding to a response of "Yes" on Item 4 (active suicidal ideation with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent) for suicidal ideation on the C-SSRS, or a history of suicidal behavior within the past year prior to the start of the screening/prospective observational phase. Subjects reporting suicidal ideation with intent to act or suicidal behavior prior to the start of the open-label induction phase should be excluded.

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5. Subject has a history of moderate or severe substance or alcohol use disorder according to DSM-5 criteria, except nicotine or caffeine, within 6 months before the start of the screening/prospective observational phase.
    - A history (lifetime) of ketamine, phencyclidine (PCP), lysergic acid diethylamide (LSD), or 3,4-methylenedioxy-methamphetamine (MDMA) hallucinogen-related use disorder is exclusionary.
  6. Subject has a current or past history of seizures (uncomplicated childhood febrile seizures with no sequelae are not exclusionary).
  7. Subject has an UPSIT total score  $\leq 18$ , indicative of anosmia, in the screening/prospective observational phase.
  8. Criterion modified per Amendment 2:
    - 8.1. Subject has one of the following cardiovascular-related conditions:
      - Cerebrovascular disease with a history of stroke or transient ischemic attack.
      - Aneurysmal vascular disease (including intracranial, thoracic, or abdominal aorta, or peripheral arterial vessels).
      - Coronary artery disease with myocardial infarction, unstable angina, or revascularization procedure (eg, coronary angioplasty or bypass graft surgery) within 12 months before the start of the screening/prospective observational phase. Subjects who have had a revascularization performed  $>12$  months prior to screening and are clinically stable and symptom-free, per investigator's clinical judgment, can be included.
      - Hemodynamically significant valvular heart disease such as mitral regurgitation, aortic stenosis, or aortic regurgitation.
      - New York Heart Association (NYHA) Class III-IV heart failure of any etiology (refer to [Attachment 2](#)).
  9. Criterion modified per Amendment 2:
    - 9.1. Subject has a history of uncontrolled hypertension despite diet, exercise, or antihypertensive therapy at the start of the screening/prospective observational 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 during screening/prospective observational phase which continues to be above this range with repeated testing during this phase. Note: On Day 1 of the open-label induction phase (prior to the first intranasal treatment session) a supine SBP  $>140$  mmHg or DBP  $>90$  mmHg is exclusionary.
      - A potential subject may have his/her current antihypertensive medication(s) adjusted during the screening/prospective observational phase and be re-evaluated to assess their blood pressure control. 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 with an arterial blood oxygen saturation (SpO<sub>2</sub>) of  $<93\%$  at the start of the screening/prospective observational phase or Day 1 of the open-label induction phase prior to the first intranasal treatment session.
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11. Criterion modified per Amendment 2:

11.1. Criterion modified per Amendment 3:

11.2. Subject has clinically significant ECG abnormalities at the start of the screening/prospective observational phase 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):  $\geq 450$  msec; if the QTcF is prolonged on the initial ECG, the average QTcF of three ECGs, recorded 4 minutes apart, must not be  $\geq 450$  msec.
- On Day 1 (predose), a QT interval corrected according to Fridericia's formula (QTcF):  $\geq 450$  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  $\geq 450$  msec.
- Evidence of 2<sup>nd</sup> and 3<sup>rd</sup> degree AV block, complete left bundle branch block (LBBB), or complete right bundle branch block (RBBB).
- Features of new ischemia.
- Arrhythmia (except premature atrial contractions [PACs] and premature ventricular contractions [PVCs]).

12. Criterion modified per Amendment 2:

12.1. Subject has a history of additional risk factors for torsades des pointes (eg, heart failure, hypokalemia, or family history of long QT syndrome).

13. Criterion modified per Amendment 2:

13.1. Subject has a history of, or symptoms and signs suggestive of, liver cirrhosis (eg, esophageal varices, ascites, and increased prothrombin time) OR alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values  $\geq 2x$  the upper limit of normal or total bilirubin  $> 1.5$  times the ULN in the screening/prospective observational phase.

- Repeat of screening test for abnormal ALT and AST is permitted once during the screening period provided per investigator discretion and provide 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/prospective observational 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 (eg, amphetamine, methylphenidate, etc.), taken for an indication other than MDD, 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/prospective observational 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. 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/prospective observational phase is not exclusionary as long as the subject does not meet the criteria for substance use disorder. A positive test for cannabinoids at the start of the screening/prospective observational phase is not exclusionary; however, a positive test result for cannabinoids predose on Day 1 of the open-label induction phase is exclusionary.

15. Criterion modified per Amendment 2:

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

16. 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.

17. Criterion modified per Amendment 2:

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

18. Criterion deleted per Amendment 2.

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

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

21. 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](#).

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



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23. Criterion modified per Amendment 2:

23.1. Subject has a score of  $\geq 5$  on the STOP-Bang questionnaire, in which case obstructive sleep apnea must be ruled out (eg, apnea-hypopnea index [AHI] must be  $< 30$ ). A subject with obstructive sleep apnea can be included if he or she is using a positive airway pressure device or other treatment/therapy that is effectively treating (ie, AHI  $< 30$ ) his or her sleep apnea.

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

25. 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). Human immunodeficiency virus (HIV) testing is not required for this study.
27. Subject has any condition or situation/circumstance for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.
28. Subject has had major surgery, (eg, requiring general anesthesia) within 12 weeks before the start of the screening/prospective observational phase, or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study.
- Note: Subjects with planned surgical procedures to be conducted under local anesthesia may participate.
29. Subject is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.

Note that the following criterion is intentionally not numbered sequentially:

31. Criterion added per Amendment 2: Subject has severe renal impairment (creatinine clearance  $< 30$  mL/min).

#### **4.2.2. Transferred-entry Subjects**

The following exclusion criterion applies to transferred-entry subjects:

30. 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.
31. Criterion added per Amendment 2, in Section [4.2.1](#).

32. Criterion added per Amendment 2: Transferred-entry subjects must meet the same criteria at the point of entry to this study as the direct-entry subjects at the same time point (ie, beginning of optimization phase).

**NOTE:** Investigators should ensure that all relevant study enrollment criteria have been met prior to Day 1 of the open-label induction phase (direct entry) or the start of the optimization phase (transferred entry). If a subject's status changes (including laboratory results or receipt of additional medical records) before the first dose of intranasal study drug is given in this study such that he or she no longer meets applicable 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 4.3 (Prestudy and Concomitant Therapy) and Attachment 1 (Prohibited Concomitant Medications With Intranasal Study Medication [Esketamine or Placebo]) for further information on prohibited therapies.
- 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/prospective observational phase can continue these medications during the induction phase. No dose increases beyond the equivalent of 6 mg/day of lorazepam, or new benzodiazepine medications are permitted during the induction phase, with the exception of the use of permitted benzodiazepine rescue medication (post-dose on the dosing day only). 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.
- A positive urine drug screen for use of phencyclidine (PCP), 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. Subjects should be accompanied by a responsible adult when released from the clinical study site. Subjects must not drive a car or work with machines for 24 hours after study drug dosing.

- Electroconvulsive therapy, DBS, transcranial magnetic stimulation (TMS), and VNS are prohibited from study entry through the end of the last treatment phase (open-label induction, optimization, or maintenance phase).
- Subjects receiving psychotherapy (including cognitive behavioral therapy [CBT]) can continue receiving psychotherapy; however, CBT must have been ongoing for the last 3 months prior to the start of the screening/prospective observational phase. With the exception of new CBT, which is prohibited, new psychotherapy is allowed during this study. Any change in existing therapy or new therapy must be documented on the concomitant therapies form.

## 5. TREATMENT ALLOCATION AND BLINDING

### Treatment Allocation and Randomization

#### *Intranasal Study Drug*

Randomization is not applicable for the screening/prospective observational phase, open-label induction phase, or optimization phase of this study.

Central randomization will be implemented in the maintenance phase of this study. At the start of the maintenance phase, subjects in stable remission after treatment with intranasal esketamine plus an oral antidepressant will be randomly assigned to 1 of 2 treatment groups (intranasal esketamine or intranasal placebo) in a 1:1 ratio based on computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by country.

Although not part of the primary analysis, at the start of this phase, subjects in stable response (but who are not in stable remission) after treatment with intranasal esketamine plus an oral antidepressant will also be randomly assigned to 1 of 2 treatment groups in a 1:1 ratio based on a separate computer-generated randomization schedule (ie, different schedule from the subjects in stable remission) prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by country.

Transferred-entry subjects who achieved stable remission or stable response after treatment with intranasal placebo plus an oral antidepressant will continue to receive the same treatment in order to maintain the blinding for the ongoing short-term studies.

The Interactive Web Response System (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching intranasal study drug kit for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject.

***Oral Antidepressant Medication***

For direct-entry subjects, after the investigator assigns the oral antidepressant treatment for the open-label induction phase, the site will enter this information into IWRS and it will be dispensed throughout the study at the time points specified in the Time and Events Schedule.

For transferred-entry subjects, the IWRS will continue to dispense the same open-label oral antidepressant used in ESKETINTRD3001 and ESKETINTRD3002 throughout the study (optimization, maintenance, and follow-up phases) of this study at the time points specified in the Time and Events Schedule.

**Blinding**

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

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

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

Under normal circumstances, the blind should not be broken until the maintenance and follow-up phases are completed and the database is finalized. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the intranasal treatment status of the subject. In such cases, the investigator may in an emergency determine the identity of the intranasal treatment by contacting the IWRS. It is recommended that the investigator contact the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date and time of the unblinding will be documented by the IWRS, and reason for the unblinding must be documented in the appropriate section of the electronic case report form (eCRF) and in the source document. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner.

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

In general, randomization codes will be disclosed fully only if the study is completed through the follow-up phase and the clinical database is closed. However, for the prespecified interim analysis, the randomization codes and, if required, the translation of randomization codes into

treatment and control groups will be disclosed to those authorized and only for those subjects included in the interim analysis. At the end of the follow-up phase, the database will be locked for the analysis and reporting of this study.

## **6. DOSAGE AND ADMINISTRATION**

### **6.1. Intranasal Study Drug**

On all intranasal treatment session days, a site staff member with training in cardiopulmonary resuscitation (eg, a basic life support course or equivalent course) that is up to date per local regulations, must be present with the subject during the intranasal treatment session and the postdose observation period. In addition, equipment for supportive ventilation and resuscitation needs to be present.

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 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 (esketamine or placebo) at treatment sessions at the study site. Intranasal treatment sessions should not take place on consecutive days.

Food will be restricted for at least 2 hours before each administration of study drug. Drinking of any fluids will be restricted for at least 30 minutes before the first nasal spray.

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

On all intranasal dosing days, subjects must remain at the clinical site until study procedures have been completed and the subject is ready for discharge. Subjects should be accompanied by a responsible adult when released from the clinical 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:**

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

- If subsequent to fulfilling the inclusion and exclusion criteria on Day 1 (ie, applicable for all other intranasal treatment session days after Day 1), a subject's pre-dose systolic blood pressure (SBP) is >140 mmHg and/or diastolic blood pressure (DBP) is >90 mmHg, it is recommended to repeat the blood pressure measurement after the subject rests in sitting or recumbent position. If after rest and repeated measurements, pre-dose SBP is >140 mmHg

and/or DBP is  $>90$  mmHg, then dosing should be postponed and the subject scheduled to return on the following day or within the given visit window. If the blood pressure elevation still persists on the next visit, the subject will be scheduled for a consultation by cardiologist, other specialist, or primary care physician, prior to further dosing.

- If at any postdose time point on the dosing day, the SBP is  $\geq 180$  mmHg but  $< 200$  mmHg and/or the DBP is  $\geq 110$  mmHg but  $< 120$  mmHg, further intranasal dosing should be interrupted and the subject should be referred to a cardiologist, other specialist, or primary care physician for a follow-up assessment.
  - After the assessment by a cardiologist, other specialist, or primary care physician, if recommended by the referring doctor and considered appropriate according to the clinical judgment for the subject to continue in the study, then 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  $\geq 200$  mmHg and/or the DBP is  $\geq 120$  mmHg, the subject must discontinue from further dosing and the subject should be referred to a cardiologist, other specialist, or primary care physician for a follow-up assessment.
- At 1.5 hours postdose, if the SBP is  $\geq 160$  mmHg and/or the DBP  $\geq 100$  mmHg, assessments should continue every 30 minutes until:
  - the blood pressure is  $< 160$  mmHg SBP and  $< 100$  mmHg DBP, or
  - in the investigator's clinical judgment, the subject it is clinically stable and can be discharged from the study site, or
  - the subject is referred for appropriate medical care, if clinically indicated.
- If the blood pressure remains  $\geq 180$  mmHg SBP and/or  $\geq 110$  mmHg DBP, 2 hours after dosing, the subject should be referred for immediate medical treatment.

### 6.1.1. Open-label Induction Phase

All direct-entry subjects will self-administer open-label intranasal esketamine (56 mg or 84 mg) twice a week for 4 weeks as a flexible dose regimen at the study site. In addition, subjects will simultaneously initiate (switch to) a new, open-label oral antidepressant (duloxetine, escitalopram, sertraline, or venlafaxine XR) on Day 1 that will be continued for the duration of this phase.

On Day 1, subjects will start with a dose of 56 mg. On Day 4, the dose may be increased to 84 mg or remain at 56 mg, as determined by the investigator based on efficacy and tolerability. On Day 8, the dose may be increased to 84 mg (if Day 4 dose was 56 mg), remain the same, or be reduced to 56 mg (if Day 4 dose was 84 mg), as determined by the investigator based on efficacy and tolerability. Similarly, on Days 11, 15, 18, and 22, the dose may be increased to 84 mg, remain the same, or be reduced to 56 mg, if applicable as determined by the investigator based on efficacy and tolerability. On Day 25, a dose reduction from 84 mg to 56 mg is permitted if required for tolerability; no dose increase is permitted.

The intranasal treatment sessions will be administered in this phase as described in [Table 1](#).

**Table 1: Intranasal Esketamine Treatment Sessions: Open-label Induction Phase**

Intranasal Treatment Intranasal Device <sup>b</sup>	Time of Administration <sup>a</sup>		
	0 <sup>a</sup>	5 minutes	10 minutes
	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

<sup>a</sup> Time 0 is defined as the time of administration of the first intranasal spray to one nostril from the first intranasal device.

<sup>b</sup> 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).

## 6.1.2. Optimization Phase

### 6.1.2.1. Transferred-entry Subjects

In the optimization phase, subjects will continue the same double-blind intranasal study drug (same dose) from the double-blind induction phase of ESKETINTRD3001 or ESKETINTRD3002.

### 6.1.2.2. Direct-entry Subjects

In the optimization phase, subjects will continue the same open-label intranasal esketamine treatment (same dose) from the open-label induction phase.

All subjects will continue their oral antidepressant medication (at the same dosage) during this phase.

### 6.1.2.3. Intranasal Treatment Session Frequency (All Subjects)

During this phase, the MADRS will be performed weekly by an independent, remote rater, and this MADRS total score will be used for intranasal treatment session frequency decisions (if applicable) at that visit.

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 phase (Week 5 to Week 8).

During this phase, there are two fixed time points (Week 8 and Week 12) in which an adjustment to the frequency will be made, if applicable:

#### Week 8

- Subjects with a MADRS total score >12 at Week 8 visit will continue to receive weekly intranasal treatment sessions for the remainder of the optimization phase. No further change to the treatment session frequency is permitted for the remainder of the optimization phase (through Week 16).

- If the MADRS total score is  $\leq 12$  at Week 8, 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 Week 10 and Week 12).
  - This is the only time during the optimization phase that a subject will be permitted to change to a frequency of every other week.
- If the MADRS assessment is missed at Week 8, 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  $\leq 12$ , 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 for the remainder of the optimization phase. No further change to the treatment session frequency is permitted for the remainder of the optimization phase (through Week 16).

**Week 12 (only for those on an every other week treatment session frequency):**

- If the MADRS total score is  $> 12$  at Week 12, the frequency of intranasal treatment sessions will be increased to weekly for the remainder of the optimization phase; no further change to the treatment session frequency is permitted for the remainder of the optimization phase (through Week 16).
- If the MADRS total score is  $\leq 12$  at Week 12, the subject will remain on the treatment session frequency of every other week for the next 4 weeks (ie, through to Week 16).
- If the MADRS is missed at Week 12, the last MADRS total score available prior to Week 12 will be used to determine if a change in treatment session frequency is indicated at Week 12. In this case:
  - If the MADRS total score is  $\leq 12$ , the subject will remain on the treatment session frequency of every other week for the next 4 weeks (ie, through to Week 16).
  - If the MADRS total score is  $> 12$  at that week, the frequency of intranasal treatment sessions will be increased to weekly for the remainder of the optimization phase; no further change to the treatment session frequency is permitted for the remainder of the optimization phase (through Week 16).

Table 2 and Table 3 describe the administration of intranasal study drug during the optimization phase.

**Table 2: Intranasal Esketamine Treatment Sessions: Optimization Phase (Direct entry Subjects)**

	Time of Administration		
	0 <sup>a</sup>	5 minutes	10 minutes
Intranasal Device <sup>b</sup>	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



- <sup>a</sup> Time 0 is defined as the time of administration of the first intranasal spray to one nostril from the first intranasal device.
- <sup>b</sup> 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).

**Table 3: Intranasal Esketamine or Placebo Treatment Sessions: Optimization Phase (Transferred-entry Subjects)**

	Time of Administration		
	0 <sup>a</sup>	5 minutes	10 minutes
Intranasal Device <sup>b</sup>	First	Second	Third
Placebo	1 spray of placebo to each nostril	1 spray of placebo to each nostril	1 spray of placebo to each nostril
Esketamine 56 mg	1 spray of esketamine to each nostril	1 spray of esketamine to each nostril	1 spray of placebo to each nostril
Esketamine 84 mg	1 spray of esketamine to each nostril	1 spray of esketamine to each nostril	1 spray of esketamine to each nostril

- <sup>a</sup> Time 0 is defined as the time of administration of the first intranasal spray to one nostril from the first intranasal device.
- <sup>b</sup> 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). The intranasal devices for each intranasal treatment session should be administered in the medication kit order provided by the Interactive Web Response System (IWRS).

### 6.1.3. Maintenance Phase

All subjects will receive double-blind intranasal study drug in this phase, as described above (see Section 3.1.1).

During this phase, the MADRS will continue to be assessed weekly by an independent, remote rater, and changes to the intranasal treatment session frequency will occur at 4-week intervals, if applicable, and be based on the MADRS total score (see below).

At the start of this phase (Visit 4.1; Week 16):

- Subjects who currently receive intranasal treatment sessions on a weekly basis will stay at the same weekly intranasal treatment session frequency for the first 4 weeks of this phase.
- For those on an every other week frequency:
  - If the MADRS total score is >12 at Week 16, the frequency of intranasal treatment sessions will be increased to weekly for the next 4 weeks.
  - If the MADRS total score is ≤12 at Week 16, the subject will stay at the same every other week intranasal treatment session frequency for the next 4 weeks.

After the first 4 weeks of this phase (ie, starting at Week 20) the intranasal treatment session frequency will be adjusted (if applicable) at fixed, 4-week intervals (eg, Week 20, 24, 28, 32, 36, 40, 44 and every 4 weeks until the end of the phase), based on the guidance below.

- If the MADRS total score is  $\leq 12$  at that week:
  - If the frequency is weekly, the frequency will be changed to every other week.
  - If the frequency is every other week, there will be no change in frequency.
- If the MADRS total score is  $>12$  at that week:
  - If the frequency is weekly, there will be no change in frequency.
  - If the 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. In this case:
  - If the MADRS total score is  $\leq 12$ , and the frequency is every other week, there will be no change in frequency.
  - If the MADRS total score is  $\leq 12$ , and the frequency is weekly, the frequency will be changed to every other week.
  - If the MADRS total score is  $>12$ , and the frequency is weekly, there will be no change in frequency.
  - If the MADRS total score is  $>12$ , and the 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 maintenance phase. After this time, if a given subject is unable to sustain improvement on every other week dosing they will remain on a weekly dosing regimen for the duration of this phase.

Table 4 describes the administration of intranasal study drug in the maintenance phase.

**Table 4: Intranasal Esketamine or Placebo Treatment Sessions: Maintenance Phase**

	Time of Administration		
	0 <sup>a</sup>	5 minutes	10 minutes
Intranasal Device <sup>b</sup>	First	Second	Third
Placebo	1 spray of placebo to each nostril	1 spray of placebo to each nostril	1 spray of placebo to each nostril
Esketamine 56 mg	1 spray of esketamine to each nostril	1 spray of esketamine to each nostril	1 spray of placebo to each nostril
Esketamine 84 mg	1 spray of esketamine to each nostril	1 spray of esketamine to each nostril	1 spray of esketamine to each nostril

<sup>a</sup> Time 0 is defined as the time of administration of the first intranasal spray to one nostril from the first intranasal device.

<sup>b</sup> 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). The 3 intranasal devices for each intranasal treatment session should be administered in the medication kit order provided by the Interactive Web Response System (IWRS).

#### 6.1.4. Follow-up Phase

No intranasal study medication will be administered during this phase.

## **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 intake between clinic visits will be provided for use.

On intranasal dosing 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/Prospective Observational Phase (Direct-entry Subjects Only)**

At the start of this phase, direct-entry subjects are to be taking a different oral antidepressant treatment (on the MGH-ATRQ) for at least the previous 2 weeks at or above the minimum therapeutic dose. This antidepressant treatment, as well as any other ongoing medications being taken for depression at screening (including adjunctive/augmentation therapies), will continue from the start of Week 1 through the end of Week 4 of the screening/prospective observational phase, to confirm non-response. Dose adjustment is permitted per clinical judgment, but the oral antidepressant treatment is to remain at or above the minimum therapeutic dose (per the MGH-ATRQ) through the end of Week 4. The sponsor will not supply these antidepressant medication(s).

During this phase, antidepressant treatment adherence will be assessed using the PAQ.

After 4 weeks subjects who are non-responders to their current oral antidepressant treatment may be eligible to proceed to the open-label induction phase. Non-response at the end of the screening/prospective observational phase is defined as  $\leq 25\%$  improvement in the MADRS total score from Week 1 to Week 4 and a MADRS total score of  $\geq 28$  on Week 2 and Week 4.

After the completion of 4 weeks of prospective antidepressant treatment and assessment of the antidepressant treatment response, eligible subjects who are entering the open-label induction phase will discontinue all of their medication(s), including adjunctive/augmentation therapies. Of note, subjects taking benzodiazepines (at dosages equal to or less than the equivalent of 6 mg/day of lorazepam) and/or permitted non-benzodiazepine sleep medications (eg, zolpidem, zaleplon) during the screening/prospective observational phase can continue these medications. No dose increases beyond the equivalent of 6 mg/day lorazepam or new benzodiazepine medications are permitted during the screening/prospective observational phase. If clinically indicated, the antidepressant medication may be tapered and discontinued over a period of up to 3 weeks per the local prescribing information or clinical judgment (eg, antidepressant treatments with short half lives, such as paroxetine and venlafaxine XR; or tolerability concerns). Eligible subjects who do not require a tapered discontinuation of their antidepressant treatment(s) can proceed immediately into the open-label induction phase.

### **6.2.2. Open-label Induction Phase (Direct-entry Subjects Only)**

Starting on Day 1 of the open-label induction phase, a new, open-label oral antidepressant treatment will be initiated for all direct-entry subjects, and continued for the duration of this

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

Dosing of the oral antidepressant will begin on Day 1. A mandatory titration schedule is provided in [Attachment 3](#). Doses are not to exceed the maximum dose defined in the titration schedule. If higher doses are not tolerated, a down-titration is permitted based on clinical judgment. However, the subject's dose should not be lower than the following minimum therapeutic doses at the end of the induction phase: sertraline (50 mg/day), venlafaxine XR (150 mg/day), escitalopram (10 mg/day), and duloxetine (60 mg/day). While subjects requiring lower doses can continue in the study and complete the induction phase, such subjects will not be eligible to participate in the optimization phase and will proceed to the follow-up phase after completion of the induction phase.

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

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

### **6.2.3. Optimization and Maintenance Phases (Direct-entry and Transferred-entry Subjects)**

For all subjects, the same oral antidepressant treatment (duloxetine, escitalopram, sertraline, or venlafaxine XR) started on Day 1 of the induction phase will be continued through the optimization and maintenance phases. The oral antidepressant dosage at the end of the induction phase will remain unchanged through the maintenance phase.

Subjects who miss  $\geq 21$  days of the oral antidepressant doses (total daily dose) in the optimization phase will not be eligible to continue into the maintenance phase.

### **6.2.4. 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 study medication will be administered during this phase. The decision to continue the oral antidepressant medication in this phase will be at the discretion of the investigator; however, in order to better assess potential withdrawal symptoms from the intranasal study medication, the oral antidepressant should be continued during the 2-week follow-up phase, unless determined as not clinically appropriate.

All subjects will be provided with an additional 2-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.

## **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 intake between clinic visits.

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).

During the screening/prospective observational phase, antidepressant treatment compliance will be assessed using the PAQ. Missing  $\geq 4$  days of antidepressant medication in the prior 2-week period will be considered as inadequate adherence.

For all other phases, antidepressant treatment compliance will be assessed by performing pill counts (ie, compliance check) and drug accountability at the time points specified in the Time and Events Schedule (see Section 14.5, Drug Accountability).

Subjects who miss  $\geq 21$  days of the oral antidepressant doses (total daily dose) in the optimization phase will not be eligible to continue into the maintenance phase.

## **8. PRESTUDY AND CONCOMITANT THERAPY**

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

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

Any medication that is listed on the MGH-ATRQ and is being taken at the start of the screening/prospective observational phase for an indication other than depression (eg, insomnia)

should be continued during the screening/prospective observational phase but must be discontinued before the start of the double-blind induction phase.

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

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

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

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

### **Rescue Medications**

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

- For agitation or anxiety: As required, midazolam (maximum dose 2.5 mg orally or IM) or short acting benzodiazepine (only permitted post-dose on the day of dosing).
- 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 Schedule summarizes 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 the number of study phases the subject participates in, but should not exceed 189 mL, as shown in [Table 5](#). Note that the values listed in [Table 5](#) represent the maximum total blood volume to be collected, based on the volume for direct-entry subjects; smaller amounts will be collected from the transferred-entry subjects, who will not participate in all study phases. 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 5: Volume of Blood to Be Collected From Each Subject**

Type of Sample	Volume per Sample (mL)	No. of Samples per Subject	Total Volume of Blood (mL) <sup>a</sup>
<b>Screening/Prospective Observational Phase</b>			
Serum chemistry <sup>b</sup>	5	1	5
TSH	3.5	1	3.5
Hematology <sup>c</sup>	2	1	2
Biomarker: protein	10	1	10
Biomarker: RNA	2.5	1	2.5
Biomarker: DNA	6	1	6
Tricyclic antidepressant blood level, if applicable <sup>d</sup>	6	1	6
FT4, if applicable <sup>e</sup>	3.5	1	3.5
<b>Open-label Induction Phase</b>			
Serum chemistry	2.5	2	5
Hematology	2	2	4
Biomarker: protein	10	3	30
Biomarker: RNA	2.5	3	7.5
Biomarker: DNA	6	1	6
<b>Optimization Phase</b>			
Serum chemistry	2.5	3	7.5
Hematology	2	3	6
Biomarker: protein	10	2	20
Biomarker: RNA	2.5	2	5
Biomarker: DNA	6	2	12
<b>Maintenance Phase</b>			
Serum chemistry	2.5	2	5
Hematology	2	2	4
Biomarker: protein	13	1	13
Biomarker: RNA	2.5	1	2.5
Biomarker: DNA	6	1	6
<b>Follow-up Phase</b>			
Serum chemistry	2.5	1	2.5
Hematology	2	1	2
Biomarker: protein	10	1	10
Biomarker: RNA	2.5	1	2.5
<b>Approximate volume of blood collected during the study</b>			<b>189 mL</b>

Key: DNA = deoxyribonucleic acid; FT4 = free thyroxine; RNA = ribonucleic acid; TSH = thyroid-stimulating hormone.

<sup>a</sup> Calculated as number of samples multiplied by amount of blood per sample.

<sup>b</sup> Serum chemistry includes highly sensitive serum  $\beta$ -human chorionic gonadotropin ( $\beta$ -hCG) pregnancy tests (for women of childbearing potential) and lipid panel.

<sup>c</sup> As needed, glycated hemoglobin (HbA1c) will be measured from the sample collected for hematology.

<sup>d</sup> During eligibility assessments, if a subject is taking a tricyclic antidepressant at a dose below the minimum therapeutic dose recommended in the MGH-ATRQ, then the blood level of that antidepressant will be assessed to determine whether the therapeutic (antidepressant) range has been attained.

<sup>e</sup> For any subject (regardless of thyroid history), if the TSH value is out of range, then the FT4 level will be assessed.

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.

Note: The values listed above represent the maximum total blood volume to be collected, based on the volume for direct-entry subjects; smaller amounts will be collected from the transferred-entry subjects, who will not participate in all study phases.



### 9.1.2. Screening/Prospective Observational Phase

This phase is only for direct-entry subjects.

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) to 64 years of age (inclusive) 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  $\geq 2$  years) or recurrent MDD, without psychotic features, based upon clinical assessment and confirmed by the MINI. In addition, at the start of the screening/prospective observational phase, the subject must have an IDS-C30 total score  $\geq 34$ .

At the start of this phase, subjects must have had non-response ( $\leq 25\%$  improvement) to  $\geq 1$  but  $\leq 5$  (if current episode is >2 years, upper limit is applicable to only the last 2 years) oral antidepressant treatments taken at adequate dosage and for adequate duration, as assessed using the MGH-ATRQ and documented by records (eg, medical/pharmacy/prescription records or a letter from treating physician, etc.) for the current episode of depression. In addition, at the start of the screening/prospective observational phase, the subject is taking a different oral antidepressant treatment (on the MGH ATRQ) for at least the previous 2 weeks at or above the minimum therapeutic dose. This antidepressant treatment, as well as any other ongoing medications being taken for depression (including adjunctive/augmentation therapies), will continue from the start of Week 1 through the end of Week 4 of the screening/prospective observational phase to confirm non-response prospectively. Dose adjustment is permitted per clinical judgment, but the oral antidepressant treatment is to remain at or above the minimum therapeutic dose (per the MGH-ATRQ) through the end of Week 4.

Antidepressant treatment adherence will be assessed using the PAQ. Missing  $\geq 4$  days of antidepressant medication in the prior 2-week period will be considered as inadequate adherence.

The subject's current major depressive episode, depression symptom severity (Week 1 MADRS total score  $\geq 28$  required), and antidepressant treatment response in the current depressive episode must be confirmed using the Site Independent Qualification Assessment.

An independent, remote, blinded rater will perform remote MADRS assessments to assess depressive symptoms during this phase.

After 4 weeks, subjects who are non-responders to the current oral antidepressant treatment may be eligible to proceed to the open-label induction phase. Non-response at the end of the screening/prospective observational phase is defined as  $\leq 25\%$  improvement in the MADRS total score from Week 1 to Week 4 and a MADRS total score of  $\geq 28$  on Week 2 and Week 4. Eligible subjects (determined by remote blinded raters) who are entering the open-label induction phase will discontinue all of their current medication(s) being used for depression treatment, including

adjunctive/augmentative therapies, and any other prohibited psychotropic medications, including adjunctive atypical antipsychotics. Subjects who were taking benzodiazepines (at dosages equal to or less than the equivalent of 6 mg/day of lorazepam) and/or permitted nonbenzodiazepine sleep medications (eg, zolpidem, zaleplon) during the screening/prospective observational phase can continue these medications during the induction phase. No dose increases beyond the equivalent of 6 mg/day of lorazepam or new benzodiazepine medications are permitted during the induction phase, with the exception of the use of permitted benzodiazepine (post-dose on the dosing day only) rescue medication. Benzodiazepines and non-benzodiazepine sleeping medications (eg, zolpidem, zaleplon, eszopiclone, and ramelteon) are prohibited within 12 hours prior to the start of each intranasal treatment session or cognition testing.

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.

#### Optional Antidepressant Taper Period

Since all non-responder 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, an optional period of up to 3 weeks is permitted to taper and discontinue the current oral antidepressant medication per the local prescribing information or clinical judgment.

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

#### **9.1.3. Open-label Induction Phase**

This phase is only for direct-entry subjects.

During this phase, subjects will self-administer open-label intranasal esketamine treatment (56 mg or 84 mg) twice a week for 4 weeks as a flexible dose regimen. In addition, subjects will simultaneously initiate (switch to) a new, open-label oral antidepressant (see Section 6, Dosage and Administration). A mandatory titration schedule is provided in [Attachment 3](#). Doses are not to exceed the maximum dose defined in the titration schedule.

An independent, remote, blinded rater will perform all MADRS assessments during this phase. At the end of the open-label induction phase, subjects who are responders (as defined in Section [3.1.2](#)) will be eligible to enter the optimization phase.

Those subjects who do not enter the optimization phase will have an Early Withdrawal Visit conducted and proceed to the follow-up phase (see Section [3.1.2](#)).

Results for all assessments performed on Day 28 of the induction phase for direct-entry subjects (Visit 2.9) and transferred-entry subjects (Visit 2.10 of Study ESKETINTRD3001 or ESKETINTRD3002) will serve as the baseline values for the optimization phase and will not be repeated as part of Visit 3.1. The Day 28 visit should coincide with Day 28 (Visit 3.1) for this

study. All transferred-entry subjects must meet all of the transferred-entry subject-specific inclusion criteria and none of the exclusion criteria in order to be enrolled.

#### **9.1.4. Optimization Phase**

##### **Transferred-entry Subjects**

Prior to conducting any study procedure for ESKETINTRD3003, the investigator (or designated study personnel) will review and explain the written ICF to each transferred entry subject. After signing the ICF, transferred-entry subjects will be evaluated to determine eligibility for study participation.

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 ESKETINTRD3001 or ESKETINTRD3002).

Results for all assessments performed on Day 28 of the induction phase for direct-entry subjects (Visit 2.9) and transferred-entry subjects (Visit 2.10 of Study ESKETINTRD3001 or ESKETINTRD3002) will serve as the baseline values for the optimization phase and will not be repeated as part of Visit 3.1. The Day 28 visit should coincide with Day 28 (Visit 3.1) for this study. All transferred-entry subjects must meet all of the transferred-entry subject-specific inclusion criteria and none of the exclusion criteria in order to be enrolled.

##### **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 this 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 from the induction phase.

An independent, remote, blinded rater will perform weekly MADRS assessments during this phase.

At the end of the optimization phase, subjects in stable remission and those with stable response (but who are not in stable remission), as defined in Section 3.1.2, may be eligible to continue into the maintenance phase; all other subjects will have an Early Withdrawal Visit conducted and proceed to the follow-up phase.

For subjects in stable remission and those with stable response at the end of this phase, the last visit of the optimization phase (Visit 3.13; Week 16) also serves as the baseline visit (Visit 4.1; Week 16) for the maintenance phase. Subjects eligible for the maintenance phase will be randomized and receive their first double-blind intranasal treatment session of the maintenance phase at this visit.

A subject will not be eligible to proceed into the maintenance phase if he or she:

- Misses  $\geq 21$  days of the oral antidepressant doses (total daily dose)

### **9.1.5. Maintenance Phase**

#### **Day of Randomization**

At the next scheduled intranasal treatment session (Day 1 of this phase):

- Approximately 211 subjects in stable remission at the end of the optimization phase (after treatment with intranasal esketamine plus an oral antidepressant) will be randomized in a 1:1 ratio to either continue with intranasal esketamine (same dose) and the same oral antidepressant or to continue with the same oral antidepressant (active comparator) but switch to intranasal placebo. The primary efficacy analysis will be performed for these subjects only.
- Additionally, subjects with stable response (but who are not in stable remission) at the end of the optimization phase (after treatment with intranasal esketamine plus an oral antidepressant) will be randomized in a 1:1 ratio (using a separate randomization list) to either continue with intranasal esketamine (same dose) and the same oral antidepressant or to continue with the same oral antidepressant (active comparator) but switch to intranasal placebo (for a secondary efficacy analysis only).
- Transferred-entry subjects who achieve stable remission or stable response at the end of the optimization phase after treatment with an oral antidepressant plus intranasal placebo will and continue to receive the same treatment in order to maintain the blinding for the ongoing short-term studies. These subjects will not be included in the efficacy analyses, but will be included in safety analyses

The last MADRS assessment performed prior to the first intranasal treatment session of the maintenance phase will be the baseline value for this phase.

#### **Assessment of Relapse**

During this phase, depressive symptom severity will be assessed weekly by independent, remote, blinded raters using the MADRS.

Time to relapse will be assessed by evaluating the time between randomization into the maintenance phase and the confirmation of a relapse, as defined in Section 3.1.2.

### **9.1.6. Early Withdrawal/End of Maintenance Phase**

#### **Early Withdrawal**

If a subject withdraws before the end of the induction, optimization, or maintenance phase for reasons other than withdrawal of consent, or has completed the induction or optimization phase but is not eligible to continue to the next treatment phase, an Early Withdrawal Visit should be 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.

A subject meeting relapse criteria during the maintenance phase is not considered an early withdrawal. These subjects, and subjects in the maintenance phase who remain relapse-free at study termination, will have an End of Maintenance Phase Visit conducted, followed by the

follow up phase. If clinically indicated, subjects who relapse in the Maintenance phase may proceed to the open-label safety extension study, 54135419TRD3008, without completing the follow up phase. If the End of Maintenance Phase Visit occurs on the same day as a scheduled visit, the End of 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 medication will continue.

Subjects who withdraw early will receive additional oral antidepressant medication, if applicable, and it will be recommended that they continue taking the oral antidepressant medication for at least the 2-week follow-up phase unless determined as not clinically appropriate.

#### **9.1.7. Follow-up Phase**

This phase will include all subjects who have received at least 1 dose of intranasal study medication in this study. For those subjects who relapse in the Maintenance phase, if clinically indicated based on investigator's judgment, after completing the end of maintenance visit, the subject may proceed to the open-label safety extension study, 54135419TRD3008, without completing the follow up phase. Similarly, when the study is stopped, subjects in the Induction phase who are responders, after completing the early withdrawal visit, may proceed to the 54135419TRD3008 study, without completing the follow up phase.

Follow-up visits will be performed at 1 and 2 weeks after the last clinic visit.

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 2-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, the oral antidepressant should be continued during the 2-week 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 ESKETINTRD3003 study. Please refer to the 54135419TRD3008 protocol for full details of potential pathways for entry.

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

Investigators may recontact the subject 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.

## **9.2. Efficacy**

### **9.2.1. Evaluations**

#### **9.2.1.1. Primary Efficacy Evaluation: Montgomery-Asberg Depression Rating Scale (MADRS)**

The primary efficacy evaluation will include the use of the MADRS total score as it pertains to relapses. The MADRS will be performed by independent remote raters during the study, using the Structured Interview Guide for the MADRS.<sup>138</sup>

The MADRS is a clinician-rated scale designed to measure depression severity and detects changes due to antidepressant treatment.<sup>83</sup> The scale consists of 10 items, each of which is scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), for a total possible score of 60. Higher scores represent a more severe condition. The MADRS evaluates apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, inability to feel (interest level), pessimistic thoughts, and suicidal thoughts. The test exhibits high interrater reliability. The MADRS will be administered with its typical recall period of 7 days. See Section 3.1.2 for the definition of relapses related to the MADRS total score.

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

#### **9.2.1.2. 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.<sup>50</sup> The CGI-S evaluates the severity of psychopathology on a scale of 0 to 7. Considering total clinical experience, a subject is assessed on severity of mental illness at the time of rating according to: 0=not assessed; 1=normal (not at all ill); 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among the most extremely ill patients. The CGI-S permits a global evaluation of the subject's condition at a given time.

#### **9.2.1.3. Patient Health Questionnaire, 9-Item (PHQ-9)**

The PHQ-9 is a 9-item, patient-reported outcome measure to assess depressive symptoms.<sup>128</sup> 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.

#### **9.2.1.4. Generalized Anxiety Disorder, 7-item (GAD-7)**

The subject-reported Generalized Anxiety Disorder, 7-item (GAD-7) will be used to measure the secondary objective of symptoms of anxiety. The GAD-7 is brief and validated measure of overall anxiety.<sup>127</sup> Each item is rated on a 4-point scale (0=not at all; 1=several days; 2=more than half the days; 3=nearly every day). Item responses are summed to yield a total score (range of 0 to 21), with higher scores indicating more anxiety. The recall period is 2 weeks.

#### **9.2.1.5. 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).

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.

#### **9.2.1.6. Sheehan Disability Scale (SDS)**

The Sheehan Disability Scale (SDS)<sup>74,117</sup> will be used to assess the secondary objective of functional impairment and associated disability. The SDS, a patient-reported outcome measure, is a 5-item questionnaire that has been widely used and accepted for assessment of functional impairment and associated disability. The first 3 items cover (1) work/school, (2) social life, and (3) family life/home responsibilities using a rating scale from 0 to 10. The SDS also has 1 item assessing days lost from school or work and 1 item assessing days of underproductivity. The score for the first 3 items are summed to create a total score of 0 to 30, where higher score indicates greater impairment. The recall period for this study is 7 days.

### **9.2.2. Endpoints**

#### **Primary Efficacy Evaluation/Endpoint**

The primary efficacy evaluation will include the MADRS total score as it pertains to relapses.

The primary efficacy endpoint includes only subjects who are in stable remission at the end of the optimization phase after treatment with intranasal esketamine plus an oral antidepressant, and is defined as the time between subject randomization and the first documentation (earliest date) of a relapse in the maintenance phase. Relapse criteria are defined in Section 3.1.2, Definitions of Terms.

### **Secondary Efficacy Evaluations/Endpoints**

Secondary efficacy evaluations/endpoints include the following:

- The time between subject randomization and the first documentation (earliest date) of a relapse in the maintenance phase for subjects with stable response (not in remission) at the end of the optimization phase after treatment with intranasal esketamine plus an oral antidepressant. Relapse criteria are defined in Section 3.1.2, Definitions of Terms.
- The change from baseline (of maintenance phase) to endpoint in:
  - Depressive symptoms, using the MADRS and the self-reported Patient Health Questionnaire 9-item (PHQ-9) scale
  - Overall severity of illness, using the Clinical Global Impression - Severity (CGI-S)
  - Symptoms of anxiety, using the Generalized Anxiety Disorder, 7-item (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)

### **9.3. 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. Protocol-mandated procedures, tests, and encounters will be excluded. The data collected may be used to conduct 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).

### **9.4. Safety Evaluations**

Details regarding the 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.



Instances may occur where a subject has started a scheduled clinic visit in which an intranasal treatment session is planned, but then a predose observation (eg, blood pressure results or nasal congestion as described in Section 6.1 or intoxication as described in Section 4.3) prompts the site staff to postpone 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 signs (ie, blood pressure, pulse, respiratory rate, and temperature), 12-lead ECG, C-SSRS (since last visit), MOAA/S, pulse oximetry, BPRS+, and CADSS.

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

### **Adverse Events**

Treatment-emergent adverse events 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.

### **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                     | - gamma-glutamyltransferase |
| - potassium                  | - total bilirubin           |
| - chloride                   | - alkaline phosphatase      |
| - bicarbonate                | - creatine phosphokinase    |
| - blood urea nitrogen        | - calcium                   |
| - creatinine                 | - phosphate                 |
| - glucose                    | - albumin                   |
| - aspartate aminotransferase | - total protein             |
| - alanine aminotransferase   |                             |

- **Urinalysis:**

Dipstick:

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

Sediment (if dipstick result is abnormal):

- red blood cells
- white blood cells
- epithelial cells
- crystals
- casts
- bacteria

If dipstick result is abnormal, flow cytometry or microscopy will be used to measure sediment. In case of discordance between the dipstick results and the flow cytometric results, the sediment will be examined microscopically.

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

- 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 exclusionary at Day 1 predose), phencyclidine, and amphetamine/methamphetamine
- Alcohol breath test
- Thyroid-stimulating hormone (TSH)
- Free thyroxine (FT4), only if required for abnormal TSH (refer to Inclusion Criteria).
- 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 Sec. 4.1, Inclusion Criteria).

### **Single, 12-Lead ECGs**

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  $\geq 60$  msec and QTcF  $> 480$  msec, or
- QTcF  $> 500$  msec.

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

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

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

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

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 timepoints. Any arterial oxygen saturation (SpO<sub>2</sub>)  $< 93\%$  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.

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### **Physical Examination, Height, Body Weight, and Neck Circumference**

Physical examinations, body weight, and height 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.

### **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.<sup>106</sup> It is a clinical interview providing a summary of both ideation and behavior that can be administered during any evaluation or risk assessment to identify the level and type of suicidality present. The C-SSRS can also be used during treatment to monitor for clinical worsening.

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

### **Clinician Administered Dissociative States Scale (CADSS)**

The CADSS is an instrument for the measurement of present-state dissociative symptoms,<sup>8</sup> 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, 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.<sup>97,98</sup> It reportedly provides a rapid and efficient evaluation of treatment response in clinic drug studies and in clinical settings.<sup>111</sup>

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  $\leq 3$  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  $\leq 3$ , 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 for all subjects on Day 25 to establish a baseline prior to discontinuation of intranasal esketamine treatment – although only relevant for those subjects not continuing to the optimization phase. For those subjects who proceed to the optimization and maintenance phases, the PWC-20 is conducted at the End of Study Visit. If subjects withdraw early from the study during any phase, the PWC-20 will be conducted at the Early Withdrawal Visit. In order to better assess potential withdrawal symptoms from the intranasal medication, the oral antidepressant medication should be continued for the 2-week 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.<sup>109</sup> 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 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.<sup>55</sup>

The BPIC-SS contains 8 questions with a recall period of the past 7 days and addresses key symptoms identified by subjects with bladder pain syndrome (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. 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.<sup>55</sup> If any items are missing, a total score cannot be calculated.

In the current study, 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 determined to have a diagnosis of ulcerative cystitis, then 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 obtain if BPIC-SS on applicable study day is >18.

### **Cognition Testing**

The tests described below should be administered in the following order: HVLT-R, computerized cognitive battery, and HVLT-R Delayed. All subjects will complete a practice session for the computerized cognitive battery during the screening/prospective observational phase. There is no practice session for the HVLT-R.

#### ***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 (HVLT-R)***

The HVLT-R, a measure of verbal learning and memory, is a 12-item word list recall test. Administration includes 3 learning trials, a delayed recall (20-minute) trial, and a 24-word recognition list (including 12 target and 12 foil words).<sup>5</sup> 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 HVLT-R is a well-validated and widely used measure of verbal episodic memory.

## University of Pennsylvania Smell Identification Test (UPSIT) and Smell Threshold Test

To assess any potential treatment-emergent effects on the sense of smell, olfactory function will be qualitatively and quantitatively assessed using validated standardized olfactory tests prior to and at specified time points during the study. The 2 tests to be administered are:

- The UPSIT assesses a subject's ability to identify odors. This standardized test, the most widely used olfactory test in the world, is derived from basic psychological test measurement theory and focuses on the comparative ability of subjects to identify odorants at the suprathreshold level. The UPSIT consists of 4 envelope-sized booklets, each containing 10 "scratch and sniff" odorants embedded in 10- to 50- $\mu$ m polymer microcapsules positioned on brown strips at the bottom of the pages of the booklets. The internal consistency and test-retest reliability coefficients of this instrument are  $>0.90$ .<sup>27,28,29</sup> Numerous studies have shown this and related tests to be sensitive to subtle changes in smell function associated with multiple etiologies, including those due to viruses, head trauma, and a number of neurodegenerative diseases.
- The Smell Threshold Test will assess the smell threshold using a forced-choice single staircase threshold procedure. This test quantifies a detection threshold for the rose-like smelling odorant phenyl ethyl alcohol (PEA). This odorant is used because it has little propensity to stimulate the trigeminal nerve within the nose. This test is sensitive to olfactory deficits from a wide range of disorders.

These tests will be administered bilaterally (ie, both nostrils at the same time). Testing will occur during the screening/prospective observational phase to establish a subject's baseline sensitivity. The degree of change from this baseline will be determined subsequently over time. The percent change from baseline will serve as the dependent measure for each subject for each test.

If the subject has significant nasal congestion on the day of a scheduled UPSIT and/or Smell Threshold Test, the site should consider postponing the smell test assessment(s) to the next scheduled clinic visit.

### 9.5. Biomarker, Pharmacogenomic (DNA), and Expression (RNA) Evaluations

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

In blood, biomarkers (protein, metabolite, and RNA) related to (but not limited to) the immune system activity, hypothalamus pituitary adrenal (HPA) axis activation, neurotrophic factors and metabolic factors will be investigated. Biomarkers may be added or deleted based on scientific information or technical innovations under the condition that the total volume of blood collected will not be increased.

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



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

## **9.6. Other Evaluations**

### **Massachusetts General Hospital Female Reproductive Lifecycle and Hormones Questionnaire (MGH-FRLHQ): Module I and Menstrual Cycle Tracking**

The MGH-FRLHQ: Module I (childbearing potential, menopausal status, and menstrual cycle) is a brief questionnaire aimed at standardizing the minimal collection of relevant information about reproductive hormones and status. It will be completed by a clinician. This information will not only assist with assessing eligibility criteria, but also may facilitate exploratory analyses of the impact of endogenous and exogenous reproductive hormones on the course of treatment of MDD and potentially inform care of women with MDD in the future.<sup>48</sup>

Menstrual cycle tracking (start date of last menstrual period) is captured as part of MGH-FRLHQ at Week 1 of the screening/prospective observational phase, and then is tracked separately thereafter only for women with a menstrual cycle at the study visits specified in the Time and Events Schedule.

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

The MGH-ATRQ is used to determine treatment resistance in MDD.<sup>25</sup>

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.

### **Inventory of Depressive Symptomatology - Clinician-rated, 30-item (IDS-C<sub>30</sub>)**

The 30-item IDS-C<sub>30</sub> was designed to assess all the criterion symptom domains designated by Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) to diagnose a

major depressive episode<sup>112</sup>; these criteria have not changed in the DSM-5.<sup>2</sup> These assessments can be used to screen for depression, although they have been used predominantly as measures of symptom severity. The 7-day period prior to assessment is the usual time frame for assessing symptom severity. The psychometric properties of the IDS-C<sub>30</sub> have been established in various study samples.<sup>131</sup>

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

The STOP-Bang Questionnaire<sup>129</sup> 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.

Study site staff will answer yes or no to questions about body mass index (more than 35 kg/m<sup>2</sup>?), 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  $\geq 5$  on the STOP-Bang indicates a moderate to severe risk for obstructive sleep apnea (apnea hypopnea index of  $>30$ ).

### **Site Independent Qualification Assessment**

Independent psychiatrists/psychologists will perform the Site Independent Qualification Assessment in the screening/prospective observational phase for all subjects to confirm the subject's current major depressive episode, depression symptom severity (including by MADRS, required at Week 1 to be total score  $\geq 28$ ), and antidepressant treatment response in the current depressive episode, in terms of eligibility for the study.<sup>130</sup>

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

### **PAQ**

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

## 9.7. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. If blood samples are collected via an indwelling cannula, an appropriate amount (1 mL) of serosanguineous fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken. After blood sample collection, the cannula will be flushed with 0.9% sodium chloride, United States Pharmacopeia (USP) (or equivalent) and charged with a volume equal to the dead space volume of the lock.

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

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

## 10. SUBJECT COMPLETION/WITHDRAWAL

### 10.1. Criteria for Completion

A subject will be considered as having completed the study if he or she either:

- Has had a relapse during the maintenance phase
- Has remained relapse-free during the maintenance phase up to the time that the study is terminated

Subjects in the Screening Prospective Observational phase at the time of study termination may be eligible to proceed to the 54135419TRD3008 study. Subjects in the induction phase of the study at the time of study termination will be allowed to complete the induction phase. These subjects, after completing the Early Withdrawal visit, may proceed to the 54135419TRD3008 study, but will not be considered completers for this study. Subjects in the optimization phase at time of study termination will not need to complete this phase, and will complete an Early Withdrawal Visit, and continue into the follow up phase, but they will not be considered completers.

### 10.2. 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 also guidance on blood pressure monitoring on intranasal dosing days in Section 6.1.
- The subject becomes pregnant.
- The blind is broken by the investigator (where applicable).

- 
- Lack of efficacy (induction and optimization phases only)
  - The subject does not meet response criteria for continuing into the optimization phase at the end of the open-label induction phase (direct-entry subjects only).
  - The subject does not meet criteria for continuing into the maintenance phase at the end of the optimization phase.
    - The subject does not meet criteria for stable remission or stable response.
    - Subject misses  $\geq 21$  days of the oral antidepressant doses (total daily dose) in the optimization phase.
  - Lost to follow-up
  - Withdrawal of consent (Note: See the "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.)
  - Violation of protocol procedures (determined on a case-by-case basis)
  - The subject is unwilling or unable to adhere to the intranasal treatment schedule.
  - At any time point after baseline (Day 1, predose), the subject has a:
    - QTcF change from baseline  $\geq 60$  msec and QTcF  $> 480$  msec, or
    - QTcF  $> 500$  msec.
  - The sponsor terminates the study.
  - Death

If a subject withdraws before the end of the induction, optimization, or maintenance phase for reasons other than withdrawal of consent, or has completed the induction or optimization phase but is not eligible to continue to the next treatment phase, an Early Withdrawal Visit should be 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.

A subject meeting relapse criteria during the maintenance phase is not considered an early withdrawal. If clinically indicated, after completing the end of maintenance visit, subjects who have met relapse criteria may proceed to the open-label safety extension study, 54135419TRD3008, without completing the follow up phase. Subjects who remain relapse-free at study termination, will have an End of Maintenance Phase Visit conducted, followed by the follow up phase. If the End of Maintenance Phase Visit occurs on the same day as a scheduled visit, the End of Maintenance Phase Visit can be performed on the same day and duplicate assessments are not required.

If a subject is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. This should include at least 3 telephone calls, certified letters, email requests, etc. To ensure access to follow-

up subjects, the study sites should attempt to obtain both primary and secondary telephone contact numbers (eg, home, work, and mobile phone numbers), as well as other contact information (eg, email addresses) from subjects before the first dose of study drug is administered. In addition, the study site should emphasize the importance of follow-up information to the subject before the first dose of study drug is administered. The attempted follow-up measures 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.

### **Withdrawal of Consent**

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

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

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

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

### **10.3. Withdrawal From the Use of 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 analyzed:

- **Full Analysis Sets for Primary Efficacy Evaluation:**
  - At Interim Analysis: All subjects who are in stable remission at the end of the optimization phase and who receive at least 1 dose of intranasal study drug and 1 dose of oral antidepressant during the maintenance phase at the time of the interim analysis data cutoff
  - At Final Analysis: All subjects who are in stable remission at the end of the optimization phase and who receive at least 1 dose of intranasal study drug and 1 dose of oral antidepressant during the maintenance phase
- **Safety Analysis Sets:**
  - For open-label induction phase: All subjects who receive at least 1 dose of intranasal study drug or 1 dose of oral antidepressant in the open-label induction phase
  - For optimization phase: All subjects who receive at least 1 dose of intranasal study drug or 1 dose of oral antidepressant in the optimization phase
  - For maintenance phase: All randomized subjects who receive at least 1 dose of intranasal study drug or 1 dose of oral antidepressant during the maintenance phase

Transferred-entry subjects who continue to receive an oral antidepressant plus intranasal placebo will be summarized separately in both optimization and maintenance phases.

## 11.2. Sample Size Determination

The maximum number of relapses (in the subjects with stable remission) required for this study is 84, which provides 90% power to detect a hazard ratio of 0.493 at the 1-sided significance level of 0.025, when a fixed-sample design is implemented, to detect superiority of esketamine plus oral antidepressant over antidepressant alone in delaying relapse of depressive symptoms in subjects with TRD who are in stable remission. The calculation of sample size assumed that the time to the first relapse follows an exponential distribution with a median time of 6 months for oral antidepressant alone and 12.17 months for intranasal esketamine plus oral antidepressant (hazard ratio = 0.493). The corresponding 6-month relapse rates are 50% for oral antidepressant alone and 28.95% for oral antidepressant plus intranasal esketamine.

Based on the subsequent assumptions, a total of approximately 211 subjects in stable remission need to be randomized (in a 1:1 ratio) in order to obtain 84 relapses:

- A maximum accrual period of 18 months and a maximum study duration of 20 months (this is the maximum duration for the full study, not for each subject);
- Accrual rate of approximately 11.7 subjects/month during the accrual period;
- Subjects are followed until relapse, dropout, or end of study;
- 35% dropout rate in each group over 6 months.

In addition to the 1:1 randomization of the 211 subjects in stable remission described above, subjects with stable response (but who are not in stable remission) also will be randomized 1:1. The actual number of subjects randomized (which includes both those in stable remission and those with stable response ) will depend on the time it takes to obtain the necessary number of relapses. Blinded surveillance of the total number of relapses in the maintenance phase will be performed during the study to assess the appropriateness of the assumptions regarding accrual and dropout rates. The number of subjects enrolled and the number of subjects who discontinue before entering the maintenance phase will be closely monitored. A sample size re-estimation rule will be provided in the SAP.

### **11.3. Efficacy Analyses**

To evaluate the assumptions used in sample size calculation, relapse rates will be monitored sequentially during the maintenance phase. In particular, a 2-stage group-sequential design will be adopted, with 1 interim analysis to be performed when a total of 30 relapses are observed. Early termination of the maintenance phase for efficacy will be based on interim analysis results. If the interim analysis results show that the study should proceed to the second stage (ie, continue to record more relapses after the interim cutoff), sample size re-estimation will be performed based on the interim analysis results to determine how many additional relapses should be obtained.

The primary analysis for efficacy will be carried out on the Full Analysis Set and only for subjects who are in stable remission at the end of the optimization phase. The primary efficacy endpoint will be the time between subject randomization into the maintenance phase and the first documentation of a relapse event. Subjects who meet at least 1 of the relapse criteria for the primary analysis while receiving treatment in the maintenance phase at the time that the study is stopped are considered to have had a relapse. All other randomized subjects with stable remission who had entered the maintenance phase but do not have a relapse by the time that the study is stopped will be considered censored.

The cumulative distribution function of the time to relapse will be estimated by the Kaplan-Meier method. Time to relapse will be summarized (number of relapses, number of censored subjects, median, 25th and 75th percentile of time to relapse, if estimable) by treatment group. Treatment differences will be compared using a 2-sided log-rank test as the primary analysis. The estimate of the hazards ratio and its 95% confidence interval will be based on the Cox proportional hazards model with treatment as a factor.

Treatment comparison between intranasal esketamine plus oral antidepressant and oral antidepressant (active comparator) plus intranasal placebo in the changes from baseline to endpoint of MADRS total score, PHQ-9, CGI-S, SDS, and GAD-7 during the maintenance phase will be performed using an analysis of covariance model with treatment and country as factors and baseline (maintenance phase) value as a covariate. Least-squares estimates of the treatment differences and 95% confidence intervals will be presented. Dimension scores of EQ-5D-5L data, health status index, and the overall health status score will be summarized over time. These analyses will be provided separately for stable remitters and stable responders (not in remission).

Additionally, the time between the randomization of a subject with stable response (but who are not in stable remission) and the first documentation of a relapse for that subject in the maintenance phase will be analyzed using the log-rank test as described above for the primary efficacy endpoint.

#### **11.4. Biomarker, Pharmacogenomic (DNA), and Expression (RNA) Analyses**

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 comparison of biomarker measures between the treatment groups and correlation with baseline and change from baseline biomarker values in the efficacy and other measures. Additional exploratory analyses may also include relationship of baseline and change from baseline in biomarker measures to clinical response, maintenance/stabilization of response, relapse, and non-response.

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

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

#### **11.5. Medical Resource Utilization Analyses**

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

#### **11.6. Safety Analyses**

All safety data will be analyzed separately for each 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). 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 by treatment group.

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 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.



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.

### **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 presented in pre- versus posttreatment cross-tabulations (with classes for below, within, and above normal ranges). Frequency tabulations of the abnormalities will be provided. Listings of subjects with laboratory results outside the reference ranges and markedly abnormal 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).<sup>4,117</sup>

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 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. The percentage of subjects with values beyond clinically important limits will be summarized.

### **Nasal Examination and Nasal Symptom Questionnaire**

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

In addition, scoring from the nasal tolerability questionnaire will be summarized descriptively for each scheduled time point by treatment group.

### **Other Safety and Tolerability Questionnaires and Assessments**

- C-SSRS: Suicide-related thoughts and behaviors based on the C-SSRS will be summarized by treatment group in incidence and shift tables. Separate endpoints for suicidal ideation and suicidal behavior will be defined and summarized descriptively by treatment group.
- BPIC-SS, BPRS+, CADSS, CGADR, MOAA/S, Smell Threshold Test, PWC-20, and UPSIT: Descriptive statistics of scores and their changes (and/or percent changes) from pre-dose or baseline will be summarized at each scheduled time point.
- Computerized cognitive battery and HVLIT-R: Descriptive statistics of each of the cognitive domain scores and changes from baseline will be summarized at each scheduled time point.

### **11.7. Interim Analysis**

See Section 11.1 for a description of the interim analysis population, Section 11.3 for efficacy analyses to be conducted at interim, and Section 11.8 for a description of the involvement of the IDMC with the interim analysis. As described in those sections, a 2-stage group-sequential design will be adopted, with 1 interim analysis to be performed when a total of 30 events (of the 84 maximum) are observed. At the interim analysis, if the study is not stopped for efficacy and a sample size re-estimation is performed, none of the esketamine team members or staff members at the investigational sites conducting the clinical study will be informed of the specific sample size adjustment resulting from this interim analysis. However, the Clinical Supplies group will be informed of the decision made at interim analysis so that only the required amount of study medication will be packaged.

### **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. In addition, the committee will review 1 interim analysis. The committee will meet every 6 months to review safety data and will meet once to review efficacy data after the interim analysis has been completed. After the reviews, the IDMC will make recommendations regarding the continuation of the study, or in the case of the interim analysis for efficacy, to stop the study due to efficacy or to adjust the sample size (ie, number of relapses) to achieve the desired power while maintaining control of the overall Type I error. 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 , the expectedness of an adverse event will be determined by whether or not it is listed in the Reference Safety Information Section of the Investigator's Brochure.

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/ US Prescribing Information.

### **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. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

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

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

### **12.3.2. Serious Adverse Events**

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

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site,

and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax).

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

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

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

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

The cause of death of a subject in a study, whether or not the event is expected or associated with the study drug, is considered a serious adverse event.

### **12.3.3. Pregnancy**

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

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.

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

#### **12.4. Contacting Sponsor Regarding Safety**

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

### **13. PRODUCT QUALITY COMPLAINT HANDLING**

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

#### **13.1. Procedures**

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

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to 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**

##### **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- $\mu$ L spray. Each individual nasal spray pump (device) contains a total of 28 mg (ie, 2 sprays).

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

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

### **Oral Antidepressant Medications**

#### ***Duloxetine***

Duloxetine 30 mg will be obtained from commercial stock and provided under the responsibility of the sponsor. Refer to the Summary of Product Characteristics (SmPC)/Package Insert (PI) for the physical description and a list of excipients.

#### ***Escitalopram***

Escitalopram 10 mg will be obtained from commercial stock and provided under the responsibility of the sponsor. Refer to the Summary of Product Characteristics (SmPC)/Package Insert (PI) for the physical description and a list of excipients.

#### ***Sertraline***

Sertraline 50 mg and 25mg (as applicable) will be obtained from commercial stock and provided under the responsibility of the sponsor. Refer to the Summary of Product Characteristics (SmPC)/Package Insert (PI) for the physical description and a list of excipients.

#### ***Venlafaxine XR***

Venlafaxine XR 75 mg and 37.5mg (as applicable) will be obtained from commercial stock and provided under the responsibility of the sponsor. Refer to the Summary of Product Characteristics (SmPC) /Package Insert (PI) for the physical description and a list of excipients.

## **14.2. Packaging**

### **Intranasal Study Drug**

Study drug (ie, intranasal esketamine and placebo solution) will be supplied by the sponsor in a bi-dose nasal spray device. The devices will contain 200  $\mu$ L. Each device delivers 16.14 mg esketamine hydrochloride (14 mg esketamine base) or 0.1  $\mu$ g of denatonium benzoate per 100- $\mu$ 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**

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

### **14.3. Labeling**

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

### **14.4. Preparation, Handling, and Storage**

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

All study 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.

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 medication
- Investigational Product (IP) Binder, including the investigational product procedures manual
- Laboratory manual and materials
- Clinician-administered and subject-completed 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
- Rater qualifications/requirements for select clinician-administered assessments
- Computerized cognitive battery and HVLT-R, and all associated equipment and materials
- Device to measure respiratory rate
- Procedural documents for Site -Independent Qualification Assessment.
- Procedural documents for independent, remote rater interviews
- Guidance on recommended order of study procedures
- MGH-ATRQ guidance document

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## **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 the efficacy of intranasal esketamine plus an oral antidepressant for delaying relapse in patients with TRD. Thus, the study cannot be completed in healthy subjects.

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

For eligibility, direct entry subjects must have had non-response to at least 1 prior antidepressant treatment and be currently taking an antidepressant treatment at the start of the screening/prospective observational phase that will be continued as prospective treatment in the screening/prospective observational phase. Only subjects with non-response to their current antidepressant treatment after 4 weeks of prospectively observed treatment (total duration of at least 6 weeks by the end of the screening/prospective observational phase), will be eligible to proceed to the open-label induction phase, when all subjects will receive a new oral antidepressant in addition to intranasal esketamine.

Direct-entry subjects will receive 4 weeks of esketamine treatment in the open-label induction phase; at the end of this phase, those who are responders will be eligible to participate in the 12-week optimization phase. At the end of the optimization phase, subjects who are stable responders or stable remitters may be eligible to enter the maintenance phase. At any time during the study, subjects may discontinue and proceed to the 2-week follow-up phase; they will be provided with an additional 2-week supply of oral antidepressant and appropriate follow-up care will be arranged.

At the start of the maintenance phase, eligible subjects in stable remission, or with stable response, will be randomized to either continue intranasal treatment with esketamine or switch to intranasal placebo. All subjects will continue to take the same oral antidepressant.

The study will be stopped once 84 relapses (in the subjects with stable remission) occur during the maintenance phase, or earlier based on the results of the interim analysis for efficacy. At the time the study is stopped, subjects in the induction phase will be able to complete the Induction

phase. Those subjects who are responders after completing an Early Withdrawal Visit may proceed to the 54135419TRD3008 study without completing the follow up phase. Those who are not responders will have an Early Withdrawal Visit and proceed directly to the follow-up phase. Subjects who are in the optimization or maintenance phase at the time the study is terminated will have an Early Withdrawal Visit/End of Maintenance Phase Visit conducted and proceed directly to the follow-up 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.

### **Justification for Using Placebo**

Intranasal placebo is being used as a double-blind for esketamine to maintain study blinding for transferred-entry subjects from 1 of the short-term double-blind studies. All subjects will also receive a newly initiated oral antidepressant during the induction phase. Subjects will not be on placebo alone. Assessment of the potential efficacy of a new compound for the treatment of treatment-resistant major depression requires adequate and well-controlled clinical studies. This study will compare intranasal esketamine plus an oral antidepressant to switching to an oral antidepressant as an active comparator. Recent analyses have shown response to placebo varies considerably, from 10% to 55%. Therefore, there is a concern that randomized, controlled studies that rely on comparison with standard antidepressants alone will generate unreliable results with limited assay sensitivity. However, some have considered it unethical to do placebo-controlled studies in major depression due to the potential risk of irreversible harm.<sup>110</sup> In a meta-analysis of drug studies conducted in MDD, it was reported that adult subjects did not have higher rates of suicide behaviors or attempts in the placebo group compared with those receiving an active antidepressant.<sup>67</sup> These studies showed annual suicide rates of 0.8% on the investigational drug, 0.7% on the active comparator, and 0.4% on placebo. Thus, the risk of irreversible harm was not higher in the placebo arm compared with the active control arms.

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

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

Subjects will visit the study site at least every other week during the study, and their symptoms will be carefully monitored during each study visit. Safety evaluations will include evaluation of suicidal ideation/behavior at each clinic visit. At any point in the study, the subject may withdraw consent or be removed from the study by the investigator if there are any clinical concerns.

Intranasal esketamine may or may not be available for subjects after the study. However, following completion of the study, subjects can be treated according to standard of care.

## **Precautions to Ensure Subject Safety in the Study**

Subjects may participate in the study only if they have adequate capacity to give consent and after fully understanding the potential risks and giving an informed consent. Determination of capacity will be made by the study investigator. Subjects may discontinue the study at any time. The probability of receiving placebo and the concept of random assignment will be explained to the subject. Potential disadvantages and adverse events of participating in the study and alternative treatment options will be discussed. 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 oral antidepressant treatment, where a clinician would consider changing it in the future due to lack of response, will be enrolled (direct entry).

Only qualified and trained investigators will participate in the study.

The total blood volume to be collected is considered to be within the normal range allowed for this subject population over this time frame. The total blood volume to be collected is approximately 189 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, where required. 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 oral antidepressants, to understand depression, to understand differential drug responders, and to develop tests/assays related to oral antidepressants, and depression. The research may begin at any time during the study or the post-study storage period.

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

### **16.2.6. Country Selection**

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product, unless explicitly addressed as a specific ethical consideration in Section 16.1 (Study-specific Design Considerations).

## **17. ADMINISTRATIVE REQUIREMENTS**

### **17.1. Protocol Amendments**

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

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

### **17.2. Regulatory Documentation**

#### **17.2.1. Regulatory Approval/Notification**

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

#### **17.2.2. Required Prestudy Documentation**

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

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.

- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable.
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable.
- Documentation of investigator qualifications (eg, curriculum vitae).
- Completed investigator financial disclosure form from the principal investigator, where required.
- Signed and dated clinical trial agreement, which includes the financial agreement.
- Any other documentation required by local regulations.

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

- Completed investigator financial disclosure forms from all 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 documentations consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: subject identification, eligibility, and study identification; study discussion and

date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

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

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

The minimum source documentation requirements for inclusion and exclusion criteria (in Section 4) 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, and 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 eCRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or study-site personnel must adjust the eCRF (if applicable) and complete the query.

If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

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

#### **17.6. Data Quality Assurance/Quality Control**

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by the sponsor, and uploading data transfers from external service providers into the sponsor's 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 may be reviewed. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

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

### **17.9.2. Study Termination**

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

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

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

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

#### **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 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.



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## ATTACHMENTS

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

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

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

Except where specifically noted, the prohibited medications listed in the following table are prohibited from 1 week (or 5 half-lives, whichever is longer) prior to the first dose of intranasal study medication until after the last dose of intranasal study medication. Note: If a medication is part of the antidepressant treatment regimen being taken at the time of signing the ICF (ie, start of screening/prospective observational phase), per protocol, the medication is continued until the end of Week 4 of the screening/prospective observational phase, therefore this requirement is not applicable. In such cases the investigator may choose to taper the relevant medication during the up to 3-week taper period based on their clinical judgment.

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

Drug Class	Episodic Use (As Needed)	Continuous Use	Comments	Reason for Prohibition
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
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



<b>Drug Class</b>	<b>Episodic Use (As Needed)</b>	<b>Continuous Use</b>	<b>Comments</b>	<b>Reason for Prohibition</b>
Antidepressants ( <i>other than the specific antidepressant started in the induction phase of the study</i> )	N	N	<ul style="list-style-type: none"> <li>- Only 1 of the 4 predefined oral antidepressant treatment options are permitted.</li> <li>- If a subject is taking a monoamine oxidase inhibitor (MAOI) during the screening/prospective observational phase, there must be a minimum washout interval of 2 weeks prior to the first dose of intranasal study medication.</li> <li>- Even if used for indications other than MDD (eg, trazodone for sleep), the use of any medication listed on the ATRQ is not permitted during study phases that include intranasal treatment.</li> </ul>	Safety and PD interaction
Antipsychotics	N	N		PD interaction
Benzodiazepines (at dosages equal to or less than the equivalent of 6 mg/day lorazepam) and non-benzodiazepine sleeping medication (including: zolpidem, zaleplon, eszopiclone, and ramelteon)	Y	Y	Prohibited within 12 hours prior to the start of each intranasal treatment session 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	Y	Y	Use for blood pressure control is allowed	
Corticosteroids (systemic)	Y	N	<p>Inhaled, intranasal, topical, and ophthalmic steroids are not prohibited.</p> <p>Intermittent IM/IV/PO corticosteroids are permitted with sponsor approval (chronic use prohibited).</p>	PD interaction
Cough/cold preparations/nasal solutions containing vasoconstrictors, decongestants	Y	Y	<p>Intranasally-administered decongestants (vasoconstrictors) should not be used from 1 hour prior to each intranasal study medication administration.</p> <p>Pseudoephedrine-containing oral products should not be used within 12 hours prior to an intranasal treatment session.</p>	Safety and PD interaction

<b>Drug Class</b>	<b>Episodic Use (As Needed)</b>	<b>Continuous Use</b>	<b>Comments</b>	<b>Reason for Prohibition</b>
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
Metyrosine	N	N		Safety and PD interaction
Non-vitamin K antagonist oral anticoagulation agents (eg, dabigatran, rivaroxaban, apixaban)	N	N		Safety
Opioids	N	N	Note: With Sponsor approval, brief treatment with opiates may be allowed for treatment of acute injuries etc.	PD interaction
Psychostimulants (eg, amphetamines, methylphenidate, <del>modafinil</del> , <del>armodafinil</del> )	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
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: 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**

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<b>Category</b>	<b>Description</b>
<b>Functional Capacity</b>	
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.
<b>Objective Assessment</b>	
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: Reference 21

**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 schedules may be required in some countries in order to conform to local labeling.

**Global Titration Schedule:**

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 <sup>a</sup>	60 mg	60 mg	60 mg
Escitalopram	10 mg	20 mg	20 mg	20 mg
Sertraline	50 mg	100 mg	150 mg	200 mg
Venlafaxine XR	75 mg	150 mg	225 mg	225 mg

<sup>a</sup>Subjects should be initiated with 60 mg/day. Subjects that have in the past shown increased sensitivity towards serotonin reuptake inhibitors (SSRI) /norepinephrine reuptake inhibitors (SNRI) can, at the discretion of the treating physician, be started on a 30 mg dose and up-titrated to 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.<sup>31,32,36,37,60,119,120,132,133</sup> 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 with 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 with 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 with 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 with 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 eCRF 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 (esketamine)

Clinical Protocol ESKETINTRD3003 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

Signature: \_\_\_\_\_ Date: 4 April, 2017  
(Day Month Year)

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

**Janssen Research & Development \***

**Statistical Analysis Plan**

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**A Randomized, Double-blind, Multicenter, Active-Controlled Study of Intranasal Esketamine Plus an Oral Antidepressant for Relapse Prevention in Treatment-resistant Depression**

Sustenance of Esketamine Treatment Response with Repeated Doses at Intervals Determined by Symptom Severity (SUSTAIN-1)

---

**Protocol ESKETINTRD3003; Phase 3**

**JNJ-54135419 (esketamine)**

Status: Approved  
Date: 16 February 2018  
Prepared by: Janssen Research & Development, LLC  
Document No.: EDMS-ERI-126947689, 8.0

**Compliance:** The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

**Confidentiality Statement**

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



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## AMENDMENT HISTORY

SAP Version	Issue Date
Original SAP	8 June 2017
Amendment 1	20 June 2017
Amendment 2	21 June 2017
Amendment 3	16 Feb. 2018

Amendments below are listed beginning with the most recent amendment.

### Amendment 3 (16 Feb. 2018)

**The overall reason for the amendment:** Modified the language pertaining to the primary estimand, corrected typos in the log-rank test statistics calculation, added details for sensitivity analysis, and updated AE terms of special interest and added analyses of TEAEs associated with discharge readiness.

Applicable Section(s)	Description of Change (s)
Section 2.4.2	Removed the sentences that transferred-entry subjects who continue to receive an oral antidepressant plus intranasal placebo will not be included for efficacy analyses during the optimization phase or maintenance phase. Clarified that these subjects will not be included in the full analysis sets.
Section 2.5	Added consented protocol (pre/post Protocol amendment 4) and entry source (direct-entry, transferred-entry) to subgroups.
Section 5.1.1	Clarified that a positive interim efficacy analysis result $Z_{IA}$ favors intranasal esketamine plus oral antidepressant in delaying relapse compared to oral antidepressant plus intranasal placebo.
Section 5.2.1	Modified the language on the variable and intercurrent event for the primary estimand.
Section 5.2.2	Clarified that if the study is not terminated at the time of the interim analysis the final analysis will be performed on the Full (stable remitters) analysis set including all the relapse events accumulated prior to final database lock. Corrected typos in the formulas for log-rank test statistics, and further clarified the notations. Added that the estimate of the hazard ratio and confidence interval will be calculated using software R and ADDPLAN.
Section 5.2.3	Added details of the multiple imputations procedures. Added unweighted log-rank tests on the Full (stable remitters) analysis set with all the relapse events accumulated prior to database lock and 59 events.
Section 6.1	Updated terms for two of the adverse events of special interest categories: drug abuse, dependence and withdrawal, and impaired cognition. Added analyses of TEAEs associated with discharge readiness.
References	Added a reference paper on multiple imputation approach

### Amendment 2 (21 June 2017)

**The overall reason for the amendment:** Added amendment history section and included the updated version of Cogstate SAP

Applicable Section(s)	Description of Change (s)
Amendment History	Added Amendment History Section

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Attachment 1	Included the updated version of the Cogstate SAP
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**Amendment 1 (20 June 2017)****The overall reason for the amendment: Modified the language pertaining to Interim analysis to be consistent with IA SAP Amendment 1.**

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Applicable Section(s)	Description of Change (s)
Section 1.4	Modified the timing of Interim Analysis to be consistent with IA SAP Amendment 1.
Section 3	Clarified that the data cut-off date for the interim analysis will only be known by Cytel, the independent statistical support group conducting the interim analysis. The changed language is consistent with IA SAP Amendment 1.

---

**ABBREVIATIONS**

AD	Antidepressant
AE	adverse event
ANCOVA	analysis of covariance
ASA	American Society of Anesthesiologists
BMI	body mass index
BP	Blood Pressure
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
CI	confidence interval
CRF	case report form
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
DB	Double-blind
D/C	Discontinued
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (4th edition)
ECG	Electrocardiogram
eCRF	electronic case report form
ECT	electroconvulsive therapy
EQ-5D-5L	EuroQol Group; 5 dimension; 5 level
EQ-VAS	EuroQol Group: visual analogue scale
EU	European Union
FDA	Food and Drug Administration
FU	Follow-Up
GAD-7	Generalized Anxiety Disorder 7-item scale
HVLT-R	Hopkins Verbal Learning Test-Revised
IDMC	Independent Data Monitoring Committee
ICH	International Conference on Harmonization
IDS-C <sub>30</sub>	Inventory of Depressive Symptoms-Clinician rated, 30 item
IWRS	Interactive web response system
LOCF	last observation carried forward
MADRS	Montgomery-Asberg Depression Rating Scale
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview
MGH-ATRQ	Massachusetts General Hospital Antidepressant Treatment Response Questionnaire
MMRM	Mixed-effects model using repeated measures
MOAA/S	Modified Observer’s Assessment of Alertness/Sedation
OL	Open-label
PD	Pharmacodynamics
PHQ-9	Patient Health Questionnaire – 9 item
PK	pharmacokinetic(s)
PWC-20	Physician Withdrawal Checklist; 20 item
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SDS	Sheehan Disability Scale
SE	Standard error
SOC	System Organ Class
SNRI	Serotonin and Norepinephrine Reuptake Inhibitors
SSRI	Selective Serotonin Reuptake Inhibitors
TEAEs	Treatment-emergent adverse events
TEMA	treatment-emergent markedly abnormal
TRD	Treatment Resistant Depression

UPSIT            University of Pennsylvania Smell Identification Test  
XR                extended release

## 1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for all planned analyses for study JNJ54135419-ESKETINTRD3003.

### 1.1. Trial Objectives

#### Primary Objective

The primary objective of this study is to assess the efficacy of intranasal esketamine plus an oral antidepressant compared with an oral antidepressant (active comparator) plus intranasal placebo in delaying relapse of depressive symptoms in subjects with treatment resistant depression (TRD) who are in stable remission (see Definitions of Terms below) after an induction and optimization course of intranasal esketamine plus an oral antidepressant.

#### Secondary Objectives

- To assess the efficacy of intranasal esketamine plus an oral antidepressant compared with an oral antidepressant (active comparator) plus intranasal placebo in delaying relapse of depressive symptoms in subjects with TRD with stable response (but who are not in stable remission) (see Definitions of Terms below) after an induction and optimization course of intranasal esketamine plus an oral antidepressant
- To assess the effect of intranasal esketamine plus an oral antidepressant compared with an oral antidepressant (active comparator) plus intranasal placebo on:
  - Depressive symptoms
  - Overall severity of depressive illness
  - Functional impairment and associated disability
  - Anxiety symptoms
  - Health-related quality of life and health status
- To investigate the safety and tolerability of intranasal esketamine plus an oral antidepressant compared with an oral antidepressant (active comparator) plus intranasal placebo in subjects with TRD, with special attention to the following:
  - Treatment-emergent adverse events (TEAEs), including AEs of special interest
  - Local nasal tolerability
  - Effects on heart rate, blood pressure, respiratory rate, and blood oxygen saturation
  - Effects on alertness and sedation
  - Potential psychosis-like symptoms
  - Dissociative symptoms
  - Potential effects on cognitive function
  - Potential effects on suicidal ideation/behavior
  - Potential treatment-emergent symptoms of cystitis and/or lower urinary tract symptoms

- 
- Potential withdrawal and/or rebound symptoms following cessation of intranasal esketamine treatment
  - Potential effects on sense of smell

### **Exploratory Objectives**

- To assess the potential relationship of biomarkers with response/non-response to intranasal esketamine plus an oral antidepressant or to an oral antidepressant plus intranasal placebo in adult subjects with TRD
- To assess medical resource utilization

### **1.2. Trial Design**

This is a randomized, double-blind, parallel-group, active-controlled, multicenter study to evaluate the efficacy, safety, and tolerability of intranasal esketamine plus an oral antidepressant compared with an oral antidepressant (active comparator) plus intranasal placebo in delaying relapse of depressive symptoms in adult men and women with TRD who are in stable remission after an induction and optimization course with intranasal esketamine plus an oral antidepressant.

Approximately 211 subjects in stable remission (see Definition of Terms below) at the end of the optimization phase will be randomized in a 1:1 ratio to either continue intranasal esketamine (same dose) or be switched to intranasal placebo; all subjects will continue the same oral antidepressant at the same dose.

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

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 (ESKETINTRD3001 or ESKETINTRD3002) (referred to as transferred-entry subjects).

The study has up to 5 phases:

- A 4-week screening/prospective observational phase, with an optional taper of up to 3 weeks for oral antidepressant medication(s) (direct-entry subjects only)
- A 4-week open-label induction phase (direct-entry subjects only)
- A 12-week optimization phase (open-label for direct-entry subjects and double-blind for transferred-entry subjects)
- A maintenance phase (double blind and variable duration)
- A 2-week follow-up phase

The maximum duration of a subject's participation will be variable, depending on whether he or she enters the study directly or is transferred from one of the double-blind short-term studies, and whether he or she meets phase-specific criteria (e.g., meets criteria for response at the end of the induction phase, is in stable remission/response at the end of the optimization phase, and when and if he or she relapses in the maintenance phase). Direct-entry subjects may participate in up to 5 phases and transferred-entry subjects may participate in up to 3 phases.



The study will be stopped once 84 relapses (in the subjects with stable remission) occur during the maintenance phase, or earlier based on the results of the interim analysis for efficacy. At the time the study is stopped, subjects in the induction phase will be able to complete the induction phase. Those subjects who are responders after completing an Early Withdrawal Visit may proceed to the 54135419TRD3008 study without completing the follow up phase. Those who are not responders will have an Early Withdrawal Visit and proceed directly to the follow-up phase. Subjects who are in the optimization or maintenance phase at the time the study is terminated will have an Early Withdrawal Visit/End of Maintenance Visit conducted and proceed directly to the follow-up phase.

### **Screening/prospective observational phase (4-week duration)**

Direct-entry subjects will participate in this phase, which prospectively assesses treatment response to the subject's current oral antidepressant treatment regimen.

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

After 4 weeks, subjects who are non-responders to their current oral antidepressant treatment may be eligible to proceed to the open-label induction phase. Non-response at the end of the screening/prospective observational phase is defined as  $\leq 25\%$  improvement in the MADRS total score from Week 1 to Week 4 and a MADRS total score of  $\geq 28$  on Week 2 and Week 4.

Eligible subjects who are entering the open-label induction phase will discontinue all of their current antidepressant treatment(s), including adjunctive/augmentation therapies. Of note, subjects taking benzodiazepines (at dosages equal to or less than the equivalent of 6 mg/day of lorazepam) and/or permitted non-benzodiazepine sleep medications (eg, zolpidem, zaleplon) during the screening/prospective observational phase can continue these medications. No dose increases beyond the equivalent of 6 mg/day lorazepam, or new benzodiazepine are permitted during the screening/prospective observational phase. If clinically indicated, a subject's current antidepressant treatment(s) may be tapered and discontinued over an additional, optional period of up to 3 weeks per the local prescribing information or clinical judgment.

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**Open-Label induction phase (4-week duration)**

Eligible direct-entry subjects will receive intranasal esketamine (flexible dose: 56 mg or 84 mg) treatment sessions twice weekly for 4 weeks. In addition, all subjects will initiate a new, open-label oral antidepressant on Day 1 that will be taken daily for the duration of the induction phase. The assigned oral antidepressant will be 1 of 4 oral antidepressant medications (duloxetine, escitalopram, sertraline, or venlafaxine extended release [XR]), that the subject has not previously had a nonresponse to in the current depressive episode, has not been previously intolerant to (lifetime), and is available in the participating country.

At the end of the induction phase, subjects who are responders (defined as  $\geq 50\%$  reduction in the MADRS total score from baseline [Day 1 prior to the first intranasal dose] to the end of the 4-week open-label induction phase) may be eligible to proceed to the optimization phase. All subjects who do not proceed to the optimization phase will have an Early Withdrawal visit conducted and proceed to the follow-up phase.

At the time the study is stopped, subjects in the induction phase will be able to complete the phase. Those who are responders, after completing an Early Withdrawal Visit, may proceed to the 54135419TRD3008 study without completing the follow up phase. Those who are not responders will have an Early Withdrawal Visit conducted and proceed directly to the follow-up phase.

**Optimization Phase**

Eligible direct-entry subjects from the open-label induction phase and transferred-entry subjects from the 2 double-blind short-term studies (ESKETINTRD3001 and ESKETINTRD3002) will participate in this 12-week phase.

The intranasal treatment session frequency will be reduced from that in the induction phase (twice weekly) to weekly for the first 4 weeks of this phase. After the first 4 weeks, the frequency of intranasal treatment sessions will be individualized to either once weekly or once every other week based on the severity of depressive symptoms, as assessed by the MADRS total score. The dose of intranasal esketamine will remain unchanged from the dose at the end of the induction phase. All subjects will continue taking the same oral antidepressant treatment (at the same dosage) that was initiated during the induction phase.

At the end of the optimization phase, subjects in stable remission and those with stable response (but who are not in stable remission) may be eligible to continue into the maintenance phase; all other subjects will have an Early Withdrawal visit conducted and proceed to the follow-up phase.

For subjects in stable remission and those with stable response at the end of this phase, the last visit of the optimization phase (Visit 3.13; Week 16) also serves as the baseline visit (Visit 4.1; Week 16) of the maintenance phase. Subjects eligible for the maintenance phase will be randomized and receive their first double-blind intranasal treatment session of the maintenance phase at this visit.

At the time the study is stopped, subjects in the optimization phase will have an Early Withdrawal visit conducted and proceed directly to the follow-up phase.

**Definitions of terms:**

- Stable remission: MADRS total score  $\leq 12$  for at least 3 of the last 4 weeks of the optimization phase, but one excursion of a MADRS total score  $> 12$  or one missing MADRS assessment is permitted at Optimization week 13 or 14 only. The MADRS total score at weeks 15 and 16 must be  $\leq 12$ .
- Stable response:  $\geq 50\%$  reduction in the MADRS total score from baseline (Day 1 of induction phase; pre-randomization/prior to the first intranasal dose) in each of the last 2 weeks of the optimization phase, but does not meet criteria for stable remission. Note: For transferred-entry subjects, Day 1 of the induction phase will take place in ESKETINTRD3001 or ESKETINTRD3002.

**Maintenance Phase**

On Day 1 of this phase:

- Approximately 211 subjects in stable remission at the end of the optimization phase (after treatment with intranasal esketamine plus an oral antidepressant) will be randomized in a 1:1 ratio to either continue with intranasal esketamine (same dose) and the same oral antidepressant or to continue with the same oral antidepressant (active comparator) but switch to intranasal placebo. The primary efficacy analysis will be performed for these subjects only.
- Additionally, subjects with stable response (but who are not in stable remission) at the end of the optimization phase (after treatment with intranasal esketamine plus an oral antidepressant) will be randomized in a 1:1 ratio (using a separate randomization list) to either continue with intranasal esketamine (same dose) and the same oral antidepressant or to continue with the same oral antidepressant (active comparator) but switch to intranasal placebo (for a secondary efficacy analysis only).
- Transferred-entry subjects who achieve stable remission or stable response at the end of the optimization phase after treatment with an oral antidepressant plus intranasal placebo will continue to receive the same treatment in order to maintain the blinding for the ongoing short-term studies. These subjects will not be included in the efficacy analyses, but will be included in safety analyses.

The frequency of intranasal treatment sessions will be further individualized during the maintenance phase to once weekly or once every other week based on the severity of depressive symptoms, as assessed by the MADRS total score. Subjects will only be permitted to switch from weekly to every other week dosing a total of 3 times during the maintenance phase. After this time, if a given subject is unable to sustain improvement on every other week dosing they will remain on a weekly dosing regimen for the duration of this phase.

This phase will have a variable duration, continuing until 84 relapses occur in the subjects with stable remission, or earlier based on interim analysis results.

Subjects who meet the relapse criteria and subjects who remain relapse-free at study termination will have an End of Maintenance Phase visit conducted and may proceed to the follow-up phase. If clinically indicated, subjects who have met relapse criteria after completing the end of maintenance visit may proceed to the open-label safety extension study, 54135419TRD3008, without completing the follow up phase. Subjects who are participating in the maintenance phase

at the time the study is stopped will have an Early Withdrawal Visit conducted and proceed directly to the follow-up phase.

**Relapse is defined as any of the following:**

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

In case both relapse criteria are met, the earlier date will be defined as the date of relapse for this subject

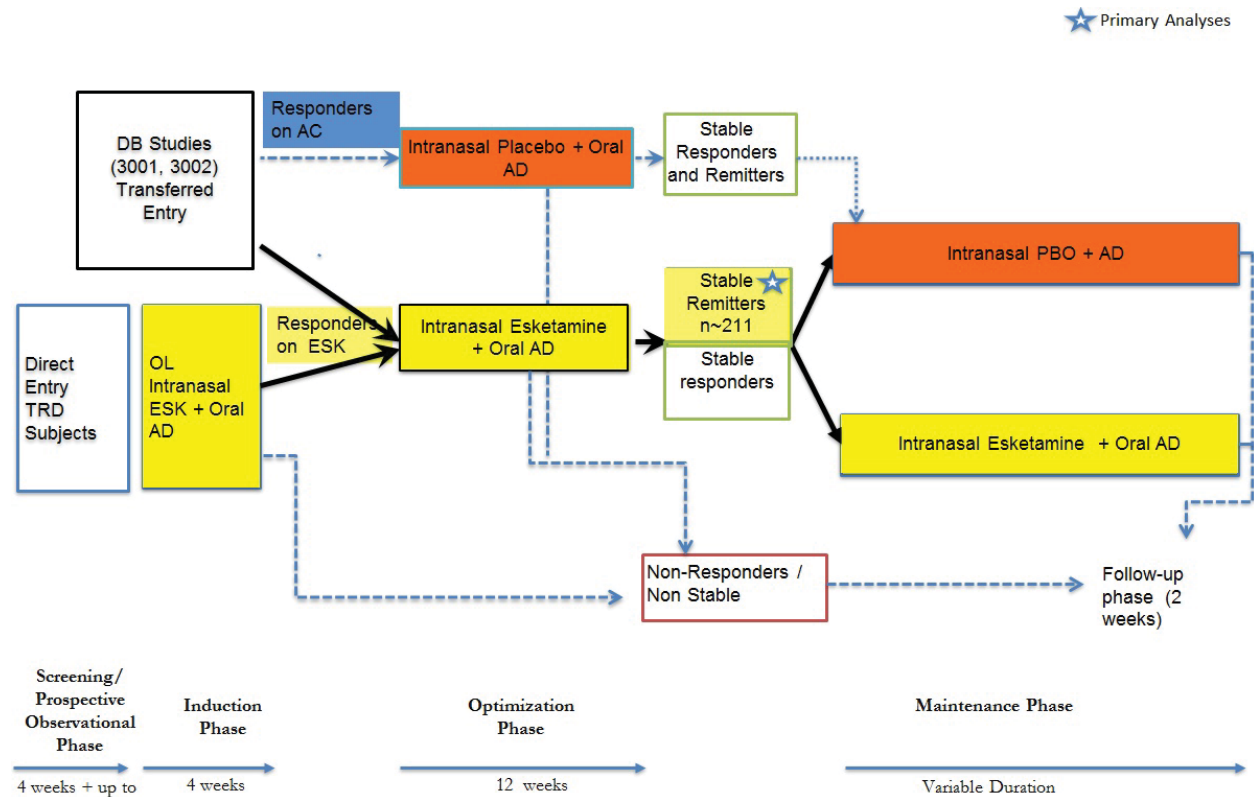
**Follow-up Phase**

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 and 2 weeks after the last clinic visit.

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 treatment administered during this phase. Subjects will be provided with an additional 2-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, it is recommended that the oral antidepressant be continued during the 2-week follow-up phase unless determined as not clinically appropriate.

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

Figure 1: Schematic Overview of the Study



AC = active comparator; AD = antidepressant; DB = double-blind; ESK = esketamine; OL = open-label; PBO = placebo; TRD = treatment-resistant depression.

The study will end when 84 relapses are reached. An interim analysis will be performed at 30 relapses.

### 1.3. Statistical Hypotheses for Trial Objectives

The hypothesis for this study is that intranasal esketamine plus an oral antidepressant is more effective than treatment with an oral antidepressant plus intranasal placebo in delaying relapse of depressive symptoms in subjects with TRD in stable remission.

### 1.4. Sample Size Justification

The maximum number of relapses (in the subjects with stable remission) required by this study is 84, which provides 90% power to detect a hazard ratio of 0.493 at the 1-sided significance level of 0.025 for a fixed-sample design to detect superiority of esketamine plus oral antidepressant over antidepressant alone in delaying relapse of depressive symptoms in subjects with TRD who are in stable remission. The calculation of sample size assumed that the time to the first relapse follows an exponential distribution, with a median time of 6 months for oral antidepressant alone and 12.17 months for intranasal esketamine plus oral antidepressant (hazard ratio = 0.493). The corresponding 6-month relapse rates are 50% for oral antidepressant alone and 28.95% for oral antidepressant plus intranasal esketamine.

Assumptions were made for accrual period and rate, maximum study duration, and dropout rate. Based on such assumptions, a total of approximately 211 subjects in stable remission need to be randomized (in a 1:1 ratio) in order to obtain 84 relapses.

## Interim Analysis

To evaluate the assumptions used in the sample size calculation, relapse rates will be monitored sequentially during the maintenance phase. In particular, a 2-stage group-sequential design will be adopted, with 1 interim analysis (IA) to be performed when at least 33 relapse events have occurred in stable remitters with at least 30 relapses from subjects treated with intranasal esketamine plus an oral antidepressant in the optimization phase. If 33 relapses are reported in stable remitters and the notification is not triggered by the IWRS system, further determination of the timing of interim analysis will be made at every third relapse reported in stable remitters. Making this assessment at every third relapse will help in maintaining the blind. Early termination of the maintenance phase for efficacy will be based on interim analysis results. At the interim analysis, if the study is not stopped for efficacy then a sample size re-estimation will be performed. The study will continue until a maximum of 84 relapses are observed.

If the study is not terminated at the interim analysis, the sample size will be re-estimated to ensure a conditional power at Stage 2 of at least 90% with a minimum number of relapses after interim to be 29 and a maximum number of relapses after interim to be 54 (with 30 relapses having occurred before the IA).

A rigorous interim statistical analysis plan (SAP) and charter will be developed detailing the algorithm for a sample size re-estimation based on the interim data and how the analysis will be executed. An IDMC will perform the interim analysis and will make recommendations for any sample size adjustment based on the rules defined in the interim SAP. Any changes to sample size will be communicated by the IDMC (or the statistician from the Statistical Support Group) to the IWRS vendor to ensure that the appropriate number of subjects is enrolled in the study. None of the esketamine team members or staff members at the investigational sites conducting the clinical study will be informed of the results of the interim analysis and any adjustments that will be made to the sample size; however, the clinical supplies group will be informed of the decision made at the interim analysis so that only the required amount of study medication will be packaged.

Procedures will be in place to ensure that the results of the interim analysis do not influence the conduct of the study, investigators, or subjects.

### 1.5. Randomization and Blinding

Blinded intranasal treatment will be used in the optimization phase (for transferred-entry subjects only) to avoid unblinding the short-term studies at the individual level, and in the maintenance phase (for all subjects) to reduce potential bias during data collection and evaluation of clinical endpoints. An intranasal placebo control will be used in the maintenance phase to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of intranasal active treatment.

Central randomization will be implemented in the maintenance phase of this study. At the start of the maintenance phase, subjects in stable remission after treatment with intranasal esketamine plus an oral antidepressant will be randomly assigned to 1 of 2 intranasal medication treatment

groups (intranasal esketamine or intranasal placebo) in a 1:1 ratio based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by country. All subjects will continue their current oral antidepressant.

Although not part of the primary analysis, subjects in stable response (but who are not in stable remission) after treatment with intranasal Esketamine plus an oral antidepressant will also be randomly assigned to 1 of 2 intranasal medication treatment groups in a 1:1 ratio based on a separate computer-generated randomization schedule (ie, different schedule for the subjects in stable remission) prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by country. All subjects will continue their current oral antidepressant.

Transferred-entry subjects who achieve stable remission or stable response after treatment with intranasal placebo plus an oral antidepressant will continue to receive the same treatment in order to maintain the blinding for the ongoing short-term studies. These subjects will not be randomized during the maintenance phase.

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

Data that may potentially unblind the treatment assignment (e.g., study drug plasma concentrations, study drug accountability data) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized.

## **2. GENERAL ANALYSIS DEFINITIONS**

### **2.1. Analysis Phases**

There are 5 analysis phases defined in this study:

- A 4-week screening/prospective observational phase, with an optional taper of up to 3 weeks for oral antidepressant medication(s) (direct-entry subjects only)
- Open-label induction phase (direct-entry subjects only)
- Optimization phase (open-label for direct-entry subjects and double-blind for transferred-entry subjects)
- Maintenance phase (double blind and of variable duration)
- Follow-up (post treatment) phase

Each analysis phase has its own analysis phase start and end dates.

#### **2.1.1. Study Reference Start and End Dates**

For direct-entry subjects, the reference start date for the study is defined as the earlier of date of the first dose of intranasal study medication or oral antidepressant (the date is missing for

screened subjects who did not take any intranasal study drug or oral antidepressant). For transferred-entry subjects, the reference start date of the study is the date of first dose of oral antidepressant in the optimization phase, if available; in instances where the start date of oral antidepressant medication is not available, the reference start date is the informed consent date. The reference end date for the study is the end of trial date including the last follow-up visit.

### **2.1.2. Analysis Phase Start and End Dates**

#### **Screening/Prospective Observational Phase**

The start date of the screening/prospective observational phase is the informed consent date. For subjects who continue to the open-label induction phase, the screening/prospective observational phase end date is the open-label induction phase start date.

The start and end dates for the screening/prospective observational phase are defined for direct entry subjects only.

#### **Open-Label Induction Phase**

The open-label induction phase will begin on the day (referred to as, 'IND start date') of the first dose of intranasal medication or oral antidepressant taken in the open-label induction phase (only for direct-entry subjects). For subjects who continue to the optimization phase, the open-label induction phase end date (referred to as, 'IND end date') (only for direct-entry subjects) is the date of first dose of oral antidepressant medication taken in the optimization phase or the date of the last visit in the open-label induction phase if the date of the first oral medication is missing. For subjects who discontinue in the open-label induction phase, the IND end date is the maximum of the date of last visit in the open-label induction phase and the date of early termination.

The start date/time of the open-label induction phase (referred to as, 'IND start date/time') is the IND start date and the time of the first dose of intranasal study medication in this phase. If no intranasal study medication is administered or it is administered after the start of oral antidepressant, then the time will be left blank.

The start and end dates for the open-label induction phase are defined for direct entry subjects only.

#### **Optimization Phase**

The optimization phase will begin on the day of first dose of oral antidepressant medication in this phase (referred to as, 'OP start date'). If the date of first dose of oral antidepressant is missing, the OP start date for direct-entry subjects is the date of last visit in the open label induction phase and for the transfer-entry subjects it is the date of their informed consent. For subjects who continue to the maintenance phase, the optimization phase end date (referred to as, 'OP end date') is the date when the intranasal medication was started in the maintenance phase. For subjects who discontinue in the optimization phase, the OP end date is the maximum of the date of last visit in the optimization phase and the date of early termination.



## Maintenance Phase

The maintenance phase will begin on the day of the first dose of intranasal medication or oral antidepressant taken in the maintenance phase (referred to as, 'MA start date'). For subjects who complete/discontinue from the maintenance phase, the maintenance phase end date (referred to as, 'MA end date') is the maximum of the date of last visit in the maintenance phase, date of completion of the maintenance phase due to relapse or study termination, and date of early withdrawal in the maintenance phase.

## Follow-Up Phase

The start date of the Follow-up (post-treatment) phase (referred to as 'F/U start date') is the day after the end date for the last treatment phase the subject participated in. The follow-up phase end date (referred to as 'F/U end date') is the maximum of the last follow-up visit date or the end of trial date.

### 2.1.3. Study Day and Relative Day

Study day is calculated relative to the reference start date for the study. Relative day is calculated relative to the analysis phase start date of the analysis phase in which the data are captured. A minus (-) sign indicates days prior to the start of study or prior to the start of the analysis phase.

Study day for an event on or after the start of the study is calculated as:

$$\text{event date} - \text{reference start date} + 1.$$

Study day for an event prior to the start of the study is calculated as:

$$\text{event date} - \text{reference start date}$$

Relative day for an event on or after the analysis phase start date is calculated as:

$$\text{event date} - \text{analysis phase start date} + 1.$$

Relative day for an event prior to the analysis phase start date is calculated as:

$$\text{event date} - \text{analysis phase start date}.$$

There is no study day 0 or relative day 0.

## 2.2. Baseline and End Point

Baseline is defined for each parameter/assessment.

- Open-label induction phase:
  - Direct-entry subjects: The last observation prior to or on the start date of open-label induction phase is denoted as, 'Baseline (IND)'. This pertains to direct-entry subjects.
  - Transferred-entry subjects: The last observation prior to or on the start date of the double-blind induction phase will be used as the baseline. This is also denoted as

‘Baseline (IND)’. (Baseline (IND) is computed in the databases for studies 3001 and 3002 and will be copied into study 3003).

- The ‘Average Predose’ value for the ECG measurements is defined as the average of all non-missing assessments on or before the first dose of study medication. For transferred-entry subjects the ‘Average Predose’ is computed in the databases for studies 3001 and 3002 and will be copied into study 3003.
- Optimization phase: The last observation prior to or on the start date of optimization phase is denoted as, ‘Baseline (OP)’.
- Maintenance phase: The last observation prior to or on the start date of maintenance phase is denoted as, ‘Baseline (MA)’.

For each variable measured over time, the ‘End Point (IND)’ value is defined as the last postbaseline assessment value during the open-label induction Phase. This value will be the same as the Baseline (OP) value for subjects who continue into the optimization phase.

The ‘End Point (OP)’ value is defined as the last postbaseline assessment value during the optimization phase. This value will be the same as the Baseline (MA) value for subjects who continue into the maintenance phase for scales without pre/post dose measurement.

The ‘End Point (MA)’ value is defined as the last postbaseline assessment value during the maintenance phase.

### **2.3. Visit Windows**

As subjects do not always adhere to the protocol visit schedule, the following rules are applied to assign actual visits to protocol visits. Listed below are the visit windows for analysis and the target days for each visit. The reference day is Study Day 1 (which is the first day that study drug was taken in the open-label induction phase for direct-entry subjects and the first day that study drug was taken in the double-blind induction phase for transferred-entry subjects).

If a subject has 2 or more scheduled or unscheduled visits in one visit window, the visit closest to the target day will be used as the protocol visit for that visit window. If 2 actual visits are equidistant from the target day within a visit window, the later visit is used. If a visit window has no scheduled visits but does have unscheduled visits, then the unscheduled visit closest to the scheduled visit will be used.

All assignments will be made in chronological order. Once a visit is assigned to a visit window, it will no longer be used for a later time point except for the end point.

Listed below are the visit windows and the target days (if applicable) for each visit defined in the protocol for all phases ([Table 1](#)).

**Table 1: Analysis Visits**

Parameter	Analysis Phase	Scheduled Day	Time Interval (label on output)	Time Interval (Day) <sup>a</sup>	Target Time Point from start of each phase (Day)	
MADRS	Screening		Week 1 (SC)			
			Week 2 (SC)			
			Week 4 (SC)			
	IND	1	Baseline (IND)	<= 1	1	
		8	Day 8 (IND)	2-11	8	
		15	Day 15 (IND)	12-18	15	
		22	Day 22 (IND)	19-24	22	
		28	Day 28 (IND)	25 to end of IND	28	
		IND final visit	End Point (IND)	2 to end of IND		
	OP	28	Baseline (OP)	<= 1	1	
		32	Week 1 (OP)	2-8	5	
		39	Week 2(OP)	9-15	12	
		46	Week 3 (OP)	16-22	19	
		53	Week 4 (OP)	23-29	26	
		60	Week 5 (OP)	30-36	33	
		67	Week 6 (OP)	37-43	40	
		74	Week 7 (OP)	44-50	47	
		81	Week 8 (OP)	51-57	54	
		88	Week 9 (OP)	58-64	61	
		95	Week 10 (OP)	65-71	68	
		102	Week 11 (OP)	72-78	75	
		109	Week 12 (OP)	79 to end of OP	82	
		OP final visit	End Point (OP)	2 to end of OP		
	MA Weekly x=1,2, 3...	109	Baseline (MA)	<= 1	1	
		116	Week 1 (MA)	2-11	8	
		116 + x*7	Week (x+1) (MA)	5 + x*7 to 11 + x*7	8 + x*7	
		MA final visit	End Point (MA)	2 to end of MA		
	F/U	F/U Day7 (Last dose +7 days)	F/U Week 1	1 - 10	7	
		F/U Day 14 (Last dose +14 days)	F/U Week 2	11 to end of F/U	14	
		F/U final visit	End Point (F/U)	1 to end of F/U		
	CGI-S	Screening		Week 1 (SC)		
		IND	1	Baseline (IND)	<=1	1
			4	Day 4 (IND)	2-6	4
8			Day 8 (IND)	7-9	8	
11			Day 11 (IND)	10-13	11	
15			Day 15 (IND)	14-18	15	
22			Day 22 (IND)	19-24	22	
28			Day 28 (IND)	25 to end of IND	28	
IND final visit	End Point (IND)	2 to end of IND				

**Table 1: Analysis Visits**

Parameter	Analysis Phase	Scheduled Day	Time Interval (label on output)	Time Interval (Day) <sup>a</sup>	Target Time Point from start of each phase (Day)
	OP	28	Baseline (OP)	<= 1	1
		32	Week 1 (OP)	2-8	5
		39	Week 2(OP)	9-15	12
		46	Week 3 (OP)	16-22	19
		53	Week 4 (OP)	23-29	26
		60	Week 5 (OP)	30-36	33
		67	Week 6 (OP)	37-43	40
		74	Week 7 (OP)	44-50	47
		81	Week 8 (OP)	51-57	54
		88	Week 9 (OP)	58-64	61
		95	Week 10 (OP)	65-71	68
		102	Week 11 (OP)	72-78	75
		109	Week 12 (OP)	79 to end of OP	82
	OP final visit	End Point (OP)	2 to end of OP		
	MA x = 1,2,3...	109	Baseline (MA)	<= 1	1
		123	Week 2 (MA)	2 – 22	15
		137	Week 4 (MA)	23 – 32	29
		144	Week 5 (MA)	33 – 39	36
		144 + x*7	Week (x + 5) (MA)	33+ x*7 to 39 + x*7	36 + x*7
	MA final visit	End Point (MA)	2 to end of MA		
F/U	F/U Day 14 (Last dose +14 days)	F/U Week 2	1 to end of F/U	14	
PHQ-9 and EQ-5D-5L	Screening		Week 1 (SC)		
	IND	1	Baseline (IND)	<= 1	1
		15	Day 15 (IND)	2-21	15
		28	Day 28 (IND)	22 to end of IND	28
		IND final visit	End Point (IND)	2 to end of IND	
	OP	28	Baseline (OP)	<= 1	1
		39	Week 2 (OP)	2-19	12
		53	Week 4 (OP)	20-33	26
		67	Week 6 (OP)	34-47	40
		81	Week 8 (OP)	48-61	54
		95	Week 10 (OP)	62-75	68
		109	Week 12 (OP)	76 to end of OP	82
		OP final visit	End Point (OP)	2 to end of OP	
	MA Every 2 weeks x= 1,2,3...	109	Baseline (MA)	<= 1	1
		123	Week 2 (MA)	2-22	15
		137	Week 4 (MA)	23-36	29
		137+14*x	Week (4 + x*2) (MA)	23 + x*14 to 36 + x*14	29 + x*14
		MA final visit	End Point (MA)	2 to end of MA	
	F/U	F/U Day 14 (Last dose +14 days)	F/U Week 2	1 to end of F/U	14

**Table 1: Analysis Visits**

Parameter	Analysis Phase	Scheduled Day	Time Interval (label on output)	Time Interval (Day) <sup>a</sup>	Target Time Point from start of each phase (Day)
GAD-7	Screening		Week 1 (SC)		
	IND	1	Baseline (IND)	<= 1	1
		28	Day 28 (IND)	2 to end of IND	28
	OP	28	Baseline (OP)	<= 1	1
		53	Week 4 (OP)	2-33	26
		67	Week 6 (OP)	34-47	40
		81	Week 8 (OP)	48-68	54
		109	Week 12 (OP)	69 to end of OP	82
		OP final visit	End Point (OP)	2 to end of OP	
	MA Every 4 weeks x=1,2,3...	109	Baseline (MA)	<= 1	1
		137	Week 4 (MA)	2-43	29
		137+x*28	Week (4+x*4) (MA)	16+ x*28 to 43+x*28	29 + x*28
		MA final visit	End Point (MA)	2 to end of MA	
	F/U	F/U Day 14 (Last dose +14 days)	F/U Week 2	1 to end of F/U	14
	SDS	Screening		Week 1 (SC)	
IND		1	Baseline (IND)	<=1	1
		15	Day 15 (IND)	2-21	15
		28	Day 28 (IND)	22 to end of IND	28
		IND final visit	End Point (IND)	2 to end of IND	
OP		28	Baseline (OP)	<= 1	1
		53	Week 4 (OP)	2-40	26
		81	Week 8 (OP)	41-68	54
		109	Week 12 (OP)	69 to end of OP	82
		OP final visit	End Point (OP)	2 to end of OP	
MA Every 4 weeks x=1,2,3...		109	Baseline (MA)	<= 1	1
		137	Week 4 (MA)	2-43	29
		137+x*28	Week (4+x*4) (MA)	16+ x*28 to 43 + x*28	29 + x*28
		MA final visit	End Point (MA)	2 to end of MA	
F/U		F/U Day 14 (Last dose +14 days)	F/U Week 2	1 to end of F/U	14
C-SSRS (BL/SC version and since last visit version)	Screening		Week 2 (SC)		
			Week 4 (SC)		
	IND	1	Baseline (IND)	<=1	1
		4	Day 4 (IND)	2-6	4
		8	Day 8 (IND)	7-9	8
		11	Day 11 (IND)	10-13	11
		15	Day 15 (IND)	14-16	15
		18	Day 18 (IND)	17-20	18
		22	Day 22 (IND)	21- 23	22
		25	Day 25 (IND)	24-26	25
		28	Day 28 (IND)	27 to end of IND	28
IND final visit	End Point (IND)	2 to end of IND			

**Table 1: Analysis Visits**

Parameter	Analysis Phase	Scheduled Day	Time Interval (label on output)	Time Interval (Day) <sup>a</sup>	Target Time Point from start of each phase (Day)
	OP	28	Baseline (OP)	<= 1	1
		32	Week 1 (OP)	2-8	5
		39	Week 2(OP)	9-15	12
		46	Week 3 (OP)	16-22	19
		53	Week 4 (OP)	23-29	26
		60	Week 5 (OP)	30-36	33
		67	Week 6 (OP)	37-43	40
		74	Week 7 (OP)	44-50	47
		81	Week 8 (OP)	51-57	54
		88	Week 9 (OP)	58-64	61
		95	Week 10 (OP)	65-71	68
		102	Week 11 (OP)	72 to end of OP	75
	OP final visit	End Point (OP)	2 to end of OP		
	MA Weekly x=1,2, 3...	102	Baseline (MA)	<= 1	1
		116	Week 1 (MA)	2-11	8
		116 + x*7	Week (x+1) (MA)	5 + x*7 to 11 + x*7	8 + x*7
		MA final visit	End Point (MA)	2 to end of MA	
F/U	F/U Day 14 (Last dose +14 days)	F/U Week 2	1 to end of F/U	14	
MOAA/S <sup>c</sup> , Pulse Oximetry <sup>d</sup> (predose and every 15 minutes to 1.5H)  BPRS+ and CADSS (predose, 40M, 1.5H)  CGADR <sup>e</sup> (1H, 1.5H)	IND	1	Day 1 (IND)	<=1	1
		4	Day 4 (IND)	2-6	4
		8	Day 8 (IND)	7-9	8
		11	Day 11 (IND)	10-13	11
		15	Day 15 (IND)	14-16	15
		18	Day 18 (IND)	17-20	18
		22	Day 22 (IND)	21- 23	22
		25	Day 25 (IND)	24 to end of IND	25
	OP	32	Week 1 (OP)	1-8	5
		39	Week 2(OP)	9-15	12
		46	Week 3 (OP)	16-22	19
		53	Week 4 (OP)	23-29	26
		60	Week 5 (OP)	30-36	33
		67	Week 6 (OP)	37-43	40
		74	Week 7 (OP)	44-50	47
		81	Week 8 (OP)	51-57	54
		88	Week 9 (OP)	58-64	61
		95	Week 10 (OP)	65-71	68
	102	Week 11 (OP)	72 to end of OP	75	
	MA Weekly x=1,2, 3...	109	Day 1 (MA)	1	1
		116	Week 1 (MA)	2-11	8
		116 + x*7	Week (x+1) (MA)	5 + x*7 to 11 + x*7	8 + x*7

**Table 1: Analysis Visits**

Parameter	Analysis Phase	Scheduled Day	Time Interval (label on output)	Time Interval (Day) <sup>a</sup>	Target Time Point from start of each phase (Day)
BPIC-SS	IND	1	Baseline (IND)	<= 1	1
		15	Day 15 (IND)	2-21	15
		28	Day 28 (IND)	22 to end of IND	28
		IND final visit	End Point (IND)	2 to end of IND	
	OP	28	Baseline (OP)	<= 1	1
		32	Week 1 (OP)	2-15	5
		53	Week 4 (OP)	16-40	26
		81	Week 8 (OP)	41-68	54
		109	Week 12 (OP)	69 to end of OP	82
		OP final visit	End Point (OP)	2 to end of OP	
		MA Every 4 weeks x=1,2, 3...	109	Baseline (MA)	<= 1
	137		Week 4 (MA)	2-43	29
	137+x*28		Week (4 + x*4) (MA)	16 + x*28 to 43 + x*28	x*28 + 29
	MA final visit		End Point (MA)	2 to end of MA	
F/U	F/U Day 14 (Last dose +14 days)	F/U Week 2	1 to end of F/U	14	
PWC-20	IND	IND final visit	End Point (IND)	2 to end of IND	
	OP (Only for subjects not entering MA)	OP final visit	End Point (OP)	1 to end of OP	
	MA	MA final visit	End Point (MA)	1 to end of MA	
	F/U	F/U Day 7 (Last dose +7 days)	F/U Week 1	1 to 10	7
		F/U Day 14 (Last dose +14 days)	F/U Week 2	11 to end of F/U	14
		F/U final	End Point (F/U)	1 to end of F/U	
Nasal Symptom Questionnaire	IND	1	Day 1 (IND)	<= 1	1
		4	Day 4 (IND)	2-7	4
		11	Day 11 (IND)	8-14	11
		18	Day 18 (IND)	15-21	18
		25	Day 25 (IND)	22 to end of IND	25
	IND final visit	End Point (IND)	1/postdose to end of IND		
	OP	32	Week 1 (OP)	1-8	5
		39	Week 2(OP)	9-15	12
		46	Week 3 (OP)	16-22	19
		53	Week 4 (OP)	23-29	26
		60	Week 5 (OP)	30-36	33
		67	Week 6 (OP)	37-43	40
		74	Week 7 (OP)	44-50	47
		81	Week 8 (OP)	51-57	54
		88	Week 9 (OP)	58-64	61
95		Week 10 (OP)	65-71	68	
102	Week 11 (OP)	72 to end of OP	75		
OP final visit	End Point (OP)	1/postdose to end of OP			
MA	109	Day 1 (MA)	1	1	

**Table 1: Analysis Visits**

Parameter	Analysis Phase	Scheduled Day	Time Interval (label on output)	Time Interval (Day) <sup>a</sup>	Target Time Point from start of each phase (Day)
	Every 4 weeks x=1,2, 3...	123	Week 2 (MA)	2-22	15
		137	Week 4 (MA)	23-43	29
		165	Week 8 (MA)	44 - 71	57
		165 + x*28	Week (8+ x*4) (MA)	44 + x*28 to 71 + x*28	57 + x*28
		MA final visit	End Point (MA)	1/postdose to end of MA	
Smell Threshold Test	IND	1	Baseline (IND)	<= 1	1
		28	Day 28 (IND)	2 to end of IND	28
		IND final visit	End Point (IND)	2 to end of IND	
	OP	28	Baseline (OP)	<= 1	1
		109	Week 12 (OP)	2 to end of OP	82
		OP final visit	End Point (OP)	2 to end of OP	
	MA Every 12 weeks x=1,2, 3...	109	Baseline (MA)	<= 1	1
		193	Week 12 (MA)	2-127	85
		277	Week 24 (MA)	128-211	169
		277 + x*84	Week (24 + x*12)	128 + x*84 to 211 + x*84	169 + x*84
		MA final visit	End Point (MA)	2 to end of MA	
	UPSIT	IND	1	Baseline (IND)	<= 1
15			Day 15 (IND)	2 -21	15
28			Day 28 (IND)	22 to end of IND	28
IND final visit			End Point (IND)	2 to end of IND	
OP		28	Baseline (OP)	<= 1	1
		81	Week 8 (OP)	2 to end of OP	54
		OP final visit	End Point (OP)	2 to end of OP	
MA Every 8 weeks x=1,2, 3...		81	Baseline (MA)	<=1	1
		137	Week 4 (MA)	2-57	29
		193	Week 12 (MA)	58-113	85
		193 + 56*x	Week (12 + x*8)	58 + x*56 to 113 + x*56	85 + x*56
		MA final visit	End Point (MA)	2 to end of MA	
HRUQ	OP	39	Week 2 (OP)	<= 19	12
		53	Week 4 (OP)	20-33	26
		67	Week 6 (OP)	34-47	40
		81	Week 8 (OP)	48-61	54
		95	Week 10 (OP)	62-75	68
		109	Week 12 (OP)	76 to end of OP	82
		OP final visit	End Point (OP)	2 to end of OP	
	MA Every 2 weeks x=1,2, 3...	109	Baseline (MA)	<= 1	1
		123	Week 2 (MA)	2-22	15
		137	Week 4 (MA)	23-36	29
		137+14*x	Week (4+x*2) (MA)	x*14+23 to x*14+36	x*14 + 29
		MA final visit	End Point (MA)	2 to end of MA	
	F/U	F/U Day 14 (Last dose +14 days)	F/U Week 2	1 to end of F/U	14



**Table 1: Analysis Visits**

Parameter	Analysis Phase	Scheduled Day	Time Interval (label on output)	Time Interval (Day) <sup>a</sup>	Target Time Point from start of each phase (Day)
Hematology, chemistry from LAB	IND	1	Baseline (IND)	<=1	1
		28	Day 28 (IND)	2 to end of IND	28
		IND final visit	End Point (IND)	2 to end of IND	
	OP	28	Baseline (OP)	<= 1	1
		53	Week 4 (OP)	2-40	26
		81	Week 8 (OP)	41-68	54
		109	Week 12 (OP)	69 to end of OP	82
		OP final visit	End Point (OP)	2 to end of OP	
	MA Every 4 weeks x=1,2,3...	109	Baseline (MA)	<= 1	1
		137	Week 4 (MA)	2-43	29
		137+x*28	Week (4+x*4) (MA)	16+ x*28 to 43 + x*28	29 + x*28
		MA final visit	End Point (MA)	2 to end of MA	
	F/U	F/U Day 14 (Last dose +14 days)	F/U Week 2	1 to end of F/U	14
Vital Signs (TEMP [predose at each visit], BP <sup>b</sup> , Pulse, RR, (at each visit, predose, 40M, 1H, 1.5H))	IND	1	Baseline (IND) <sup>†</sup> Day 1 (IND): 40M Day 1 (IND): 1H Day 1 (IND): 1.5H	<=1/predose	1
		4	Day 4 (IND): Predose Day 4 (IND): 40M Day 4 (IND): 1H Day 4 (IND): 1.5H	2-6	4
		8	Day 8 (IND): Predose Day 8 (IND): 40M Day 8 (IND): 1H Day 8 (IND): 1.5H	7-9	8
		11	Day 11 (IND): Predose Day 11 (IND): 40M Day 11 (IND): 1H Day 11 (IND): 1.5H	10-13	11
		15	Day 15 (IND): Predose Day 15 (IND): 40M Day 15 (IND): 1H Day 15 (IND): 1.5H	14-16	15
		18	Day 18 (IND): Predose Day 18: 40M Day 18: 1H Day 18: 1.5H	17-20	18
			Day 22 (IND): Predose		

**Table 1: Analysis Visits**

Parameter	Analysis Phase	Scheduled Day	Time Interval (label on output)	Time Interval (Day) <sup>a</sup>	Target Time Point from start of each phase (Day)
		22	Day 22 (IND): 40M Day 22 (IND): 1H Day 22 (IND): 1.5H	21-23	22
		25	Day 25 (IND): Predose Day 25 (IND): 40M Day 25 (IND): 1H Day 25 (IND): 1.5H	24 to end of IND	25
		IND final visit	End Point (IND)	Day 1: 40M to end of IND	
	OP	25	Baseline (OP)	<= 1	1
		32	Week 1 (OP): Predose Week 1 (OP): 40M Week 1 (OP): 1H Week 1 (OP): 1.5H	1-8	5
		39	Week 2 (OP): Predose Week 2 (OP): 40M Week 2 (OP): 1H Week 2 (OP): 1.5H	9-15	12
		46	Week 3 (OP): Predose Week 3 (OP): 40M Week 3 (OP): 1H Week 3 (OP): 1.5H	16-22	19
		53	Week 4 (OP): Predose Week 4 (OP): 40M Week 4 (OP): 1H Week 4 (OP): 1.5H	23-29	26
		60	Week 5 (OP): Predose Week 5 (OP): 40M Week 5 (OP): 1H Week 5 (OP): 1.5H	30-36	33
		67	Week 6 (OP): Predose Week 6 (OP): 40M Week 6 (OP): 1H Week 6 (OP): 1.5H	37-43	40
		74	Week 7 (OP): Predose Week 7 (OP): 40M Week 7 (OP): 1H Week 7 (OP): 1.5H	44-50	47
			Week 8 (OP):		

**Table 1: Analysis Visits**

Parameter	Analysis Phase	Scheduled Day	Time Interval (label on output)	Time Interval (Day) <sup>a</sup>	Target Time Point from start of each phase (Day)
		81	Predose Week 8 (OP): 40M Week 8 (OP): 1H Week 8 (OP): 1.5H	51-57	54
		88	Week 9 (OP): Predose Week 9 (OP): 40M Week 9 (OP): 1H Week 9 (OP): 1.5H	58-64	61
		95	Week 10 (OP): Predose Week 10 (OP): 40M Week 10 (OP): 1H Week 10 (OP): 1.5H	65-71	68
		102	Week 11 (OP): Predose Week 11 (OP): 40M Week 11 (OP): 1H Week 11 (OP): 1.5H	72-79	75
		109 (only for Predose)	Week 12 (OP) Predose	80 to end of OP	82
		OP final visit	End Point (OP)	Day 1: 40M to end of OP/Day 1(MA):Predose	
	MA Weekly x=1,2, 3...	109	Baseline (MA) <sup>g</sup> Day 1 (MA): 40M Day 1 (MA): 1H Day 1 (MA): 1.5H	<=1/predose	1
		116	Week 1 (MA) Predose Week 1 (MA): 40M Week 1 (MA): 1H Week 1 (MA): 1.5H	2-11	8
		116 + x*7	Week (x+1) (MA) Predose Week (x+1) (MA): 40M Week (x+1) (MA): 1H Week (x+1) (MA): 1.5H	x*7 + 5 to x*7 + 11	x*7 + 8
		MA final visit	End Point (MA)	Day 1: 40M to end of MA	
		F/U	F/U Day 14 (Last dose +14 days)	F/U Week 2	1 to end of F/U

**Table 1: Analysis Visits**

Parameter	Analysis Phase	Scheduled Day	Time Interval (label on output)	Time Interval (Day) <sup>a</sup>	Target Time Point from start of each phase (Day)	
Urinalysis	IND	1	Baseline (IND)	<= 1	1	
		15	Day 15 (IND)	2-21	15	
		28	Day 28 (IND)	22 to end of IND	28	
		IND final visit	End Point (IND)	2 to end of IND		
	OP	28	Baseline (OP)	<= 1	1	
		53	Week 4 (OP)	2-40	26	
		81	Week 8 (OP)	41-68	54	
		109	Week 12 (OP)	69 to end of OP	82	
	OP final visit	OP final visit	End Point (OP)	2 to end of OP		
		MA Every 4 weeks x=1,2, 3...	109	Baseline (MA)	<= 1	1
			137	Week 4 (MA)	2-43	29
			137+x*28	Week (4+x*4) (MA)	16+ x*28 to 43+x*28	x*28 + 29
	MA final visit		End Point (MA)	2 to end of MA		
F/U (only for Urinalysis)	F/U Day 14 (Last dose +14 days)	F/U Week 2	1 to end of F/U	14		
12-lead ECG	IND	Screening, 1	Average Predose	<=1/Predose	1	
		1	Day 1 (IND):1H	1	1	
		8	Day 8 (IND): 1H	2-11	8	
		15	Day 15 (IND): 1H	12-20	15	
		25	Day 25 (IND): 1H	21 to end of IND	25	
		IND final visit	End Point (IND)	2 to end of IND		
	OP	25	Baseline (OP)	<= 1, Predose	1	
		32	Week 1 (OP): 1H	1-15	5	
		53	Week 4 (OP): 1H	16-29	26	
		60	Week 5 (OP): 1H	30-40	33	
		74	Week 7 (OP): 1H	41-50	47	
		81	Week 8 (OP): 1H	51-57	54	
		88	Week 9 (OP): 1H	58-68	61	
		102	Week 11 (OP): 1H	69 to end of OP	75	
	OP final visit	OP final visit	End Point (OP)	2 to end of OP		
		MA Every 4 weeks x=1,2, 3...	109	Baseline (MA)	<= 1, Predose	1
			109	Day 1(MA): 1H	1	1
			123	Week 2 (MA): 1H	2 - 29	15
			151	Week 6 (MA): 1H	30 - 57	43
			151 + x*28	Week (6 + x*4) (MA): 1H	30 + x*28 to 57+x*28	x*28 + 43
	MA final visit		End Point (MA)	2 to end of MA		
	F/U	F/U Day 14 (Last dose +14 days)	F/U Week 2	1 to end of F/U	14	

**Table 1: Analysis Visits**

Parameter	Analysis Phase	Scheduled Day	Time Interval (label on output)	Time Interval (Day) <sup>a</sup>	Target Time Point from start of each phase (Day)
Nasal Exam, Weight and BMI	IND	1	Baseline (IND)	<=1	1
		28	Day 28 (IND)	2 to end of IND	28
		IND final visit	End Point (IND)	2 to end of IND	
	OP	28	Baseline (OP)	<= 1	1
		53	Week 4 (OP)	2-43	26
		81	Week 8 (OP)	44-68	54
		109	Week 12 (OP)	69 to end of OP	82
		OP final visit	End Point (OP)	2 to end of OP	
	MA Every 4 weeks x=1,2, 3...	109	Baseline (MA)	<= 1	1
		137	Week 4 (MA)	2-43	29
		137+x*28	Week (4+x*4) (MA)	16+ x*28 to 43+x*28	x*28 + 29
		MA final visit	End Point (MA)	2 to end of MA	
F/U (not for Weight and BMI)	F/U Day 14 (Last dose +14 days)	F/U Week 2	1 to end of F/U	14	
Cogstate/ HVLTR	IND	1	Baseline (IND)	<=1	1
		28	Day 28 (IND)	2 to end of IND	28
	OP	28	Baseline (OP)	<= 1	1
		109	Week 12 (OP)	2 to end of OP	82
	MA Every 12 weeks x=1,2, 3...	109	Baseline (MA)	<= 1	1
		193	Week 12 (MA)	2-127	85
		277	Week 24 (MA)	128-211	169
		277 + x*84	Week (24 + x*12)	128 + x*84 to 211 + x*84	169 + x*84
	F/U	F/U Day 14 (Last dose +14 days)	F/U Week 2	1 to end of F/U	14

<sup>a</sup> For each phase, the time interval is relative to the first day of that phase.

<sup>b</sup> During each phase, at 1.5 hours post dose if the SBP is  $\geq 160$  and/or DBP  $\geq 100$ , assessments should continue every 30 minutes until the blood pressure is  $< 160$  and/or  $< 100$  or in the investigator's clinical judgment, the subject is clinically stable and can be discharged from the clinical site, or the subject is referred for appropriate medical care, if clinically indicated.

<sup>c</sup> If the MOAA/S score is  $\leq 3$  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  $\leq 3$ , 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.

<sup>d</sup> If pulse oximetry is  $< 93\%$  at any time during the 1.5 hour postdose interval, pulse oximetry will be performed every 5 minutes until oxygen saturation returns to  $\geq 93\%$  or until the subject is referred for appropriate medical care, if clinically indicated.

<sup>e</sup> 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.

<sup>f</sup> This would be labeled as Day 1(IND): Predose for changes from Predose summaries.

<sup>g</sup> This would be labeled as Day 1(MA): Predose for changes from Predose summaries.

## 2.4. Analysis Sets

Subjects will be classified into the following analysis sets: all enrolled, full analysis sets, interim full analysis set, safety analysis sets and follow-up analysis set. Due to Good Clinical Practice (GCP) issues, [REDACTED] subjects will not be included in any of the analysis sets. However, data for this site will be presented in listings.

### 2.4.1. All Enrolled Analysis Set

This analysis set will include all transferred-entry and direct-entry subjects who are not screen failures.

### 2.4.2. Efficacy Analysis Sets

#### 2.4.2.1. Full Analysis Sets

Full (IND): All subjects who receive at least 1 dose of intranasal study drug and 1 dose of oral antidepressant in the open-label induction phase (for direct-entry subjects only).

Full (OP): All subjects who receive at least 1 dose of intranasal esketamine study drug and 1 dose of oral antidepressant in the optimization phase.

Maintenance phase: There are 2 full analysis sets defined for this phase.

One set will be used to perform primary and secondary efficacy evaluations on randomized subjects who are in stable remission at the end of the optimization phase and who receive at least 1 dose of intranasal study drug and 1 dose of oral antidepressant during the maintenance phase. This analysis set will be referred to as 'Full (stable remitters)'.

Another set will be used to perform secondary efficacy evaluations on randomized subjects who are stable responders (who are not stable remitters) at the end of the optimization phase and who receive at least 1 dose of intranasal study drug and 1 dose of oral antidepressant during the maintenance phase. This analysis set will be referred to as 'Full (stable responders)'.

Transfer entry oral AD plus intranasal placebo subjects who are stable remitters or stable responders will not be included in the above analysis sets.

### 2.4.3. Interim Full Analysis Set

Interim Full (stable remitters): All subjects who are in stable remission at the end of the optimization phase and who receive at least 1 dose of intranasal study drug and 1 dose of oral antidepressant during the maintenance phase at the time of the interim analysis data cutoff (see IA SAP for details).

### 2.4.4. Safety Analysis Sets

The following safety analysis sets are defined for each phase. Analyses of change from baseline will include only those subjects who have baseline and at least 1 post-baseline observation in that phase.

Safety (IND) analysis set: All subjects who receive at least 1 dose of intranasal study medication or 1 dose of oral antidepressant in the open-label induction phase (for direct-entry subjects only).

Safety (OP) analysis set: All subjects who receive at least 1 dose of intranasal esketamine study medication or 1 dose of oral antidepressant in the optimization phase (who are not in Safety (OP TEP) analysis set).

Safety (OP\_TEP) analysis set: Transferred-entry subjects who continue to receive an oral antidepressant plus intranasal placebo will be summarized separately in the optimization phase.

Safety (MA) analysis set: All randomized subjects who receive at least 1 dose of intranasal study medication or 1 dose of oral antidepressant during the maintenance phase. This analysis set includes both stable remitters and stable responders (who are not stable remitters).

Safety (stable remitters) analysis set: All randomized subjects who receive at least 1 dose of intranasal study medication or 1 dose of oral antidepressant during the maintenance phase. This analysis set includes only stable remitters and only AE summaries will be provided for this set.

Safety (MA\_TEP) analysis set: Transferred-entry subjects who continue to receive an oral antidepressant plus intranasal placebo will be summarized separately in the maintenance phase. Safety (MA\_TEP) analysis set and Safety (MA) analysis set are mutually exclusive.

#### **2.4.5. Follow-up Analysis Set**

The Follow-up analysis set includes all subjects who enter the follow-up phase. This analysis set will be used to summarize all efficacy and safety evaluations during the follow-up phase.

#### **2.5. Definition of Subgroups**

Analyses will be provided for the primary endpoint, time to relapse, for the Full (stable remitters) analysis set by the following subgroups.

- Sex
- Race (White, Black, Other)
- Age Group in years (18-44 years, 45-64 years)
- Region: North America (US and Canada), Europe (Belgium, Czech Republic, Estonia, France, Germany, Hungary, Italy, Poland, Slovakia, Spain, Sweden, Turkey), Other (Mexico and Brazil)
- Country (Brazil, Belgium, Canada, Czech Republic, Estonia, France, Germany, Hungary, Italy, Mexico, Poland, Slovakia, Spain, Sweden, Turkey, US)
- Number of Previous antidepressant Treatment Failures in Current Episode (based on ATRQ data)
- Functional Impairment based on Baseline (IND) SDS Total Score: not impaired (0-3), mild (4-11), moderate (12-19), marked (20-26) or extreme (27-30)
- Class of antidepressant study treatment (SNRI or SSRI)

- Consented Protocol (pre/post protocol amendment 4)
- Entry source (direct-entry, transferred-entry)

## 2.6. Imputation Rules for Missing AE Dates

Treatment-emergent adverse events (AEs)

- For direct-entry subjects, treatment-emergent AEs are those events with an onset date/time on or after the start of IND phase study medication, and occurred on or before the end of the maintenance phase. A conservative approach will be used to handle the missing dates for AEs
- For transferred-entry subjects, treatment-emergent AEs are those events with an onset date/time on or after the start of optimization phase study medication, and occurred on or before the end of the maintenance phase. A conservative approach will be used to handle the missing dates for AEs

### Onset Date

AEs for each phase are those events with an onset date/time on or after the start of that particular phase, and occurred before the end of that phase. The rules for estimating incomplete AE onset dates will be as follows:

#### **Direct-entry subjects:**

If the onset date of an adverse event is missing the day only, it will be set to:

- i) First day of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of IND start date
- ii) The day of IND start date, if the month/year of the onset of AE is the same as month/year of the IND start date and month/year of the AE resolution date is different
- iii) The day of IND start date or day of AE resolution date, whichever is earliest, if month/year of the onset of AE and month/year of the IND start date and month/year of the AE resolution date are the same.

If the onset date of an adverse event is missing both day and month, it will be set to the earliest of:

- i) January 1 of the year of onset, as long as this date is after the IND start date
- ii) One day after the IND start date, if this date is the same year that the AE occurred.

A completely missing onset date of an adverse event will be set to the IND start date.

#### **Transferred-entry subjects:**

If the onset date of an adverse event is missing day only, it will be set to:

- i) First day of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of OP start date
- ii) The day of OP start date, if the month/year of the onset of AE is the same as month/year of the OP start date and month/year of the AE resolution date is different



- iii) The day of OP start date or day of AE resolution date, whichever is earliest, if month/year of the onset of AE and month/year of the OP start date and month/year of the AE resolution date are the same.

If the onset date of an adverse event is missing both day and month, it will be set to the earliest of:

- i) January 1 of the year of onset, as long as this date is after the OP start date
- ii) One day after the OP start date, if this date is the same year that the AE occurred.

A completely missing onset date of an adverse event will be set to the OP start date.

Similar rules will be applied for MA missing onset date

### **Resolution Date**

The missing day of resolution of an adverse event will be set to the last day of the month of resolution.

If the resolution date of an adverse event is missing both day and month, it will be set to December 31 of the year.

A completely missing resolution date of an adverse event that is not recorded as ongoing will be set to the date of withdrawal or study completion.

### **Direct-entry subjects:**

If the time of onset is missing, it will be imputed as follows:

- (i) 00:00 if the date of onset is after IND start date
- (ii) 00:00 if the date is the same as IND start date, but the intranasal study medication in the (open-label) induction phase was started after the oral antidepressant medication in this phase
- (iii) The time of intranasal medication start in the (open-label) induction phase if the intranasal medication was started on or before the oral antidepressant medication in this phase

### **Transferred-entry responder subjects:**

If the time of onset is missing, it will be imputed as follows:

- (i) 00:00 if the date of onset is after OP start date
- (ii) 00:00 if the date is the same as OP start date, but the intranasal study medication in the optimization/maintenance phase was started after the oral antidepressant medication in this phase
- (iii) The time of intranasal medication start in the optimization/maintenance phase if the intranasal medication was started on or before the oral antidepressant medication in this phase

If a missing time is associated with a partial or missing date, the date will be imputed first prior to imputing the time.

### 2.6.1. Imputation Rules for Missing Concomitant Medication Dates

If a partial date is reported, it is assumed the medication (or therapy) was taken in all phases that overlap with the partial date. If both start and end dates are missing but this concomitant medication was taken both prior to the study entry and still ongoing at study end, it is assumed medication was taken in all phases.

The rules for estimating an incomplete concomitant medication start date are as follows:

**Direct-entry subjects:** If the month of the concomitant medication start date is equal to the month of the start of the induction phase, then the estimated start date is the IND start date;

If the month of the concomitant medication start date is greater than the month of the start of the induction phase and earlier than the study end date, then the estimated start date of the concomitant medication is the first day of the month;

If the month of the concomitant medication start date is greater than the month of the study end date, then no imputation will be done;

If the month and year of the concomitant medication start date are known and the IND start date is after the month of the concomitant medication start date, then no imputation will be done;

If either the month or year of the concomitant medication start date is missing, no imputation is to be performed.

**Transferred-entry subjects:**

If the month of the concomitant medication start date is equal to the month of the start of the optimization phase, then the estimated start date is the OP start date;

If the month of the concomitant medication start date is greater than the month of the start of the optimization phase and earlier than the study end date, then the estimated start date of the concomitant medication is the first day of the month;

If the month of the concomitant medication start date is greater than the month of the study end date, then no imputation will be done;

If the month and year of the concomitant medication start date are known and the OP start date is after the month of the concomitant medication start date, then no imputation will be done;

If either the month or year of the concomitant medication start date is missing, no imputation is to be performed.

## 3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

An IDMC will be established to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study. In addition, the committee will review the interim analysis data. The committee will meet every 6 months to review safety data and will meet once to review

efficacy data after the interim analysis has been completed. After the reviews, the IDMC will make recommendations regarding the continuation of the study, or in the case of the interim analysis for efficacy, to either stop the study due to efficacy or to adjust the sample size (i.e., number of relapses) to achieve the desired power while maintaining control of the overall Type I error.

The data cut-off date for the interim analysis is defined as the date when the 30<sup>th</sup> relapse event is observed in the maintenance phase for stable remitters treated with intranasal esketamine plus an oral antidepressant in the optimization phase (IDMC SAP). This date will only be known by Cytel, the independent statistical support group conducting the interim analysis. If the result of the interim analysis using the log-rank test is significant for the Interim Full (stable remitters) analysis set at a level of 0.0086 (two-sided), the study will be stopped based on the IDMC recommendation. Note that the trial will be ongoing during the period of conducting the interim analysis (data cleaning, analysis and holding the interim analysis committee meeting), which leads to overrunning data, including possible succeeding events. In this case, a final analysis using all data will be analyzed using the log-rank test to support the findings from the interim analysis. The interim analysis of time to relapse is considered as primary and the final analysis is considered as supportive if the study is stopped due to the efficacy at the time of the interim analysis. If the study is not stopped based upon the interim analysis results, a sample size re-estimation will be performed. The study will continue until the total number of relapses is at least 59, but no more than 84. The final analysis using the weighted log-rank test (Section 5.2.2) for the Full (stable remitters) analysis set will be conducted. In this case, the final analysis to compare intranasal ESK+AD with PBO+AD in terms of delaying time to relapse will be considered as primary.

## **4. SUBJECT INFORMATION**

### **4.1. Demographics and Baseline Characteristics**

Demographic and baseline characteristics (Table 2) and psychiatric history at baseline (Table 3) will be summarized by treatment group for the All Enrolled, Full (Stable Remitters and Stable Responders), Safety (MA and Stable Remitters) analysis sets (described in Section 2.4). Continuous variables will be summarized using descriptive statistics (N, mean, standard deviation [SD], median, minimum, and maximum). Categorical variables will be summarized using a frequency distribution with the number and percentage of subjects in each category. Baseline (IND) values will be used for these summaries.

**Table 2: Demographic Variables and Baseline Characteristics**

## Continuous Variables:

- Age (years) (informed consent date (for transfer entry subjects use 3001/3002 informed consent date) – date of birth + 1) / 365.25
- Baseline weight (kg)
- Baseline height (cm)
- Baseline BMI (kg/m<sup>2</sup>) calculated as Weight (kg)/[Height (m)]<sup>2</sup>

## Categorical Variables:

- Age in years (18-44, 45-64)
- Sex (male, female)
- Race<sup>a</sup> (White, Black or African American, Asian, American Indian or Alaskan native, Native Hawaiian or other Pacific islander, other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)
- Baseline BMI (underweight <18.5kg/m<sup>2</sup>; normal: 18.5 to <25 kg/m<sup>2</sup>, overweight: 25 kg/m<sup>2</sup> to <30 kg/m<sup>2</sup>, obese:30 to <40 kg/m<sup>2</sup>; morbidly obese: ≥40 kg/m<sup>2</sup>)
- Employment Status
- Hypertension Status
- Class of antidepressant (SSRI/SNRI)
- Oral antidepressant
- Country
- Region

<sup>a</sup> If multiple race categories are indicated, then Race is recorded as “Multiple”.

**Table 3: Psychiatric History at Baseline Variables**

## Continuous Variables:

- Baseline MADRS total score
- Baseline IDS-C<sub>30</sub> total score
- Baseline CGI-S score
- Baseline PHQ-9 total score
- Age (years) when diagnosed with MDD

## Categorical Variables:

- Baseline CGI-S score
- Baseline C-SSRS category (no event, suicidal ideation, suicidal behavior)
- Antidepressant treatment history (number of medications with non-response taken for at least 6 weeks during the current episode as obtained in the MGH-ATRQ)
- Family history of
  - Depression
  - Anxiety Disorder
  - Bipolar Disorder
  - Schizophrenia
  - Alcohol Abuse
  - Substance Abuse

**4.2. Disposition Information**

The number of subjects who enrolled from study ESKETINTRD3001, study ESKETINTRD3002 and direct-entry into ESKETINTRD3003 will be provided.

The following disposition summaries by treatment groups will be provided for each phase separately. These summaries will be provided for each of the Full and Safety analysis sets described in Section 2.4

- The number of subjects who entered a specific treatment phase
- The number of subjects who completed a specific treatment phase and their reasons for completion (only applicable for the maintenance phase). The reasons for completion for the maintenance phase include relapse during the maintenance phase or completion of the maintenance phase without a relapse.
- The number of subjects who discontinued a specific treatment phase prematurely and their reasons for discontinuation
- The number of subjects who are ongoing in each phase at the time the sponsor terminated the study

The number of subjects who terminated the trial and the reasons for ending study participation will also be summarized.

### 4.3. Extent of Exposure

Extent of exposure in terms of total duration of exposure and number of dosing sessions of intranasal study medication will be summarized by phase and treatment group for Full (Stable Remitters and Stable Responders) and Safety (IND, OP, and MA) analysis sets, and across phases for the All Enrolled described in Section 2.4.

The total duration of exposure for the intranasal study drug and for each type of oral antidepressant (AD) during each phase is defined as the time between the first and the last dose of each type of study medication in that specific phase (last day of study medication-first day of study medication +1). If a subject only receives a partial dose it is considered as a day of dosing.

Modal dose for a subject is defined as the most frequently taken dose by a subject during that phase. Mean dose of a subject is calculated as the sum of doses during the phase divided by the total number of days exposed. The final dose is the last non-zero dose received during that phase. The calculation of mean, modal and final dose will exclude days off study drug.

Descriptive statistics (N, mean, SD, median, minimum and maximum) of modal dose, mean dose and final dose will be presented for the induction phase for intranasal study drug.

Doses of oral AD will be summarized using descriptive statistics of the mean dose (days on drug), final dose and mode dose (days on drug), by each type of oral AD during the induction phase.

At the end of the induction phase and the optimization phase, the number and percentage of subjects at each dose (56 mg and 84 mg) will be provided.

At Weeks 8 and 12 of the optimization phase, the number and percentage of subjects at each dosing frequency (weekly or every other week) will be provided.

During the maintenance phase, the number and percentage of subjects at each dosing frequency (weekly or every other week) and the number of subjects who changed their frequency (weekly to every other week and every other week to weekly) will be summarized every 4 weeks starting at Week 16. A frequency distribution of the dosing frequency used the majority of the time during the maintenance phase will be provided.

#### **4.4. Protocol Deviations**

Deviations that occurred during the study will be tabulated for the All Enrolled analysis set. Major deviations will be tabulated as they are grouped prior to unblinding in the following categories: subject not withdrawn as per protocol, selection criteria not met, excluded concomitant treatment, treatment deviation, non-compliance, regulatory requirement. More categories may be included depending on the nature of the protocol deviation.

#### **4.5. Prior and Concomitant Medications**

The number and percent of subjects receiving prior antidepressant medications will be summarized by treatment group for the Safety (IND) analysis set.

The number and percent of subjects who receive concomitant therapies will be summarized by phase and treatment group using the generic term of the medication for the Safety (IND, OP, and MA) analysis sets and Follow-up analysis set described in Section 2.4.

### **5. EFFICACY**

#### **5.1. Analysis Specifications**

##### **5.1.1. Level of Significance**

A 2-stage group sequential design with 1 interim analysis will be implemented to allow for early stopping if there is significant evidence of efficacy based upon the interim analysis after 30 relapse events have occurred for randomized stable remitters who were treated with esketamine in the optimization phase. In either case of stopping at the interim analysis or continuing with sample size re-estimation, control of overall Type I error will be maintained at 5% level (2-sided).

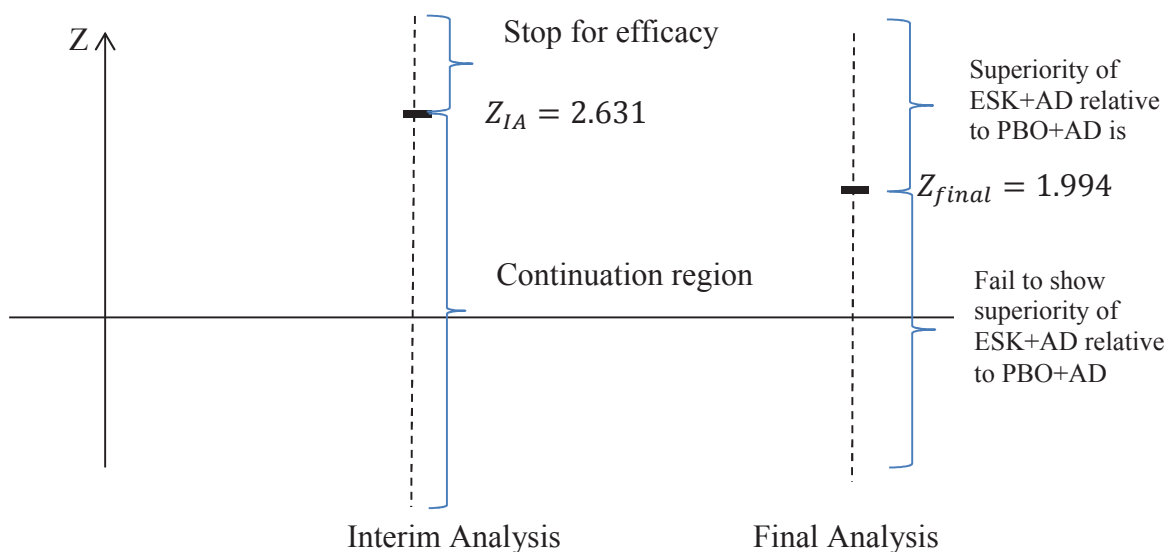
At the time of the interim analysis, time to relapse will be evaluated and compared between intranasal esketamine plus oral antidepressant and oral antidepressant plus intranasal placebo. The Wang-Tsiatis boundary<sup>11</sup> with shape parameter  $\Delta=0.1$  will be used for detection of early efficacy.

In accordance with the design given above, the interim efficacy analysis will be performed at a significance level of 0.0086 (two-sided). If the result of the interim efficacy analysis is significant (i.e.,  $Z_{IA} \geq 2.631$  where a positive  $Z_{IA}$  favors intranasal esketamine plus oral antidepressant in delaying relapse compared to oral antidepressant plus intranasal placebo) the study will be terminated and intranasal esketamine plus oral antidepressant will be declared superior to oral antidepressant plus intranasal placebo in delaying relapse. Otherwise, this study

is in the continuation region (Figure 2) and the sample size will be re-estimated using the observed value of  $Z_{IA}$ .

If the study is not stopped at the interim analysis, then the study will be stopped once the number of relapses determined by the sample size re-estimation (in the subjects with stable remission) occur during the maintenance phase. The final efficacy analysis will be performed at a significance level of 0.046 (two-sided). If the result of the final efficacy analysis is significant (i.e.,  $Z_f \geq 1.994$ ), intranasal esketamine plus oral antidepressant will be declared superior to oral antidepressant plus intranasal placebo in delaying relapse.

**Figure 2: Two-stage Adaptive Group Sequential Design for Randomized Stable Remitters Who Received Esketamine During the Optimization Phase (List 1)**



### 5.1.2. Data Handling Rules

For the efficacy scales MADRS, CGI-S, PHQ-9, GAD-7 and SDS, both observed case and last observation carried forward (LOCF) values will be determined for the induction, optimization and maintenance phases. These imputed time points will be labeled as ‘DAY X LOCF’ or ‘WEEK X LOCF’. Because it is possible for more than 1 visit to occur during the same interval for a protocol-specified visit, rules for choosing the visit to use for the analysis are those given in Section 2.4. Imputed time points Day 28 (IND) LOCF, Week 16 (OP) LOCF and Week XX (MA) LOCF (where ‘XX’ corresponds to the last window in the Maintenance Phase, excluding the end point visit) are not needed as they are essentially equivalent to End Point (IND), End Point (OP), and End Point (MA), respectively. If there are multiple visits in a time interval with non-missing values, the visit closest to the protocol-specified time is used as both observed case and LOCF. If there is no visit in a time interval with a non-missing value, then the observed case is missing and the last non-missing, post-baseline value prior to the interval is used for LOCF. For example, if a subject has a visit on Day 7 and then a final visit on Day 10. The data on Day

7 will be slotted for the ‘Day 8 (IND)’, because Day 7 is closer to the target Day 8 than Day 10 is. The data on Day 10 will be used for finding the End Point (IND) and all LOCF windows from ‘Day 15 (IND) LOCF’ through ‘Day 22 (IND) LOCF’.

### 5.1.3. Imputation Methods for Missing Items

Imputation of the MADRS total score is described in Section 5.3.2. For all other scales where multiple items are summed to create a total, if any item of the scale is missing at a visit, the total score for that scale at that visit will be considered missing.

## 5.2. Primary Efficacy Endpoint

The primary efficacy endpoint is the time from randomization to the first relapse during the maintenance phase in esketamine-treated subjects who achieved stable remission at the end of optimization phase.

Relapse is defined as any of the following:

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

The date of relapse will be the date of the first assessment of relapse. The time to relapse and censoring are defined as follows:

Subject status during maintenance phase	Time to relapse/Censoring	Censoring indicator
Randomized subjects who relapse during maintenance phase	(Date of relapse – maintenance phase start date) + 1	No
Randomized subjects who remained relapse-free at the end of the maintenance phase	(End of maintenance phase date – maintenance phase start date)+1	Yes
Early withdrawal/discontinued during the maintenance phase without relapse	(Date of early withdrawal – maintenance phase start date) + 1	Yes



### 5.2.1. Primary Estimand

The primary estimand, the main clinical quantity of interest to be estimated in the study, is defined by the following variable and summary measure in the population, under the specified intervention effect:

**Population:** subjects with treatment-resistant depression who are in stable remission on esketamine at the end of the optimization phase

**Variable:** time to relapse during the maintenance phase, while on their initially randomized treatment

**Intercurrent Event:** the intercurrent event of treatment discontinuation is captured through the variable definition

**Summary Measure:** Kaplan–Meier estimate of the survival function.

The primary analysis will be based on the Full (stable remitters) analysis set, as described in Section 2.4.2.1 and the relapse defined above collected during the maintenance phase.

### 5.2.2. Analysis Methods

At the interim analysis, the cumulative distribution function of the time to relapse will be estimated by the Kaplan-Meier method and the treatment groups will be compared using a 2-sided log-rank test for the Interim Full (stable remitters) analysis set. For further details refer to IA SAP.

If the result of the interim analysis using the log-rank test is significant (i.e. two-sided significance level of 0.0086) and based on the recommendation of the IDMC, the study is stopped, then the interim analysis of time to relapse is considered as the primary analyses.

Note that the trial will be ongoing during the period of conducting the interim analysis (data cleaning, analysis and holding the interim committee meeting), which leads to overrunning data, including possible succeeding events. In this case, a final analysis using all data will be analyzed using the log-rank test and will be considered as supportive analysis to the interim primary analysis.

If the study is not terminated at the time of the interim analysis, the sample size will be re-estimated to ensure a conditional power at Stage 2 of at least 90% based on the interim analysis data, using the approach proposed by Wassmer<sup>12</sup>. The interim analysis SAP provides details on the sample size re-estimation. The final analysis, if a sample size re-estimation occurred, will be based on a 2-stage group sequential survival design with the decision based on the log rank test on accumulated information from both stages. The Full (stable remitters) analysis set will be used and the analysis will include all the relapse events accumulated prior to final database lock.

In this 2-stage group sequential design the decision is based on the following test on accumulated data on both stages. Under the null hypothesis, the following test statistics are approximately standard normal. This test statistic is performed on the Full (stable remitters) analysis set mentioned in Section 2.4.2.1 with the final number of events determined by the sample size re-estimation (between 59 and 84), including any additional events that occurred after the notification that the required number of events have been met and completion of the study. Final test statistic  $Z_f$ , is weighted combination of the one-sided log-rank test statistics  $LR_1$  and  $LR_2$ .  $LR_2$  is performed on the full analysis set and  $LR_1$  is calculated on the interim full analysis set

$$Z_f = \sqrt{\frac{30}{59}} LR_1 + \sqrt{\frac{29}{59}} \left( \left( \sqrt{\frac{d_2}{d_2 - d_{IA}}} \right) LR_2 - \left( \sqrt{\frac{d_{IA}}{d_2 - d_{IA}}} \right) LR_1 \right)$$

$$\text{where, } LR_1 = \frac{\sum_{i=1}^{d_{IA}} \left( I_{2i1} - \frac{n_{2i1}}{n_{1i1} + n_{2i1}} \right)}{\sqrt{\sum_{i=1}^{d_{IA}} \frac{n_{1i1} n_{2i1}}{(n_{1i1} + n_{2i1})^2}}} \quad \text{and} \quad LR_2 = \frac{\sum_{i=1}^{d_2} \left( I_{2i2} - \frac{n_{2i2}}{n_{1i2} + n_{2i2}} \right)}{\sqrt{\sum_{i=1}^{d_2} \frac{n_{1i2} n_{2i2}}{(n_{1i2} + n_{2i2})^2}}}$$

Let  $n_{1i1}$  and  $n_{2i1}$  be the number of randomized stable remitters at risk in treatment group ESK+AD and PBO+AD, respectively, when the  $i^{\text{th}}$  event occurred during stage 1, and  $I_{2i1} = 1$  if the event occurred in the treatment group PBO+AD and 0 otherwise,  $d_{IA}$  = number of events observed in stage 1. Let  $n_{1i2}$  and  $n_{2i2}$  be the number of randomized stable remitters at risk in treatment group ESK+AD and PBO+AD, respectively, when the  $i^{\text{th}}$  event occurred during stage 2, and  $I_{2i2} = 1$  if the event occurred in the treatment group PBO+AD and 0 otherwise,  $d_2$  = accumulated events for stage 1 and stage 2.

The treatment groups will be compared using the test statistic  $Z_f$  and the corresponding two-sided p-value will be provided. Time to relapse will be summarized (number of events, number of censored subjects and quartiles of time to relapse). The cumulative distribution function of the time to relapse will be estimated by the Kaplan-Meier method. The estimate of the hazards ratio and its 95% confidence interval will be based on Wassmer<sup>12</sup> and will be calculated using ADDPLAN Adaptive Designs - Plans and Analyses<sup>®</sup> software<sup>1</sup> and software R.

### 5.2.3. Sensitivity Analyses

The primary analysis relies on the assumption of ignorable censoring. Therefore, sensitivity analyses will be performed to stress-test the robustness of results to deviations from ignorable censoring. Specifically, it is assumed that subjects on experimental treatment who discontinue prematurely from the maintenance phase have a higher relapse hazard starting from the discontinuation time, compared with similar subjects who remain in this phase. The higher relapse hazard is determined by the single sensitivity parameter Delta, representing the ratio of subject-specific hazard at any given time point t following discontinuation compared to that

same subject's hazard at the same time  $t$  if he or she had continued the study. A multiple imputation non-parametric approach (based on the Kaplan-Meier method) will be used for the imputation of relapse events, as described in Taylor, Murray and Hsu (2002)<sup>13</sup> and Lipkovich, Ratitch and O'Kelly (2016)<sup>14</sup>. A sequence of Delta values will be used for all subjects with non-administrative censoring from the esketamine group (i.e. subjects censored due to other reasons than the study cut-off date, which occurs when the pre-planned number of events is accumulated), starting with 1 (ignorable censoring) and increasing by 1 until the tipping point, where the results are no longer significant according to the level of significance specified in [Section 5.1.1](#). For the control group, the sensitivity parameter Delta will be set to one, i.e. maintaining the ignorable censoring assumption. For the multiple imputation procedure under each delta adjustment, the seed will be set to 234 and 1000 multiple imputations will be used.

Notes:

- If the study is stopped at the interim analysis, the approximately normal log-rank test  $LR_1$  will be used for the primary and sensitivity analyses.
- If the study is not stopped at the interim analysis, the approximately normal log-rank type test statistic  $z_f$  will be used for the final primary and sensitivity analyses. For sensitivity analyses, the multiple imputation procedure under each Delta adjustment will be performed separately for each stage. If the imputed times for the interim stage exceed the cut-off date for the interim analysis, these events will be censored at the interim cut-off date. Similarly, if the imputed times for the final stage exceed the final cut-off date, these events will be censored at the final cut-off date. The imputations performed at the interim stage will not be carried over to the final stage. A subject who discontinues prematurely from the maintenance phase, prior to the interim analysis cut-off, will be imputed differently in the interim and final stages, according to the information at each stage.

In addition, unweighted log-rank tests will be performed on the Full (stable remitters) analysis set with the accumulated events  $d_2$  and 59 events. The estimate of the hazards ratio and its 95% confidence interval will be based on the Cox proportional hazards model with treatment as a factor.

#### **5.2.4. Model Diagnostics**

To assess the appropriateness of the proportional hazards assumption, a log-log survival plot of the Kaplan-Meier estimates will be generated. If the proportional hazards assumption is correct, this plot should present approximately parallel lines corresponding to the two treatment groups. Cumulative sums of Schoenfeld residuals over time may also be used to assess the proportional hazards assumption.

### **5.2.5. Subgroup Analyses**

Subgroup analyses will be performed using the Cox proportional hazards model. The model will include treatment and one subgroup (defined in Section 2.5) and treatment-by-subgroup at a time. A forest plot with the corresponding hazard ratios and 95% CI will be presented for the subgroups. If there are insufficient numbers in the subgroups to draw meaningful conclusions, the subgroup analysis will not be performed.

### **5.3. Secondary Endpoints**

No multiplicity adjustments will be made for secondary endpoints. All p-values are considered nominal.

#### **5.3.1. Time to Relapse in Stable Responders (but not remitters)**

The cumulative distribution function of the time to relapse will be estimated by the Kaplan-Meier method and the treatment groups will be compared using a 2-sided log-rank test for the Full (stable responders) analysis set. Time to relapse will be summarized (number of relapses, number of censored subjects, median, 25<sup>th</sup> and 75<sup>th</sup> percentile, if estimable). Confidence intervals of 25<sup>th</sup>, 50<sup>th</sup> and 75<sup>th</sup> percentile of time to relapse will also be provided. Standard error estimates will be based on Greenwood's formula. The estimate of the hazards ratio and its 95% confidence interval will be based on the Cox proportional hazards model with treatment as a factor.

#### **5.3.2. MADRS**

##### **5.3.2.1. Definition**

The Montgomery-Asberg Depression Rating Scale (MADRS)<sup>6</sup> is a clinician-rated scale designed to measure depression severity and to detect changes due to antidepressant treatment. The scale consists of 10 items, each of which is scored from 0 (item is not present or is normal) to 6 (severe or continuous presence of the symptoms), for a total possible score of 60. Higher scores represent a more severe condition. The MADRS evaluates apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, interest level, pessimistic thoughts, and suicidal thoughts. The test exhibits high inter-rater reliability.

If 2 or more items are missing, no imputation will be performed and the total score will be left missing. Otherwise, the total score will be calculated as sum of the non-missing items multiplied by the ratio of the maximum number of items (i.e., 10) to the number of non-missing items

##### **5.3.2.2. Analysis Methods**

Descriptive statistics of the total score and change from baseline (of the respective phase) will be provided for each visit during the induction phase, optimization phase, maintenance phase for the Full analysis sets and follow-up phase for the Follow-up analysis set defined in Section 2.4. Summaries of both observed and LOCF data will be presented.

The change from baseline (MA) at each visit, including observed case and LOCF data, during the double-blind maintenance phase and at end point (MA) will be analyzed using an ANCOVA

model with factors for treatment and country and baseline (MA) score as a covariate. Least-squares estimates of the treatment differences and 95% confidence intervals will be presented.

### **5.3.3. PHQ-9**

#### **5.3.3.1. Definition**

The PHQ-9 is a 9-item, self-report scale assessing depressive symptoms<sup>8</sup>. 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), with a total score range of 0-27. A higher score indicates greater severity of depression. The recall period is 2 weeks. The scale scores each of the nine symptom domains of the Diagnostic and Statistical Manual of Mental Disorders (DSM) Major Depressive Disorder criteria and it has been used both as a screening tool and a measure of response to treatment for depression. The severity of the PHQ-9 is categorized as follows: None-minimal (0-4), Mild (5-9), Moderate (10-14), Moderately Severe (15-19) and Severe (20-27).

#### **5.3.3.2. Analysis Methods**

Descriptive statistics of the total score and change from baseline (of the respective phase) will be provided for each visit during the induction phase, optimization phase and maintenance phase for the Full analysis sets defined in Section 2.4. In addition, a frequency distribution by severity will be provided for each assessment visit for all phases, including the follow-up phase. Summaries of both observed and LOCF data will be presented.

The change from baseline (MA) at each visit, including observed case and LOCF data, during the double-blind maintenance phase and at end point (MA) will be analyzed using an ANCOVA model with factors for treatment and country and baseline (MA) score as a covariate. Least-squares estimates of the treatment differences and 95% confidence intervals will be presented.

### **5.3.4. CGI-S**

#### **5.3.4.1. Definition**

The Clinical Global Impression of Severity (CGI-S)<sup>5</sup> 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. 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.

#### **5.3.4.2. Analysis Methods**

Descriptive statistics of the total score and change from baseline (of the respective phase) will be provided for each visit during the induction phase, optimization phase, maintenance phase for the Full analysis sets and follow-up phase for the Follow-up analysis set defined in Section 2.4. In

addition, a frequency distribution by severity will be provided for each assessment visit for all phases, including the follow-up phase. Summaries of both observed and LOCF data will be presented.

The ranks of the change from baseline (MA) for the CGI-S score at each visit, including observed case and LOCF data, during the double-blind maintenance phase and at end point (MA) will be analyzed using an ANCOVA model with factors for treatment and country and baseline (MA) score as a covariate.

### **5.3.5. GAD-7**

#### **5.3.5.1. Definition**

The GAD-7 (Generalized Anxiety Disorder - 7 Items)<sup>9</sup> is a brief and validated 7-item self-report assessment of overall anxiety. Subjects respond to each item using a 4 point scale with response categories of 0=not at all, 1=several days, 2=more than half the days, and 3=nearly every day. Item responses are summed to yield a total score with a range of 0 to 21, where higher scores indicate more anxiety. The recall period is 2 weeks. The severity of the GAD-7 is categorized as follows: None (0-4), Mild (5-9), Moderate (10-14) and Severe (15 -21).

#### **5.3.5.2. Analysis Methods**

Descriptive statistics of the actual values and change from baseline (of the respective phase) will be provided for each visit during the induction phase, optimization phase and maintenance phase for the Full analysis sets defined in Section 2.4. In addition, a frequency distribution of GAD-7 severity categories will be provided for each assessment visit for all phases, including the follow-up phase.

The change from baseline (MA) for the GAD-7 total score at each visit, during the double-blind maintenance phase and at end point (MA) will be analyzed using an ANCOVA model with factors for treatment and country and baseline (MA) score as a covariate. Least-squares estimates of the treatment differences and 95% confidence intervals will be presented.

### **5.3.6. Sheehan Disability Scale (SDS)**

#### **5.3.6.1. Definition**

The SDS is a subject-reported outcome measure and is a 5-item questionnaire which has been widely used and accepted for assessment of functional impairment and associated disability. 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. Scores  $\leq 4$  for each item and  $\leq 12$  for the total score are considered response. Scores  $\leq 2$  for each item and  $\leq 6$  for the total score are considered remission. If any of the first three items are missing, the total score will be set to missing as well as response and remission status.

### 5.3.6.2. Analysis Methods

Descriptive statistics of the actual values and change from baseline (of the respective phase) will be provided for each visit during the induction phase, optimization phase, maintenance phase for the Full analysis sets and follow-up phase for the Follow-up analysis set defined in Section 2.4. The total score as well as the individual item scores will be summarized separately. Summaries of both observed and LOCF data will be presented.

The change from baseline (MA) in SDS total score at each visit, including observed case and LOCF data, during the double-blind maintenance phase and at end point (MA) will be analyzed using an ANCOVA model with factors for treatment and country and baseline (MA) score as a covariate. Least-squares estimates of the treatment differences and 95% confidence intervals will be presented.

### 5.3.7. EuroQol Group; 5 Dimension; 5 Level (EQ-5D-5L)

#### 5.3.7.1. Definition

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

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

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

Individual scores from the 5 dimensions will be used to obtain a weighted health status index as shown below:

- (i) Scores from each dimension will be combined to obtain a 5L profile score or health state: eg, a score of 1 for each dimension will give a 5L profile score of 11111. Dimension scores will be combined in the following order: Mobility, Self-Care, Usual Activities, Pain/Discomfort, Anxiety/Depression
- (ii) The value set of the Health Status Index for various values of 5L profile scores is published for Canada in the following website:  
<https://www.ncbi.nlm.nih.gov/pubmed/26492214>

The Canadian value set will be used to get the HSI values for all the countries participating in the study. In addition, a sum score will be derived as follows: The scores of the five dimensions (values 1-5) will be added (sums between 5 and 25). From this score, subtract 5 (range 0-20) and multiply by 5 (range 0-100).

### 5.3.7.2. Analysis Methods

Descriptive statistics of actual values and changes from baseline for the weighted EQ-5D health status index, the EQ-VAS, and the sum score by treatment group will be summarized for each visit for all phases including the follow-up phase. In addition, individual dimension responses using a frequency distribution by treatment group will also be summarized for each visit for the all phases, including the follow-up phase.

## 6. SAFETY

Safety summaries for each phase will be based on the Safety analysis sets described in Section 2.4.4.

### 6.1. Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) (version 18.1 or above) will be used to classify AEs by system organ class and preferred term. Treatment-emergent adverse events (TEAEs) that occurred in each study phase will be summarized by system organ class and preferred term.

The number (%) of subjects with TEAEs, serious TEAEs (SAEs), and TEAEs that led to study drug discontinuation will be summarized by system organ class and preferred term. Data listings will be generated for deaths, other SAEs, and discontinuations due to AEs.

A TEAE is an event that is new in onset or increased in severity following treatment initiation. An event that starts prior to, and ends after the initiation of study medication will be considered treatment-emergent only if the severity increases after the start of medication.

TEAEs are defined as follows for each study phase:

- TEAEs in the induction phase:
  - a. If AE onset time is not missing:
    - i. If subjects continue to OP phase: IND phase start date/time  $\leq$  AE onset date and time  $<$  IND phase end date
    - ii. If subjects discontinue in the IND phase: IND phase start date/time  $\leq$  AE onset date and time  $\leq$  IND phase end date
  - b. If AE onset time is missing:
    - i. If subjects continue to OP phase: IND phase start date  $\leq$  AE onset date  $<$  IND phase end date
    - ii. If subjects discontinue in the IND phase: IND phase start date  $\leq$  AE onset date  $\leq$  IND phase end date



- TEAEs in the optimization phase:
  - a. If AE onset time is not missing:
    - i. If subjects continue to MA phase: OP phase start date  $\leq$  AE onset date and time  $<$  OP phase end date
    - ii. If subjects discontinue in the OP phase: OP phase start date  $\leq$  AE onset date and time  $\leq$  OP phase end date
  - b. If AE onset time is missing:
    - i. If subjects continue to MA phase: OP phase start date  $\leq$  AE onset date  $<$  OP phase end date
    - ii. If subjects discontinue in the OP phase: OP phase start date  $\leq$  AE onset date  $\leq$  OP phase end date
- TEAEs in the maintenance phase:
  - a. If AE onset time is not missing:
 

MA start date/time  $\leq$  AE onset date and time  $\leq$  MA end date
  - b. If AE onset time is missing: MA start date  $\leq$  AE onset date  $\leq$  MA end date
- AEs in follow-up phase: F/U start date  $\leq$  AE onset date  $\leq$  F/U end date
- For the AEs that have both day and month missing, treatment emergent flag is assigned based on the rules presented in Section 2.6

In addition, TEAEs will be summarized by severity and relationship to study medication using the preferred term. For the summaries of AEs by severity/relationship to study medication, the observation with the most severe occurrence/closest relationship to study medication will be chosen if there is more than one incident of an adverse event reported during the analysis phase by the subject. AE duration for transient dizziness/vertigo and anxiety will also be summarized.

### Adverse Events of Special Interest

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

- drug abuse, dependence and withdrawal (Aggression, Confusional state, Decreased activity, Dependence, Disorientation, Dissociation, Dissociative disorder, Dizziness, Drug abuse, Drug abuser, Drug dependence, Drug use disorder, Drug detoxification, Drug diversion, Drug rehabilitation, Drug tolerance, Drug tolerance increased, Drug withdrawal convulsions, Drug withdrawal headache, Drug withdrawal syndrome, Euphoric mood, Feeling abnormal, Feeling drunk, Feeling of relaxation, Hallucination, Hallucination, auditory, Hallucination, gustatory, Hallucination, olfactory, Hallucination, synaesthetic, Hallucination, tactile, Hallucination, visual, Hallucinations, mixed, Inappropriate affect, Mental impairment, Product tampering, Psychomotor hyperactivity, Psychotic disorder, Rebound effect, Somatic hallucination, Somnolence, Substance abuser, Substance dependence, Substance use, Substance use disorder, Substance-induced mood disorder, Substance-induced psychotic disorder, Thinking abnormal, Withdrawal arrhythmia, Withdrawal syndrome);

- 
- increased blood pressure (Blood pressure increased, Blood pressure diastolic increased, Blood pressure systolic increased, Hypertensive crisis, Hypertensive emergency, Hypertension)
  - increased heart rate (Heart rate increased, Tachycardia)
  - transient dizziness/vertigo (Dizziness, Dizziness exertional, Dizziness postural, Dizziness procedural, Vertigo, Vertigo labyrinthine, Vertigo positional, Vertigo CNS origin);
  - impaired cognition (Cognitive disorder);
  - cystitis (Allergic cystitis, Chemical cystitis, Cystitis, Cystitis erosive, Cystitis haemorrhagic, Cystitis interstitial, Cystitis noninfective, Cystitis ulcerative, Cystitis-like symptom);
  - anxiety (Anticipatory anxiety, Anxiety, Anxiety disorder).

The number and percentage of subjects taking concomitant medication for dissociation events (preferred term of Dissociation) at any time during each treatment phase will be provided.

Summary statistics for the duration of all episodes of TEAEs associated with discharge readiness (Dissociation, Dizziness, Feeling abnormal, Feeling drunk, Nausea, Somnolence, Vertigo, and Vomiting) with an onset on the day of intranasal study drug administration is summarized for each treatment phase. These summaries are presented for each dosing session during each treatment phases. In addition, the number of occurrences of TEAEs associated with discharge readiness and the proportion of subjects with TEAEs associated with discharge readiness will be presented by dosing session for each treatment phase.

## 6.2. Clinical Laboratory

Descriptive statistics (N, mean, median, minimum, maximum and range) for values and changes from baseline will be provided for clinical laboratory tests (hematology, chemistry and urinalysis) at each scheduled time point for all the phases, including the follow-up phase. Baseline (IND) will be used for the change summaries and to determine abnormal values during the treatment phases (IND, OP, MA) and during the follow-up phase for those subjects who discontinue during the induction and optimization phases. Baseline (MA) values will be used for summaries during the maintenance phase and follow-up phase for those subjects who discontinue during the maintenance phase. Baseline values are defined in Section 2.2.

Clinical laboratory tests that meet the criteria for markedly abnormal will be listed by subject for each treatment phase. The incidence of treatment-emergent markedly abnormal laboratory values that occurred at any time during each treatment phase will be presented. Clinical laboratory test values will be considered “TEMA using the criteria defined by the Sponsor (Janssen Research & Development, LLC)” listed in [Attachment 2](#). The identification of TEMA laboratory values is based on the postbaseline value being out of range while the baseline value (defined above) is either missing or within the range given in [Attachment 2](#). If post-baseline laboratory results are above the upper limit and the baseline value is below the lower limit, then the post-baseline abnormality will also be considered TEMA. The same applies to the postbaseline value being below the lower limit with the baseline value being above the upper limit.

The incidence of subjects with ALT values  $> 3 \times$  upper normal limit (ULN) will be presented for each study phase. Additionally, incidence of hepatic toxicity (Hy's Law)<sup>10</sup> defined as ALT values  $> 3 \times$ ULN and total bilirubin values  $> 2 \times$ ULN will be presented for each study phase. Similar to the markedly abnormal analysis, only subjects with baseline (IND) ALT values  $\leq 3 \times$ ULN (and baseline (IND) total bilirubin values  $\leq 2 \times$ ULN for hepatic toxicity or if the baseline (IND) value is missing) will be eligible for these analyses.

### 6.3. Vital Signs, Weight, and BMI

Descriptive statistics for values and changes from baseline at each scheduled time-point during each treatment phase (IND, OP and MA) only will be presented for temperature, systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, oxygen saturation, weight, and BMI. Baseline (IND) will be used for change summaries and to determine abnormal values during all treatment phases (IND, OP, MA) and during the follow-up phase for those subjects who discontinued study agent during the induction and optimization phases. Baseline (MA) will be used for summaries during the maintenance phase and during the follow-up phase for those subjects who discontinued during the maintenance phase. Baseline values are defined in Section 2.2.

The proportion of subjects who have a treatment-emergent abnormality, as defined in Table 4 below, during each treatment phase will be presented. A listing of subjects meeting any of the following criteria during each treatment phase will also be provided.

**Table 4: Treatment-Emergent Abnormality Categories for Vital Signs**

Vital Parameter	Post-baseline value outside of normal limit if:	
	Abnormally low	Abnormally high
<b>Pulse (bpm)</b>	A decrease from baseline of $\geq 15$ to a value $\leq 50$	An increase from baseline of $\geq 15$ to a value $\geq 100$
<b>Systolic BP (mmHg)</b>	A decrease from baseline of $\geq 20$ to a value $\leq 90$	An increase from baseline of $\geq 20$ to a value $\geq 180$
<b>Diastolic BP (mmHg)</b>	A decrease from baseline of $\geq 15$ to a value $\leq 50$	An increase from baseline of $\geq 15$ to a value $\geq 105$

BP = blood pressure

The proportion of subjects who experienced treatment-emergent acute hypertension (systolic BP  $\geq 180$  or diastolic BP  $\geq 110$ ) at any time during the study will be summarized by study phase, treatment group and hypertension status.

A listing of subjects with oxygen saturation less than 93% will be provided.

### 6.4. Electrocardiogram

ECG variables that will be analyzed include heart rate, RR, PR interval, QRS interval, QT interval and QTc intervals. The corrected QT (QTc) intervals will include QTcB (Bazett) and QTcF (Fridericia).

Baseline ECG is defined as the average of all ECG results collected up to and including the day of first dose of study medication (either intranasal or oral AD). Baseline (IND) will be used as the baseline for change summaries and to determine abnormal values during all treatment phases (IND, OP, MA) and during the follow-up phase for those subjects who discontinued during the induction and optimization phases. Baseline (MA) will be used for change summaries and to determine abnormal values during the maintenance phase and during the follow-up phase for those subjects who discontinued during the maintenance phase. The baseline values are defined in Section 2.2.

The maximum post-baseline value during each treatment phase will be computed for each ECG parameter using data from both scheduled and unscheduled visits.

Summary tables for observed values and changes from baseline will be presented by treatment at each scheduled time point during each treatment phase and the follow-up phase.

The frequency of treatment-emergent abnormalities will be tabulated and presented for all treatment phases. The identification of treatment-emergent abnormal ECG values is based on the post-baseline value (a value occurring after the start of the phase) being out of range while the baseline value is either missing or within the limits given in Table 5. If post-baseline ECG results are above the upper limits (abnormally high) and the baseline value is below the lower limits (abnormally low), then the post-baseline abnormality will also be considered treatment-emergent. The same applies to the post-baseline value being below the lower limits (abnormally low) with the baseline value being above the upper limits (abnormally high). Abnormal ranges for the HR, PR, QRS and QT intervals are given in Table 5.

**Table 5: Limits for HR, PR, QRS and QT Interval Abnormality**

<b>ECG parameter</b>	<b>Abnormally Low</b>	<b>Abnormally High</b>
HR (bpm)	≤ 50	≥ 100
PR interval (msec)	--	≥ 210
QRS interval (msec)	≤ 50	≥ 120
QTc interval (msec)	≤ 200	≥ 500

Based on the maximum QTc value for each subject during a given phase (separate for each QTc correction, QTcB and QTcF) the incidence of abnormal QTc values and changes from baseline will be summarized by treatment group. Criteria for abnormal corrected QT intervals and changes from baseline are given in Table 6 and are derived from the ICH E14 Guidance (the same criteria apply to all QT corrections).

**Table 6: Criteria for Abnormal QTc Values and Changes From Baseline**

Parameter	Classification	Criteria
Clinically Significant QTc Value	No	≤500
	Yes	>500
QTc change from baseline <sup>a</sup>	No concern	≤30
	Concern	>30 – 60
	Clear concern	> 60
QTc value	Normal	≤450
	> 450 – 480	>450 - ≤480
	> 480 – 500	>480 – ≤500
	> 500	> 500

*These criteria are based on ICH E14 Guideline*

<sup>a</sup>Baseline is defined as the average pre-dose.

The proportion of subjects with treatment-emergent abnormalities will be presented for all treatment phases. A listing of subjects with abnormalities will also be provided.

## 6.5. Nasal Examination

Targeted nasal examinations (including the upper respiratory tract/throat) will be conducted by a qualified healthcare practitioner. The objective of the examination at Screening is to rule out any subjects with anatomical or medical conditions that may impede drug delivery or absorption.

Subsequent examinations will consist of a visual inspection of the nostrils, nasal mucosa, and throat for nasal erythema, rhinorrhea, rhinitis, capillary/blood vessel disruption and epistaxis and graded as follows: absent, mild, moderate, or severe.

Changes in findings from baseline (of the respective phase) for each examination (including the upper respiratory tract/throat) will be listed by treatment group for all phases.

### 6.5.1. Nasal Symptom Questionnaire

Subjects will complete a nasal symptom questionnaire on every dosing day at predose and again at 1 hour postdose. The questionnaire was developed to assess nasal tolerability following intranasal administration of study drug. Subjects will rate nasal symptoms as none, mild, moderate, or severe for the following items: stuffy nose, blocked nose, runny nose, itching nose, crusting discharge in or on nose, dryness of nose, burning sensation in the nose, discomfort of nose, bleeding from the nose, postnasal drip, cough, sore throat, taste disturbance and sneezing.

Frequency distributions will be provided by treatment group for each of the items at each timepoint during the each of the treatment phases. Shift from predose to postdose questionnaires during each time point throughout the study will be provided by treatment group to see if there is any change after repeated administrations of study drug. Frequency of subjects who report moderate or severe symptoms at any postdose timepoint during each treatment phase will be presented by treatment group. In addition, a listing of severe symptoms will also be presented.

## 6.6. Other Safety Parameters

### 6.6.1. Columbia Suicide Severity Rating Scale (C-SSRS)

The Columbia Suicide Severity Rating Scale (C-SSRS)<sup>7</sup> 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. It is a semi structured clinician-administered questionnaire designed to solicit the occurrence, severity, and frequency of suicide-related ideation and behaviors during the assessment period. Using the C-SSRS, potentially suicide-related events will be categorized using the following scores:

#### **Suicidal Ideation (1-5)**

- 1: Wish to be Dead
- 2: Non-specific Active Suicidal Thoughts
- 3: Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
- 4: Active Suicidal Ideation with Some Intent to Act, without Specific Plan
- 5: Active Suicidal Ideation with Specific Plan and Intent

#### **Suicidal Behavior (6-10)**

- 6: Preparatory Acts or Behavior
- 7: Aborted Attempt
- 8: Interrupted Attempt
- 9: Actual Attempt (non-fatal)
- 10: Completed Suicide

If no events qualify for a score of 1 to 10, a score of 0 will be assigned (0="no event that can be assessed on the basis of C-SSRS"). Higher scores indicate greater severity.

The summaries of the C-SSRS outcomes will be based on the Safety analysis set for a given treatment phase for subjects who have at least 1 post-baseline C-SSRS measurement and a pre-treatment C-SSRS assessment (assessment at Baseline (IND) visit).

A frequency distribution at each scheduled time point by treatment will be provided. Shifts from the Baseline (IND) value to the most severe/maximum score during each phase will be summarized by treatment.

The maximum score assigned for each subject will also be summarized into one of three broad categories: No suicidal ideation or behavior (0), Suicidal ideation (1-5), Suicidal behavior (6-10).

Shifts from the Baseline (IND) value to the maximum category during each phase, including the follow-up phase, will be summarized by treatment.

### 6.6.2. Clinician Administered Dissociative States Scale (CADSS)

The Clinician Administered Dissociative States Scale (CADSS)<sup>2</sup> is an instrument for the measurement of present-state dissociative symptoms, and is administered to assess treatment-emergent dissociative symptoms. The CADSS comprises 23 subjective items and participant's responses are coded on a 5-point scale (0 = "Not at all", 1 = "Mild", 2 = "Moderate", 3 = "Severe" and 4 = "Extreme"). The CADSS is divided into 3 components using the following scoring method:

Component	Questions	Range
Depersonalization	Sum of 3, 4, 5, 6, 7, 20, 23	0-28
Derealization	Sum of 1, 2, 8, 9, 10, 11, 12, 13, 16, 17, 18, 19, 21	0-52
Amnesia	Sum of 14, 15, 22	0-12
Total Score	Sum of 1 through 23	0-92

For the total score and each component, a higher score represents a more severe condition. If any response is missing the total score is set to missing. The CADSS is measured prior to each dose, at 40 minutes, and at 1.5 hours postdose.

Descriptive statistics (N, median, minimum, and maximum) of the total scores and component scores at each time point and visit, changes from predose and proportion of subjects with an increase in CADSS total score from the predose value at any time during the phase will be summarized by treatment phase. Mean (SD) CADSS values will be presented graphically for each intranasal dosing day.

### 6.6.3. Brief Psychiatric Rating Scale (BPRS)

The Brief Psychiatric Rating Scale (BPRS) is an 18 item rating scale which is used to assess potential treatment-emergent psychotic symptoms. The BPRS assesses a range of psychotic and affective symptoms rated from both observation of the subject and the subject's own report. Only the four-item positive symptom subscale (BPRS<sup>+</sup>) will be used in the study to assess treatment-emergent psychotic symptoms. The BPRS<sup>+</sup> consists of: suspiciousness, hallucinations, unusual thought content and conceptual disorganization. Each symptom is rated on a scale of 0 to 6 as follows: 0: not present, not evident or absent; 1: very mild; 2: mild; 3: moderate; 4: moderate severe; 5: severe; or 6: extreme. A total score will be derived by summing the individual items, with a range of 0 to 24 with a higher score representing a more severe condition.

The BPRS<sup>+</sup> is measured prior to each dose, at 40 minutes, and at 1.5 hours post dose during each of the treatment phases.

Descriptive statistics (N, median, minimum, and maximum) of the total scores at each time point and the change from the pre-dose time point within each visit, and the proportion of subjects with an increase in BPRS<sup>+</sup> from the predose value at any time will be provided for each treatment phase. Mean (SD) BPRS<sup>+</sup> values will be presented graphically for each intranasal dosing day.

#### **6.6.4. Modified Observer's Assessment of Alertness/Sedation (MOAA/S)**

The Modified Observer's Assessment of Alertness/Sedation (MOAA/S) will be used to measure treatment-emergent sedation with correlation to levels of sedation defined by the American Society of Anesthesiologists (ASA) continuum. 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].

The MOAA/S is measured on each dosing day every 15 minutes from predose to 1.5 hours postdose or longer, if necessary, until the subject has a score of 5.

- If the score is  $\leq 3$  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 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  $\leq 3$ , 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.

Descriptive statistics of the MOAA/S score, changes from predose, and the proportion of subjects experiencing sedation (score less than or equal to 3) will be summarized at each scheduled time point.

Mean MOAA/S scores will be presented graphically for each intranasal dosing day.

#### **6.6.5. Clinical Global Assessment of Discharge Readiness (CGADR)**

The Clinical Global Assessment of Discharge Readiness (CGADR) will be used to measure a 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 (e.g., 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, repeated every 15 minutes if necessary until the response is ‘Yes’. A subject should not be discharged prior to the 1.5-hour time point.

The proportion of subjects with a response of ‘No’ at each time point will be presented by treatment during each of the treatment phases.

#### **6.6.6. Physician Withdrawal Checklist (PWC-20)**

The PWC-20 is a 20-item simple and accurate method to assess potential withdrawal symptoms following cessation of intranasal esketamine treatment. The PWC-20 will be performed for all subjects on Day 25 to establish a baseline prior to discontinuation of esketamine treatment – although only relevant for those subjects not continuing to the optimization phase. For those subjects who proceed to the optimization and maintenance phases, the PWC-20 is conducted at the End of Study Visit. If subjects withdraw early from the study during any phase, the PWC-20 will be conducted at the Early Withdrawal Visit.

The proportion of subjects with withdrawal symptoms at the end of each treatment phase (IND, OP and MA) and during the follow-up phase will be presented by treatment. In addition, symptoms at follow-up will be compared to the last assessment in the relevant treatment phase (IND, OP and MA) for subjects who discontinue during that treatment phase and will be summarized using the following categories: new or worsened symptoms, symptoms present and unchanged, no symptoms, and improved.

#### **6.6.7. Computerized Cognitive Battery and Hopkins Verbal Learning Test-Revised (HVLTR)**

The effect of intranasal esketamine on cognition will be assessed using the computerized cognitive battery and the HVLTR.

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 HVLTR is a measure of verbal learning and memory and is a 12-item word list recall test. The total number of correct responses are captured for 4 trials as well as the number of true-positive responses and false-positive errors in Trial 4 (Delayed Recall). The Total Recall will be derived as the sum of trials 1, 2 and 3. Retention % will be derived as (the number of correct responses in Trial 4)/(higher score of Trials 2 and 3) X 100. Recognition Discrimination Index will be derived as the total number of true-positives – the total number of false-positives.

The computerized cognitive battery and HVLTR will be assessed at Day 1 predose, Day 28/ET of the open-label induction phase, Week 16 of the optimization phase, and every 12 weeks during the maintenance phase. It will also be assessed again at 2 weeks post-treatment during the follow-up phase.

See [Attachment 3](#) for details of this analysis.

### **6.6.8. University of Pennsylvania Smell Inventory Test (UPSIT)**

The UPSIT is a 40-item standardized test to assess a subject's ability to identify odors. The UPSIT will be administered bilaterally (i.e., both nostrils at the same time); testing will occur during screening to establish a subject's baseline sensitivity.

The UPSIT total score is defined as the total number of correct responses; therefore, the total score ranges from 0-40, where higher scores indicate greater smell function. Descriptive statistics of the observed values for UPSIT total score (%) and percent changes from baseline will be summarized at each scheduled time point during each treatment phase. Baseline (IND) will be used for computing change. UPSIT total score (%) will be defined as  $[(\# \text{ correct responses})/(\# \text{ completed responses})]*100$ .

### **6.6.9. Smell Threshold Test**

The Smell Threshold Test will assess the smell threshold using a forced-choice single staircase threshold procedure. This test will be administered bilaterally (i.e., both nostrils at the same time); testing will occur during screening to establish a subject's baseline sensitivity and also throughout each treatment phase.

The smell threshold will be derived as the average of the non-missing results for the fourth through seventh reversals, as recorded on the CRF. If there are any missing results, the average will be set to missing. A small deficit is defined as thresholds above -2.40. Descriptive statistics for observed values and changes from baseline (IND) will be summarized at each scheduled time point during each treatment phase.

## **7. HEALTH ECONOMICS**

### **7.1. Healthcare Resource Use Questionnaire (HRUQ)**

Medical resource utilization data, associated with medical encounters, will be collected using the Healthcare Resource Use Questionnaire (HRUQ) during the optimization, maintenance, and follow-up phases bi-weekly.

The number and percentage of subjects who visited at least one healthcare professional or had a hospital emergency room visit because of their depression in the 2 weeks preceding each time point will be summarized for each type of healthcare professional. The total number of visits to each type of healthcare professional, total number of visits to any healthcare professional, and the total number of hospital emergency room visits related to depression in the 2 weeks preceding each time point will be summarized at each time point with descriptive statistics. All summaries will be presented by treatment group.

---

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**LIST OF ATTACHMENTS****Attachment 2: Criteria of Markedly Abnormal Laboratory Values**

Laboratory Parameter	Markedly Abnormal Limits	
	Low	High
Albumin [g/L]	24	60
Alkaline phosphatase [U/L]	N/A	250
Alanine transaminase (SGPT) [U/L]	N/A	200
Alanine transaminase (SGPT) [U/L]	N/A	>3X ULN
Aspartate transaminase (SGOT) [U/L]	N/A	250
Bicarbonate [mmol/L]	15.1	34.9
Blood urea nitrogen [mmol/L]	N/A	17.9
Calcium [mmol/L]	1.5	3
Chloride [mmol/L]	94	112
Creatine kinase (U/L)	N/A	990
Creatinine [ $\mu$ mol/L]	N/A	265.2
Gamma glutamyl transferase [U/L]	N/A	300
Glucose [mmol/L]	2.2	16.7
Phosphate [mmol/L]	0.7	2.6
Potassium [mmol/L]	3.0	5.8
Sodium [mmol/L]	125	155
Bilirubin, total [ $\mu$ mol/L]	N/A	51.3
Protein, total [g/L]	50	N/A
Urine pH	N/A	8.0
Hematocrit [fraction] - female	0.28	0.5
- male	0.24	0.55
Hemoglobin [g/L]	80	190
Neutrophils, segmented [%]	30	90
Monocytes [%]	N/A	20
Eosinophils [%]	N/A	10
Basophils [%]	N/A	6
Lymphocytes [%]	10	60
Platelet count [ $\times 10^9$ /L]	100	600
Erythrocytes (RBC) [ $\times 10^{12}$ /L] -- female	3.0	5.5
-- male	3.0	6.4
Leukocytes(WBC) [ $\times 10^9$ /L]	2.5	15.0
Hy's Law criteria:		
Alanine transaminase (SGPT) [U/L]		> 3X ULN
AND		
Bilirubin, total [ $\mu$ mol/L]		>2X ULN

Note: The same limits apply to both males and females unless gender is indicated; N/A = Not applicable.

**Attachment 3: Statistical Analysis Plan for COGSTATE**



**STATISTICAL ANALYSIS PLAN**

**RANDOMIZED, DOUBLE-BLIND, MULTICENTER, ACTIVE-CONTROLLED STUDIES TO  
EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF FIXED DOSES OF  
INTRANASAL ESKETAMINE PLUS AN ORAL ANTIDEPRESSANT IN ADULT SUBJECTS  
WITH TREATMENT-RESISTANT DEPRESSION**

**AND**

**AN OPEN-LABEL, LONG-TERM, SAFETY AND EFFICACY STUDY OF INTRANASAL  
ESKETAMINE IN TREATMENT-RESISTANT DEPRESSION**

---

**PROTOCOL ESKETINTRD3001/2/3/4/5; PHASE 3**

**Prepared for:** Janssen Research & Development, LLC

**Prepared by:** Cogstate Biostatistics Group  
Level 8, 195 Church Street  
New Haven, CT, USA, 06510

**Version:** V3  
**Date:** 27-Jul-2016  
**Protocol Version:** Approved Date: 17 Feb 2016



## 1 NOTE

Cogstate has prepared a Statistical Analysis Plan (SAP) for the Sponsor to review and sign-off for all ESKETINTRD studies. Analyses will be provided after this document has been finalized and officially signed. In this SAP, anything in italics is taken directly from the protocol. For more details, please refer to the study protocols and SAPs.

Notice that this SAP will be used for all the five ESKETINTRD studies (3001, 3002, 3003, 3004 and 3005).



**2 SIGNATURE PAGE FOR SAP APPROVAL**

The following signatures indicate the approval of the statistical analysis plan for ESKETINTRD studies.

**Approved by:**

**Name (print):** Phillip Phiri  
**Position:** [Redacted]  
**Signature:** [Redacted]  
**Date (ddmmyyyy):** 30 Aug 2016

**Approved by:**

**Name (print):** Jaskaran Singh  
**Position:** \_\_\_\_\_  
**Signature:** JASKARAN  
**Date (ddmmyyyy):** SINGH

Digitally signed by JASKARAN SINGH  
DN: c=US, o=JNJ, ou=Subscribers,  
0.9.2342.19200300.100.1.1=364610,  
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Reason: I am approving this document.  
Date: 2017.06.14 14:22:10 -07'00'

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**Position:** \_\_\_\_\_  
**Signature:** PILAR LIM  
**Date (ddmmyyyy):** \_\_\_\_\_

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cn=PILAR LIM  
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Reason: I am approving this document.  
Date: 2017.06.14 19:01:45 -04'00'



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#### 4 ABBREVIATIONS

<b>Abbreviation</b>	<b>Description</b>
DET	Detection test
HVLT-R	Hopkins Verbal Learning Test-Revised
IDN	Identification test
ISLT	International Shopping List test
OCL	One Card Learning test
ONB	One Back Memory test
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SPP	Statistical Programming Plan



## 5 INTRODUCTION

This Statistical Analysis Plan (SAP) contains technical and detailed elaboration of the principal features of the analysis described in the protocol related to computerized cognitive battery and HVLTR and includes detailed procedures for executing the statistical analysis of the data.

The SAP will be finalized and signed prior to database lock. If needed, revisions to the approved SAP may be made prior to database lock. Revisions will be version controlled.

This statistical analysis is coordinated by the responsible Cogstate statistician. Any changes from the analyses planned in the SAP will be justified in the Cogstate statistical report.

## 6 VISIT SCHEDULE

### Scheduled Visits

Table 1: Scheduled visits related to Cogstate battery and HVLTR

Period	Visit Number	Study Day	Study Week by phase	Computerized test battery & HVLTR Assessment Included
Screening/prospective Observation Phase	1.2	-	2	Computerized test battery Practice Session
Double-blind Induction Phase	2.1	1	1	Yes
	2.10 or 2.9	28	4	Yes
	EW <sup>b</sup>	EW	-	Yes
Follow-up Phase	3.2	-	2 after last intranasal dose	Yes
Follow-up Phase	3.6 to 3.x	Every 84 days	Every 12 Weeks	Yes for ESKETINTRD3004

<sup>b</sup> If a subject withdraws before the end of the double-blind induction phase (i.e., before completing Visit 2.10/Day 28) for reasons other than withdrawal of consent, an early withdrawal visit should be conducted within 1 week of the date of discontinuation, followed by the follow-up phase. If the early withdrawal visit is conducted on the same day as a scheduled visit, duplicate assessments are not required.

## 7 STUDY OBJECTIVES RELEVANT TO COGSTATE ANALYSIS

The objective is to assess the effect of intranasal esketamine on cognition.

## 8 STUDY DESIGN

The study designs for each study are described in their respective protocols.



## 9 SAMPLE SIZES

The sample sizes for each study are as follows:

- 116 subjects per treatment for ESKETINTRD3001.
- 98 subjects per treatment for ESKETINTRD3002.
- A total of 211 subjects for ESKETINTRD3003.
- There is no formal sample size calculation for ESKETINTRD3004 study (Note: the total number of subjects will be based on subjects from this study and subjects from other intranasal esketamine Phase 3 studies).
- 74 subjects per treatment for ESKETINTRD3005.

## 10 ANALYSIS SETS

**Safety Analysis Set:** All randomized subjects who receive at least 1 dose of intranasal study medication or 1 dose of oral antidepressant medication in the double-blind induction phase. This analysis set will be used for ESKETINTRD3001/2/5.

For ESKETINTRD3003, the safety analysis set for each phase is defined as all subjects who receive at least 1 dose of intranasal study drug or 1 dose of oral antidepressant during that phase.

**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.

These analysis sets will be used for ESKETINTRD3004

## 11 ANALYSIS VARIABLES

### 11.1 Computerized cognitive battery and Hopkins Verbal Learning Test-Revised (HVLTR) Endpoints

The endpoints for computerized cognitive battery (DET, IDN, ONB, OCL, and GML) and HVLTR are the scores and change from baseline (Day 1 prior to randomization) scores at each scheduled post baseline time point.

### 11.2 The computerized tests from the Cogstate Battery.

#### 11.2.1 Summary of the Cogstate Battery

##### Detection (DET; Psychomotor Function)

The Detection test is a measure of psychomotor function and uses a well-validated simple reaction time paradigm with playing card stimuli. In this test, the playing cards all depict the same joker. The subject is asked to press the Yes key as soon as the card in the center of the screen turns face up. The software



measures the speed and accuracy of each response. The test terminates when a subject has correctly responded to 35 trials. The time to respond (to a maximum) is recorded for each trial.

**Duration of test 3 minutes**

#### Identification (IDN; Attention)

The Identification test is a measure of visual attention and uses a well-validated choice reaction time paradigm with playing card stimuli. In this test, the playing cards are all either red or black jokers. The subject is asked whether the card displayed in the center of the screen is red. The subject responds by pressing the Yes key when the joker card is red and No when it is black. The software measures the speed and accuracy of each response. The time to respond (to a maximum) is recorded for each trial. Wrong responses are counted but do not have an effect on the number of correct responses required for the test to terminate.

**Duration of test: 2 minutes**

#### One Card Learning (OCL; Visual Learning)

The One Card Learning test is a measure of visual learning and uses a well-validated pattern separation paradigm with playing card stimuli. In this test, the playing cards are identical to those found in a standard deck of 52 playing cards (without the joker cards). The subject is asked whether the card displayed in the center of the screen was seen previously in this test. The subject responds by pressing the Yes or No key. The software measures the speed and accuracy of each response. Because no card has been presented yet, the first response is always "No". Eighty trials are displayed during this test.

**Duration of test 3 minutes**

#### One Back (ONB; Working Memory)

The One Back test is a measure of working memory and uses a well-validated n-back paradigm with playing card stimuli. In this test, the playing cards are identical to those found in a standard deck of 52 playing cards (without the joker cards). The subject is asked whether the card displayed in the center of the screen is the same as the card presented immediately previously. The subject responds by pressing the Yes or No key. Because no card has been presented yet on the first trial, a correct first response is always No. The software measures the speed and accuracy of each response. The time to respond (to a maximum) is recorded for each trial. Wrong responses are counted but do not have an effect on the number of correct responses required for the test to terminate.

**Duration of test: 4 minutes**

Version: V2  
Date: 30-Mar-2016  
Protocol: Approved Date 17 Feb 2016

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### The Groton Maze Learning test (GML; Executive Function)

The Groton Maze Learning test is a measure of problem solving and reasoning and uses a well-validated maze learning paradigm. In this test, the subject is shown a [10 x 10] grid of boxes on a computer screen. A [28]-step pathway is hidden among these [100] possible locations. Each box represents move locations, and the grid refers to the box array (i.e., [10 × 10]). Subjects are required to find the hidden pathway guided by [four] search rules. These rules are: do not move diagonally, do not move more than one box (i.e., do not jump), do not move back on the pathway, and (return to the last correct location after an error). At each step only the most recently selected box is shown. Feedback is given with visual and auditory cues (green check marks and red crosses) to indicate whether the selected box is correct or incorrect. The head of path, or the last correct location, flashes with a green check when two errors are made in succession to indicate to the subject that they must return to this location. [A delayed recall condition is available for this test and requires the subject to find the hidden pathway after a 10-30 minute delay]. There are [20] well-matched alternate pathways available. The software records each move as an error or as a correct move.

**Duration of test: 7 minutes**

#### **11.2.2 The outcome measures for the Cogstate battery**

Although each of these cognitive tests yields multiple outcome measures, research by Cogstate has identified a set of measures that are optimal for the detection of cognitive change in clinical trials at both the group and individual level (Faletti et al., 2006; Maruff et al., 2009; Bland & Altman, 1996).

For each cognitive test, a single primary outcome measure was selected prior to data analysis from each test in the battery. Each primary outcome measure was selected because it has been shown to be optimal for the detection of change:

- a) it is drawn from a data distribution that contains only a small probability of floor or ceiling effects and no restriction in the range of possible performance values (Faletti et al., 2006; Bland & Altman, 1996).
- b) it is drawn from a distribution that is distributed normally or which can be corrected to normal through the use of appropriate mathematical transformation (e.g., logarithmic base 10, or arcsine) (Faletti et al., 2006; Bland & Altman, 1996).

Table 1 below summarizes the outcome measures for the Cogstate battery, with the tests from which they were derived, the operational definition, and the variable code.



**Table 2: Cogstate tests Administered in ESKETINTRD studies, the Cognitive Domains they Assess, and their Primary Outcome Measures**

Cogstate test	Cognitive Domain	Primary Outcome Measure	Interpretation of Primary Outcome Score
Detection test(DET)	Attention (simple reaction time)	Speed of performance (mean of the log <sub>10</sub> transformed reaction times for correct responses)	Lower score = better performance
Groton Maze Learning test(GML)	Executive Function	Number of errors across all learning trials	Lower score = better performance
Identification test (IDN)	Attention (choice reaction time)	Speed of performance (mean of the log <sub>10</sub> transformed reaction times for correct responses)	Lower score = better performance
One Card Learning test (OCL)	Visual Learning	Accuracy of performance (arcsine square root proportion correct)	Higher score = better performance
One Back test (ONB)	Working Memory	Speed of performance (mean of the log <sub>10</sub> transformed reaction times for correct responses)	Lower score = better performance

### 11.2.3 Data Quality Assurance

Data from the Cogstate battery will be collected on computers at all sites and uploaded to the Cogstate database for processing. Cogstate data management staff will query any data discrepancies. Queries will be confirmed and resolved with the sponsor.

### 11.2.4 Test Completion Criteria

For each of the Cogstate tests, subjects must provide sufficient responses to allow computation of reliable performance measures. For the majority of Cogstate tests, the term “sufficient” has been defined as a test Completion criterion. The number of trials required for test Completion is unique to each test. They do not vary for different patient groups or study samples.

The completion criteria set forth a priori for each test were as follows:

- DET: The number of responses provided by the subject is  $\geq 75\%$  of the desired number of trials (responses  $\geq 27$ ).
- IDN: The number of responses provided by the subject is  $\geq 75\%$  of the desired number of trials (responses  $\geq 23$ ).
- ONB: The number of responses provided by the subject is  $\geq 75\%$  of the desired number of trials (responses  $\geq 24$ ).
- OCL: 75% of the desired numbers of trials were displayed to the subject (trials  $\geq 60$ ).



- GML: The subject provided 28 correct moves in each of the 5 learning trials.

### 11.3 The HVLТ-R

*The HVLТ-R, 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 (20-minute) trial. Administration is computer-assisted; instructions and word lists appear on-screen. The test administrator records each word correctly recalled, and scores for learning, short-term, and delayed recall are generated via the test software. The HVLТ-R is a well-validated and widely used measure of verbal episodic memory. The tests will be administered in the following order: HVLТ-R, computerized cognitive test battery, and HVLТ-R Delayed.*

## 12 STATISTICAL METHODOLOGY

### 12.1 Analysis Overview

All statistical analyses and summary information will be generated according to this Statistical Analysis Plan (SAP).

For continuous variables, descriptive statistics will include number of subjects (n), mean, standard deviation, median, minimum and maximum. Frequencies and percentages will be displayed for categorical data.

Listings will be produced and displayed.

#### 12.1.1 Analysis of Cogstate Endpoints and HVLТ-R

Descriptive statistics (n, mean, SD, min, median, max) of scores and change from baseline scores will be summarized and plotted at each scheduled time point.

For HVLТ-R, Scores and change from baseline scores will include the following:

- Total Recall (sum of total correct responses for Trials 1, 2, & 3),
- Delayed Recall (Trial 4)
- Total number of true-positive errors and
- Recognition Discrimination Index (Total no. of true-positives)-(Total no. of false-positives).

#### 12.1.2 Baseline Definition

Baseline is defined as Induction phase, Day 1.

#### 12.1.3 Handling of Missing Data and data transformation

##### *Missing Data*

No imputations will be performed in the event of missing data due to dropouts or omitted visits. All incomplete subject profiles, consisting of time points that passed Test completion criteria, will be retained in the analysis. In view of issues of reliability, based on the recommendation of Cogstate scientists, all analyses will be conducted with values which failed completion criteria (listed in Section 11.2.3) removed.



### ***Data Transformation***

#### **Speed outcome measure**

Since Cogstate speed outcome measures are skewed to the right,  $\log_{10}$  transformation will be used to normalize the data. The transformed data will be used in the analyses which are specified in this SAP:

$$\text{LMN} = \text{mean}(\log_{10} \text{ transformed reaction times for correct responses}) \quad (1)$$

#### **Proportion of accuracy outcome measure**

Cogstate correct responses follow a binomial distribution. Since a binomial distribution is not well approximated by a normal distribution, especially when  $n$  is small, arcsine square root transformation (which is a variance stabilizing transformation) will be used on Cogstate data on the proportion of correct responses measure and this transformed data will be used in the analysis which is specified in this SAP:

$$\text{ACC} = \text{arcsine}(\text{sqrt}[\text{proportion of correct responses}]) \quad (2)$$

### **12.2 Unblinding Procedure**

Once all data discrepancies within the Cogstate database are resolved with the clinical research units, the database will be locked and Cogstate will receive the randomization codes from the sponsor.

Table, listing and figure (TLF) shells will be generated in a separate document (Statistical Programming Plan<SPP>).





### 13 REFERENCES

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