Janssen Research & Development *

Clinical Protocol

An Open-label Long-term Extension Safety Study of Esketamine Nasal Spray in Treatment-resistant Depression

Safety and Sustenance of Esketamine Treatment Response With Repeated Doses at Intervals Determined by Symptom Severity (SUSTAIN-3)

Protocol 54135419TRD3008; Phase 3
AMENDMENT 4

JNJ-54135419 (esketamine)

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This compound is being investigated in Phase 3 clinical studies.

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

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

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	08 February 2016
Amendment 1	14 December 2016
Amendment 2	21 August 2017
Amendment 3	24 April 2019
Amendment 4	05 October 2020

Amendments below are listed beginning with the most recent amendment.

Amendment 4 (05 October 2020)

The overall reason for the amendment: Following the conclusion of the post-marketing commitment to FDA for 3 years of US data at the end of 2020, the sponsor is extending the study duration to allow for ongoing subjects to continue to receive esketamine treatment if clinically warranted and until it is available in the subject's respective country, or December 2022, whichever is earlier. The number/frequency of assessments is therefore being reduced to mimic clinical practice and reduce burden on sites and subjects while ensuring adequate clinical oversight and monitoring of subject safety.

Applicable Section(s)	Description of Change(s)
Rationale: To update subject completion criteria due to extension of study. Updated text in Optimization/Maintenance Phase since duration is no longer based on the results of the pivotal Phase 3 trials, which have concluded.	
Synopsis Overview of Study Design; 1.2 Overall Rationale for the Study	This study provides an opportunity for subjects who have participated in select Phase 3 studies to receive open label esketamine nasal spray until: • esketamine is approved in the respective country and accessible through the local healthcare system funding or until end of December 2022, whichever is earlier; or • the subject does not benefit from further treatment (based on the investigator's clinical judgment) or withdraws consent; or • the company terminates clinical development of esketamine nasal spray for TRD in that country/region
3.1. Overview of Study Design; 9.1.3. Optimization/Maintenance Phase	The duration that a subject may participate in the study is variable and is based on the subject's point of entry into the study and the timing of when the predefined criteria (below) for ending study participation occurs. Study participation will be stopped: • when esketamine is approved in the respective country and accessible through the local healthcare system funding or until end of December 2022, whichever is earlier; or • the subject no longer benefits from further treatment (based on the investigator's clinical judgment), or withdraws consent; or • the company terminates clinical development of esketamine nasal spray for TRD in that country/region
3.2.2. Study Phases	Optimization/Maintenance Phase (Variable) The duration of the optimization/maintenance phase is variable and based on the subject's individual efficacy and tolerability to esketamine nasal spray, or when esketamine is approved in the respective country and accessible through the local healthcare system funding or until end of December 2022, whichever is earlier.

Applicable Section(s)	Description of Change(s)
10.1. Completion	A subject will be considered to have completed the study if he/she is actively participating in the induction or optimization/maintenance phase when one of the following is reached: • esketamine is approved in the respective country and accessible through the local healthcare system funding or until end of December 2022, whichever is earlier • the company terminates clinical development of esketamine nasal spray for TRD in that country/region
17.9.1. Study Completion	The end of the study will occur based on the subject's individual efficacy and tolerability to esketamine nasal spray, and/or until esketamine is approved in the respective country and accessible through the local healthcare system funding or until end of December 2022, whichever is earlier. Study participation will be stopped: • when esketamine is approved in the respective country and accessible through the local healthcare system funding or until end of December 2022, whichever is earlier; or • the subject no longer benefits from further treatment (based on the investigator's clinical judgment), or withdraws consent; or • the company terminates clinical development of esketamine nasal spray for TRD in that country/region
Rationale: To update implementation and frequency of subject-completed assessments, safety assessments, and clinical laboratory tests in the Optimization/Maintenance Phase to mimic clinical practice and reduce burden on sites and subjects while ensuring adequate clinical oversight and monitoring of subject safety.	
Time and Events Schedule (Optimization/Maintenance Phase)	Modified frequency of subject-completed assessments PHQ-9, SDS, EQ-5D-5L, TSQM-9, and QLDS from every 4 weeks to every 12 weeks. Removed MAGDA assessment and related footnote. MOAA/S assessment will not be required for all visits following Visit 2.4. Pulse oximetry assessments will not be required for all visits following Visit 2.4. Alcohol breath test will not be required every 8 weeks. Updated HRUQ footnote for completion until end of December 2020.
Synopsis Medical Resource Utilization	Removed requirement to complete the Health Resource Utilization Questionnaire (HRUQ) every 4 weeks and at early withdrawal/end of study.
Rationale: To clarify that the choice of oral antidepressant use during the study will be based on the clinical judgment of the investigator upon assessment of the benefit risk.	
Synopsis Study Phases; Section 3.1. Overview of Study Design; Section 8. Prestudy and Concomitant Therapy	All study subjects should be taking a permitted oral antidepressant (per clinical judgment) throughout the duration of study participation.

Applicable Section(s)	Description of Change(s)
Rationale: To remove Magda Avatar Game Depression Implicit Association (MAGDA) assessment as it was never developed or implemented.	
Synopsis Objectives, Endpoints, and Hypothesis; Synopsis Efficacy Analysis; 2.1.2. Endpoints; 3.2.6. Efficacy Measures; 9.5.1. MAGDA; 11.4. Efficacy Analyses	Removed text regarding MAGDA assessment, which was never used in the study.
Rationale: To update text regarding the Independent Data Monitoring Committee and clarify that meetings will continue through the end of 2020. Additional safety monitoring will continue in-house as this is an open-label, single arm study.	
Synopsis Overview of Study Design; 3.1. Overview of Study Design; 11.7. Independent Data Monitoring Committee	The committee will meet approximately every 6 months to review select safety data through the end of 2020.
Rationale: Remove text related to "anticipated adverse events" to align with current protocol template text for open-label studies.	
12.3.1. All Adverse Events	Deleted text related to anticipated adverse events and updated text to align with current protocol template text.
12.3.2. Serious Adverse Events	Updated text to align with current protocol template text.
Attachment 2: Anticipated Events	Attachment 2 was removed from the protocol.
Rationale: To include instructions on handling of missed doses.	
6.1.2. Optimization/Maintenance Phase	Added text regarding missed doses, clarifying that if a subject missed a dose/s and the depression symptoms worsened, the investigator can go back to more frequent dosing if clinically applicable until the subject is stable.
Rationale: Align with current protocol template text.	
13. Product Quality Complaint Handling	Update text and add definition for "technical complaints".
13.1. Procedures	Added text for sample retention of suspected product.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 3 (24 April 2019)

The overall reason for the amendment: The protocol was modified to 1) Extend the study to collect data characterizing the long-term effects of esketamine on cognitive function and urinary symptoms (cystitis). 2) Update categories of treatment emergent adverse events (TEAEs) of special interest. 3) Update Attachment 1 (Prohibited Concomitant Medications With Esketamine Nasal Spray Study Medication) with new guidelines.

Applicable Section(s)	Description of Change(s)
Rationale: To better characterize the safety risks of long-term use of esketamine, the study was extended to collect data on the long-term effects of esketamine on cognitive function and urinary symptoms (cystitis).	
Synopsis; 1.2. Overall Rationale for the Study	This study provides an opportunity for subjects who have participated in select Phase 3 studies to receive open label esketamine nasal spray until: • the end of December 2020 or when it is commercially available in the subject's respective country (whichever is later), in order to have a reasonable number of subjects participating for 3 years or longer to collect long term safety data; or • the subject does not benefit from further treatment (based on the investigator's clinical judgment) or withdraws consent; or • the company terminates clinical development of esketamine nasal spray for TRD in that country/region
Synopsis Overview of Study Design; 3.1. Overview of Study Design; 9.1.3. Optimization/Maintenance Phase	Study participation will be stopped: • at the end of December 2020 or when esketamine nasal spray is commercially available in the subject's respective country (whichever is later); or • the subject no longer benefits from further treatment (based on the investigator's clinical judgment), or withdraws consent; or • the company terminates clinical development of esketamine nasal spray for TRD in that country/region
3.2.2. Study Phases	**Optimization/Maintenance Phase (Variable)** The duration of the optimization/maintenance phase is variable and based on the subject's individual efficacy and tolerability to esketamine nasal spray, results of the pivotal Phase 3 efficacy and safety studies, or when esketamine nasal spray is commercially available in the subject's respective country / the end of December 2020 (whichever is later).
10.1. Completion	A subject will be considered to have completed the study if he/she is actively participating in the induction or optimization/maintenance phase when one of the following is reached: • end of December 2020 or when esketamine nasal spray is commercially available in the subject's respective country (whichever is later) • the company terminates clinical development of esketamine nasal spray for TRD in that country/region
17.9.1. Study Completion	The end of the study will occur based on the subject's individual efficacy and tolerability to esketamine nasal spray, results of the pivotal Phase 3 efficacy and safety studies, and/or until the end of December 2020 or when esketamine nasal spray is commercially available in the subject's respective country (whichever is later). Study participation will be stopped: • at the end of December 2020 or when esketamine nasal spray is commercially available in the subject's respective country (whichever is later); or • the subject no longer benefits from further treatment (based on the investigator's clinical judgment), or withdraws consent; or • the company terminates clinical development of esketamine nasal spray for TRD in that country/region

Applicable Section(s)	Description of Change(s)
Rationale: To update categories of treatment emergent adverse events (TEAEs) of special interest.	
Synopsis Statistical Methods; 3.2.5. Safety Evaluations; 11.3. Safety Analyses	Treatment emergent AEs of special interest will be examined separately grouped in the following categories: drug abuse, dependence and withdrawal, increased blood pressure, increased heart rate, transient dizziness/vertigo, impaired cognition, cystitis, anxiety, events potentially related to suicidality, hepatic adverse events, events related to renal disorders, and symptoms of dissociation persisting beyond the typical ≤2 hour post esketamine administration, as well as delirium, psychosis or mania.
Rationale: Attachment 1 (Prohibited and Permitted Concomitant Medications With Esketamine Nasal Spray Study Medication) was modified to clarify the list of prohibited/permitted concomitant medications and the guidelines for concomitant medication use.	
Attachment 1	The following text for the use of corticosteroids was added to the table since it was erroneously omitted in previous versions: Corticosteroids: Inhaled, intranasal, topical, and ophthalmic steroids are not prohibited. Intermittent IM/IV/PO corticosteroids are permitted with sponsor approval (chronic use prohibited). The following text was added for the use of opioids: With Sponsor approval, brief treatment with opiates may be allowed for treatment of acute injuries etc. Modafinil and armodafinil were removed from the list of permitted psychostimulants.
Rationale: Update for preferred terminology.	
Throughout the protocol, protocol title	Changed the name of treatment drug from “intranasal esketamine” to “esketamine nasal spray”.
4.2. Exclusion Criteria	In Exclusion Criterion 1, the name of the treatment drug was changed: The evaluation of the benefit versus risk of continued esketamine nasal spray treatment is not favorable for the subject in the opinion of the investigator.
9.2. Safety Evaluations	Update for preferred terminology to be consistent with current template language. Replaced “endpoint” with “condition”. 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 condition is reached.
Rationale: Deletion of Section 1.1.3. Marketing Experience since it is not a required section in the protocol and is covered in the Investigator’s Brochure.	
1.1.3. Marketing Experience	Deletion of Section 1.1.3. Marketing Experience including statement below: No intranasal formulation of esketamine is currently marketed.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 2 (21 August 2017)

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

The overall reason for the amendment: The protocol was modified 1) to allow the investigator to adjust the frequency of intranasal dosing sessions to every 2 weeks instead of every 4 weeks, depending on the subject's depressive symptomatology, in order to allow greater flexibility with the aim of preventing depression relapse; 2) to permit the investigator to review machine read ECG tracing where initiation of treatment or safety follow-up is time-critical, or if action needs to be taken for safety reasons; 3) to clarify the rationale for removal of the Mini Mental State Examination; and 4) to clarify that (i) pulse oximetry is to be performed at all intranasal dosing sessions, and (ii) to correct erroneous text relating to the MADRS assessment and permitted benzodiazepine medication.

Applicable Section(s)	Description of Change(s)
Rationale: Changes have been made to allow the investigator to adjust the frequency of intranasal dosing sessions during the Maintenance/Optimization Phase at 2 week intervals instead of 4 week intervals, depending on the subject's depressive symptomatology, in order to allow greater flexibility with the aim of preventing depression relapse.	
Synopsis, Dosage and Administration, Intranasal Study Medication, Optimization/Maintenance Phase; Section 6.1.2. Optimization/Maintenance Phase	Frequency of intranasal treatment sessions reduced from a 4 week interval to a 2 week interval The text was revised as follows (bold text added; strikeout text deleted): Starting at Week 4, the frequency for subsequent intranasal treatment sessions will be adjusted (if applicable) based on the algorithm outlined in Table 5 at fixed, 4**2**-week intervals. Table 5. Algorithm for Adjusting Treatment Session Frequency. Footnote (a): Note: ~~Although t~~**T**he CGI-S is administered every 2 weeks from Week 4 through the end of the Optimization/Maintenance Phase, adjustment of the intranasal treatment session frequency is only permitted at the fixed 4 **2**-week interval (based on CGI-S performed at that visit**), and every 4 weeks for subjects dosed at the 4 week interval**.
Time and Events Schedule, Optimization/Maintenance Phase	Study Drug: Adjustment of intranasal treatment session frequency (if applicable) based on CGI-S An "X" added to indicate that intranasal treatment session frequency is permitted at the fixed 2-week interval
Rationale: Clarification that the investigators review of the machine read ECG tracing (provided by the central reader) is considered acceptable in determining if it is appropriate in determining eligibility in cases where initiation of treatment or safety follow-up is time-critical and the central cardiology results are not expected to be available before the need to begin dosing, or if actions need to be taken for safety reasons.	
Section 9.2. Safety Evaluations, Electrocardiogram (ECG)	Electrocardiogram The following text was added: The investigator's review of the machine read ECG tracing (provided by the central reader) is considered acceptable in determining if it is appropriate in determining eligibility in cases where initiation of treatment or safety follow-up is time-critical, and where the central cardiology results are not expected to be available before the need to begin dosing, or if actions need to be taken for safety reasons. All ECG tracings will be sent to the central ECG vendor, where it will be used to determine whether it is appropriate to proceed with dosing.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification that if the postmenopausal status of subjects had been previously confirmed in the following phase 3 studies: ESKETINTRD3001, ESKETINTRD3002, ESKETINTRD3003, ESKETINTRD3004 and EKETINTRD3006, there is no need to perform the FSH again in this study.	
Section 4.1. Inclusion Criteria	Criterion 4 was modified as follows (text added in bold): Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies. 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.* ***Note: FSH not required if post-menopausal status previously confirmed in either ESKETINTRD3001, ESKETINTRD3002, ESKETINTRD3003, ESKETINTRD3004 or ESKETINTRD3006. FSH is not required if subject is ≥ 65 years.*** – permanently sterile *Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.*
Rationale: Text relating to the MADRS assessment that is no longer relevant following changes made in the previous 54135419TRD3008 protocol amendment 1, has now been deleted.	
Section 3.2.6. Efficacy Measures	***MADRS*** The following text was deleted: At the end of the induction phase of this study, the MADRS will be used to determine response. Subjects who are responders (defined as ≥50% reduction in the MADRS total score from baseline [Day 1 prior to the first intranasal dose] to the end of the 4-week induction phase) will proceed to the optimization/maintenance phase.
Rationale: Rationale provided for the removal of the Mini Mental State Examination (MMSE) at study entry has been revised to more clearly outline the clinical rationale. Revisions as follows (bold text): "**Mini Mental State Examination (MMSE) was removed from 54135419TRD3008 because the MMSE would already have been conducted in the phase 3 ESKETINTRD3001-3005 studies and in addition there are continuous cognitive function assessments during the ESKETINTRD3001-3005 studies. Cognition function testing will also be assessed in this 54135419TRD3008 study using the Computerized Cognitive Battery and Hopkins Verbal Learning Test-Revised (HVLT-R)**."	
Changes made to the 54135419TRD3008 Protocol Amendment 1 are listed below:	
Synopsis, Subject Population	Deleted the exclusion of subjects with a MMSE<25.
Time and Events Schedule (Induction Phase)	Deleted the row for MMSE.

Applicable Section(s)	Description of Change(s)
4.2. Exclusion Criteria	In Exclusion Criteria 3, the following sentence was deleted: A Mini Mental *S*tate Examination (MMSE) <25 (only applicable to subjects entering the 54135419TRD3008 study at the Induction Phase).
9.5. Other Evaluations	The subsection (formerly numbered 9.5.1) on MMSE was deleted.
Rationale: Clarification that since this is a safety study rather than an efficacy study, new benzodiazepines or dose increases in benzodiazepine medications are permitted during the study provided the dosages remain at or below the protocol specified cut-off.	
Section 4.3 Prohibitions and Restrictions	The following text was revised as follows (bold text added; strike-out text deleted): 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) can continue these medications. **Dose increases or new benzodiazepines are permitted during the study as long as dosages are equal to or less that the equivalent of 6 mg/day of lorazepam.** ~~No dose increases or new benzodiazepine medications are permitted during the induction phase with the exception of the use of permitted benzodiazepine rescue medication.~~
Rationale: Clarification that pulse oximetry measurements will be performed on all intranasal treatment session days during the Optimization/Maintenance Phase.	
Time and Events Schedule, Optimization/Maintenance Phase	Safety Assessments (Clinician): Pulse oximetry Time and Events Schedule: An "X" was added to the relevant columns for clarification purposes that pulse oximetry will be performed on all intranasal treatment session days (ie, every week, 2 weeks, 4, 8, 12 and 24 weeks during the Optimization/Maintenance Phase). Footnote d): The following text was added (bold): Performed predose and at t = 30 minutes and 60 **minutes** postdose on **all** intranasal treatment session days.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 1 (14 December 2016)

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

The overall reason for the amendment: To update the entry pathways from other Phase 3 esketamine protocols into this protocol, and to make other administrative changes to the protocol.

Applicable Section(s)	Description of Change(s)
Rationale: Based on feedback from investigators and related design changes affecting the esketamine Phase 3 parent studies in subjects with treatment resistant depression, the study team has identified the need to provide additional subjects access to the 54135419TRD3008 study.	
Synopsis Overview of Study Design, Study Entry Table; 3.1 Overview of Study Design – Table 1 and Figure 1	The following revisions were made for the entry pathways from each of the other esketamine Phase 3 studies to 54135419TRD3008 (strikethrough text deleted; **bold** text added): Studies ESKETINTRD3001 / ESKETINTRD3002: Edited Inclusion requirement: Subject completed induction phase-and **the 2-week** ~~6 month~~ follow-up phase **visit** Added Inclusion requirement / Point of entry: **Subject completed the induction phase and was a responder and ESKETINTRD3003 is terminated/ Optimization/maintenance phase** Study ESKETINTRD3003: Added the following Inclusion requirements/Points of entry: **At Week 16 of Optimization, the subject was not eligible to proceed to the maintenance phase and sponsor has approved subject's entry into 54135419TRD3008/ Induction phase or Optimization/maintenance phase** **Subject was in the induction phase and after completion of induction phase, was determined to not meet criteria for response, and sponsor has approved subject's entry into 54135419TRD3008 / Induction phase or Optimization/ maintenance phase** Study ESKETINTRD3004: Edited Inclusion requirement: Subject completed the optimization/maintenance phase ~~and follow-up phase~~ Added the following Inclusion requirement /Point of entry: **Subject was in the induction phase and did not meet criteria for response, and sponsor has approved subject's entry into 54135419TRD3008/ Induction phase or Optimization/ maintenance phase** Added Study ESKTEINTRD3006 United States study sites only and the following Inclusion requirements/Points of entry: **Subject completed the induction phase and was a responder/ Optimization/maintenance phase** **Subject completed induction phase and did not meet the response criteria, and sponsor has approved subject's entry into 54135419TRD3008/ Induction phase or Optimization/Maintenance Phase** Figure 1 was revised according to the entry criteria described above.
Synopsis, Subject Population; 3.2.1. Study Population	Added ESKETINTRD3006 (US sites only) as a study from which subjects may enter 54135419TRD3008.

Applicable Section(s)	Description of Change(s)
3.2.2. Study Phases	Clarified entry into the induction phase with the addition of subjects from Study ESKETINTRD3006 (US sites only), and with sponsor's approval, subjects not meeting criteria for response from ESKETINTRD3003 and ESKETINTRD3004.
4. Subject Population	The list of studies from which subjects may enter 54135419TRD3008 was revised with the addition of ESKETINTRD3006 US Sites only.
4.1. Inclusion Criteria	Inclusion Criterion 1 was modified as follows (strikethrough text deleted; **bold** text added): Based on the prior study the subject is entering 54135419TRD3008 from: **a**. From ESKETINTRD3001 or ESKETINTRD3002 study: **i.** Subject has completed the induction phase and **the 2-week** ~~6 month~~ follow up phase **visit**; **or**. ~~i.~~**ii. Subject completed the induction phase and was a responder and study ESKETINTRD3003 is terminated.** b. From ESKETINTRD3003 study: i. Subject relapsed during the maintenance phase; or ii. Subject was in the induction phase of the ESKETINTRD3003 study when the study was terminated and, after completion of the induction phase, was determined to be a responder; or iii. Subject was in the optimization or maintenance phases at the time the study was terminated; **or** **iv. At Week 16 of Optimization, the subject was not eligible to proceed to the Maintenance phase and sponsor has approved subject's entry into 54135419TRD3008; or** ~~i.~~**v. Subject was in the induction phase and after completion of induction phase was determined to not meet response criteria, and sponsor has approved subject's entry into 54135419TRD3008.** c. From ESKETINTRD3004 study: i. Subject completed ~~the~~ ESKETINTRD3004 study ~~(ie, Week 52 of the~~ optimization/maintenance phase ~~and the follow up phase)~~ or ii Subject was in the induction phase of the ESKETINTRD3004 study when the study was terminated and, after completion of the induction phase, was determined to be a responder; or iii. Subject was in the optimization/maintenance phase at the time the study was terminated; **or**~~.~~ ~~ii~~ **iv**. **Subject was in the induction phase and did not meet criteria for response, and sponsor has approved subject's entry into 54135419TRD3008.** **d**. From ESKETINTRD3005 study: Subject was in the induction phase of the ESKETINTRD3005 study at the time enrollment into the ESKETINTRD3004 study was closed and, after completion of the induction phase, was determined to be a responder or ~~a non-responder~~ **did not meet the criteria for response**. **e. From ESKETINTRD3006 study (US Study sites only):** **i. Subject completed the induction phase and was a responder, or** ~~iv.~~**ii. Subject completed the induction phase and did not meet the response criteria and sponsor has approved subject's entry into 54135419TRD3008.**
9.1.2. Induction Phase	The third bullet for subjects who could enter at the Induction Phase was revised as follows (strikethrough text deleted; **bold** text added): • Subjects who completed the induction phase and **the 2-week** ~~6 month~~ follow up phase **visit** in ESKETINTRD3001 or ESKETINTRD3002 studies

Applicable Section(s)	Description of Change(s)
9.1.3. Optimization/ Maintenance Phase	Two new bullets were added for subjects who could enter at the Optimization/Maintenance Phase, as follows: • Subjects who completed the induction phase of ESKETINTRD3001 or ESKETINTRD3002 and were responders, and study ESKETINTRD3003 is terminated. • Subjects (US only) who completed the induction phase of ESKTEINTRD3006 and were responders. It was clarified that subjects only had to complete the optimization/maintenance phase of ESKETINTRD3004 (no longer required to complete the follow-up phase of that study)
9.1.4. Induction Phase and Optimization/ Maintenance Phase – Study Entry	This section was newly added for subjects who could enter either at the Induction Phase or the Optimization/ Maintenance Phase, as follows: The following subjects are eligible to enter the study at either the Induction Phase or the Optimization/Maintenance Phase: • Subjects in ESKETINTRD3003, who at Week 16 of Optimization were not eligible to proceed to the maintenance phase and the sponsor has approved subject's entry into 54135419TRD3008; or • Subjects in ESKETINTRD3003 and ESKETINTRD3004, who were in the induction phase and (for ESKETINTRD 3003, after completion of the induction phase) were determined to not meet response criteria, and sponsor has approved subject's entry into 54135419TRD3008; or • Subjects in ESKETINTRD3006 (US sites only) who completed the induction phase but did not meet the response criteria, and sponsor has approved subject's entry into 54135419TRD3008.
16.1. Study-Specific Design Considerations	Revised text in this section (under subheading "Selection of subjects") as follows (strikethrough text deleted; **bold** text added): All subjects will be from Phase 3 studies ESKETINTRD3001, ESKETINTRD3002, ESKETINTRD3003, ESKETINTRD3004, ~~and~~ ESKETINTRD3005, **and ESKETINTRD3006 (US Sites only)**. For subjects who have participated in the ESKETINTRD3003, ESKETINTRD3004, and ESKETINTRD3005 studies and have responded to intranasal esketamine treatment~~,~~ **or did not the meet study criteria for response but per clinical judgment have benefitted,** it is considered an ethical obligation to provide continued intranasal esketamine treatment if the benefit/risk profile is favorable for the subject at the time of completion of the previous study. For subjects who have completed the induction phase of ESKETINTRD3005 **or ESKETINTRD3006 (US Sites only)** and ~~are non-responders~~ **did not meet the study criteria for response**, or for subjects who have completed the induction phase and ~~6-month~~ **2-week** follow up phase **visit** of the ESKETINTRD3001 or ESKETINTRD3002 study, as the double-blind treatment (intranasal esketamine or placebo) in these studies will be blinded, the second induction phase of this study provides the following: • Subjects who are non-responders to intranasal placebo and oral antidepressant in the prior study have the potential of receiving esketamine in this study, and • Subjects who are non-responders to intranasal esketamine in the prior study who decide to participate in this study may not benefit from additional treatment with intranasal esketamine. The benefit of additional treatment with esketamine remains unknown. In case of no perceived benefit of intranasal esketamine to the subject during this study, the subject and/or investigator may choose to discontinue study participation.

Applicable Section(s)	Description of Change(s)
Rationale: To allow more flexibility when clinically indicated, the sponsor is removing the requirement that a subject should rollover from the parent study within a specific period of time. There is now no maximum duration between completing the parent study and starting the 54135419TRD3008 study	
Time and Events Schedule (Induction Phase)	Footnote "b" was revised as follows (strikethrough text deleted; **bold** text added): ~~Visit 1.1 (Day 1) of 54135419TRD3008 study must occur within 4 weeks of the last study visit of the subject's prior study (ie, ESKETINTRD3001, 3002, 3003, or non-responders from 3005).~~ **There is no maximum time limit between completing the prior study and enrolling into 54135419TRD3008.** If a study procedure from the prior study has already been performed on the same day, duplicate predose assessments do not need to be repeated on Visit 1.1 (Day 1) of 54135419TRD3008 study.
Time and Events Schedule (Optimization/ Maintenance Phase)	Footnote "c" was revised as follows (strikethrough text deleted; **bold** text added): For subjects entering the 54135419TRD3008 Optimization/Maintenance Phase after completing the induction phase of the ESKETINTRD3003, ESKETINTRD3004, or ESKETINTRD3005 studies, the Day 28 visit of the prior study is expected to coincide with Visit 2.1 for this study. **If so,** results for all ~~predose~~ assessments performed on Day 28 of the induction phase of the prior study will not be repeated as part of Visit 2.1. **If there is a gap between Day 28 and Visit 2.1, assessments listed for Visit 2.1 should be completed. If the MADRS is completed less than 1 week prior to Visit 2.1, it does not need to be repeated. Similarly,** ~~All other~~ **for** subjects from the ESKETINTRD3003and ESKETINTRD3004 studies entering 54135419TRD3008 at the optimization/maintenance phase, ~~Visit 2.1 of the 54135419TRD3008 study must occur within 4 weeks of the last study visit of the subject's prior study (ie, ESKETINTRD3003, ESKETINTRD3004);~~ if the visits occur the same day **as the last visit of the parent study**, duplicate predose assessments are not required.
Rationale: Based on feedback from investigators and to mimic clinical practice, rather than using the MADRS total score cut-off for responders at the end of the induction phase in this long term open-label safety extension study, the sponsor will now allow the investigator to determine whether or not it is clinically appropriate for the subject to proceed to the optimization/maintenance phase.	
Synopsis, Study Phases; 3.1. Overview of Study Design	The text in the following paragraphs concerning the induction phase was revised (strikethrough text deleted; **bold** text added): At the end of the induction phase, subjects ~~who are responders (defined as ≥50% reduction in the MADRS total score from baseline [prior to the first intranasal dose in 54135419TRD3008 study] to the end of the 4-week induction phase)~~ may be eligible to proceed to the optimization/maintenance phase, **according to the investigator's clinical assessment of the benefit versus risk for the subject.**
9.1.2. Induction Phase	At the end of the induction phase of 54135419TRD3008, ~~responder~~ subjects ~~(defined as ≥50% reduction in the MADRS total score from baseline [Day 1 prior to the first intranasal dose in 54135419TRD3008 study] to the end of the 4-week induction phase)~~ may be eligible to proceed to the optimization/maintenance phase, **according to the investigator's clinical assessment of the benefit versus risk for the subject.**
Rationale: To mimic clinic practice, going from induction to optimization will be determined by the clinician instead of an arbitrary cutoff on the MADRS total score; the text was updated accordingly, where relevant	
3.2.2. Study Phases	In the subsection concerning the optimization maintenance phase, the following revision was made (strikethrough text deleted): ~~Responder~~ Subjects entering this phase from the induction phase of this study (54135419TRD3008) will ~~be able to~~ reduce the frequency of intranasal treatment sessions and subsequently individualize and stabilize the treatment session frequency to weekly, every other week, or every 4 weeks based on the severity of depression during this phase.

Applicable Section(s)	Description of Change(s)
3.2.4. Intranasal Treatment Group and Dose Selection	In the subsection concerning the optimization maintenance phase, the following revisions were made (**bold** text added; ~~strikethrough~~ text deleted): ~~Responder~~ Subjects ~~entering this phase~~ from the induction phase of 54135419TRD3008, **who enter the optimization/maintenance phase will continue on the same dose of intranasal esketamine from the induction phase and have a weekly intranasal treatment session frequency (ie, reduced frequency from the twice-weekly frequency in the induction phase).** **Subjects who were responders at the end of the induction phase of ESKETINTRD3001, ESKETINTRD3002 or ESKETINTRD3006 (US sites only) who enter the optimization/maintenance phase will have a weekly intranasal treatment session frequency (ie, reduced frequency from the twice-weekly frequency in the induction phase). However, as the ESKETINTRD3001, 3002 and 3006 intranasal study medication is blinded at the time of entry into the current study, subjects entering the optimization/maintenance phase should start at 56 mg. The dose may remain at 56 mg or be increased to 84 mg, as determined by the investigator based on efficacy and tolerability.** **With sponsor approval, subjects from** ESKETINTRD3003 **and** ~~(if entering directly from ESKETINTRD3003 induction phase), or~~ ESKETINTRD3004 (~~if~~ entering directly from ~~ESKETINTRD3004~~ **the** induction phase) **who were determined to not meet the criteria for response in those** studies~~, will~~ **may enter the optimization /maintenance phase of 54135419TRD3008 and will** have ~~the~~ **a weekly** intranasal treatment session frequency **from week 1 to week 4 (ie,** reduced from that in the induction phase (twice weekly) to weekly ~~for the first 4 weeks of this phase~~**). In addition, a one-time dose change will be allowed at study entry.**~~There will be no changes to the intranasal dose permitted during the first 4 weeks of this phase (ie, Week 1, 2, 3, and 4) and subjects will continue to receive intranasal esketamine treatment at the same dose from the induction phase.~~ **With Sponsor approval subjects from ESKETINTRD3006 (US sites only) entering directly from induction phase and determined to not meet criteria for response in that study may enter the optimization/maintenance phase. However, as the ESKETINTRD3006 intranasal study medication is blinded at the time of entry into the current study, subjects entering the optimization/maintenance phase from study ESKETINTRD3006 will start at 56 mg. The dose may remain at 56 mg or be increased to 84 mg, as determined by the investigator based on efficacy and tolerability. Subjects will have a weekly intranasal treatment session frequency from week 1 to week 4 (ie, reduced frequency from the twice-weekly frequency in the induction phase).** ~~From Week 1 to 4 (inclusive),~~ Subjects entering the optimization/maintenance phase from study ESKETINTRD3003 **(Direct Entry)** or ESKETINTRD3004 who were ongoing in the Optimization, Maintenance, or Optimization/Maintenance phase respectively, will **have the option to have their current intranasal dosing frequency adjusted at the time of entry into 54135419TRD3008 study and should remain on the selected frequency from week 1 to week 4 (inclusive).** ~~continue on the same~~ **A one-time** dose **change will be permitted at study entry.** ~~and frequency of intranasal esketamine from the prior study as they had been receiving at the time of completion of those studies.~~ **Subjects entering the optimization/maintenance phase from study ESKETINTRD3003 (Transferred Entry) will start at 56 mg. The dose may remain at 56 mg or be increased to 84 mg, as determined by the investigator based on efficacy and tolerability. In addition, subjects will have the option to have their current intranasal dosing frequency adjusted at the time of entry into 54135419TRD3008 study and should remain on the selected frequency from week 1 to week 4 (inclusive).**

Applicable Section(s)	Description of Change(s)
	~~Responder~~ Subjects from the induction phase of ESKETINTRD3005 will have the intranasal treatment session frequency reduced to weekly. However, as the ESKETINTRD3005 study will be blinded at the time of entry into the current study, these subjects will start intranasal esketamine with an initial dose of 28 mg (Week 1; Study Day 1) and have their dose adjusted over the following 3 weeks of the optimization/maintenance phase as described under the Section 6 Dosage and Administration.
Synopsis, Dosage and Administration, Optimization/ Maintenance Phase; 6.1.2. Optimization/ Maintenance Phase	Starting with the first bullet the following revisions were made (**bold** text added; strikethrough text deleted): • ~~Responder~~ Subjects from the induction phase of study~~ies~~ 54135419TRD3008, **who enter the optimization/maintenance phase will continue on the same dose of intranasal esketamine from the induction phase and have a weekly intranasal treatment session frequency (ie, reduced frequency from the twice-weekly frequency in the induction phase).** • **Subjects who were responders at the end of the induction phase of ESKETINTRD3001, ESKETINTRD3002 or ESKETINTRD3006 (US sites only) who enter the optimization/maintenance phase will have a weekly intranasal treatment session frequency (ie, reduced frequency from the twice-weekly frequency in the induction phase). However, as the ESKETINTRD3001, 3002 and 3006 intranasal study medication is blinded at the time of entry into the current study, subjects entering the optimization/maintenance phase should start at 56 mg. The dose may remain at 56 mg or be increased to 84 mg, as determined by the investigator based on efficacy and tolerability.** • **With sponsor approval, subjects from** ESKETINTRD3003 **and** ~~(if entering directly from ESKETINTRD3003 induction phase) or~~ ESKETINTRD3004 ~~(if~~ entering directly from ~~ESKETINTRD3004~~ **the** induction phase~~)~~ **who were determined to not meet the criteria for response in those studies** may **enter the optimization/maintenance phase of 54135419TRD3008** ~~continue on the same dose of intranasal esketamine from the induction phase~~ and **will** have a weekly intransal treatment session frequency **from week 1 to week 4** (ie, reduced frequency from the twice-weekly frequency in the induction phase). **In addition, a one-time dose change will be allowed at study entry.** • **With sponsor approval, subjects from ESKETINTRD3006 (US sites only) entering directly from induction phase and determined to not meet criteria for response in that study may enter the optimization/maintenance phase. However, as the ESKETINTRD3006 intranasal study medication is blinded at the time of entry into the current study, subjects entering the optimization/maintenance phase from study ESKETINTRD3006 will start at 56 mg. The dose may remain at 56 mg or be increased to 84 mg, as determined by the investigator based on efficacy and tolerability. Subjects will have a weekly intranasal treatment session frequency from week 1 to week 4 (ie, reduced frequency from the twice-weekly frequency in the induction phase).** • ~~Responder~~ Subjects entering the optimization/maintenance phase from study ESKETINTRD3005 will also have a weekly intranasal treatment session frequency. However, as the ESKETINTRD3005 intranasal study medication is blinded at the time of entry into the current study, the dose of intranasal esketamine will be administered as outlined in the table below. (Table 4 in Section 6.1.2) • Subjects entering the optimization/maintenance phase from study ESKETINTRD3003 **(Direct Entry**) or ESKETINTRD3004 who were ongoing in the Optimization, Maintenance, or Optimization/Maintenance phase, respectively, will **have the option to have their current intranasal dosing frequency adjusted at the time of entry into 54135419TRD3008 study and should remain on the selected frequency from week 1 to week 4 (inclusive).** ~~continue from week 1 to 4 (inclusive) on the same~~ **A**

Applicable Section(s)	Description of Change(s)
	one-time dose **change will be permitted at study entry.** ~~and frequency of intranasal esketamine as they had been receiving at the time of completion of those studies~~ • **Subjects entering the optimization/maintenance phase from study ESKETINTRD3003 (Transferred Entry) will start at 56 mg. The dose may remain at 56 mg or be increased to 84 mg, as determined by the investigator based on efficacy and tolerability. In addition, subjects will have the option to have their current intranasal dosing frequency adjusted at the time of entry into 54135419TRD3008 study and should remain on the selected frequency from week 1 to week 4 (inclusive).**
Rationale: To allow appropriate study subjects to enter study 54135419TRD3008 without having to wait for laboratory results, as long as the investigator attests that the subject is medically stable per their clinical judgment.	
4.1 Inclusion Criteria	Inclusion Criterion 3 revised as follows (strikethrough text deleted; **bold** text added): Subject must be medically stable **according to the investigator's judgment and knowledge of the subject's medical stability in the parent study**. ~~on the basis of clinical laboratory tests performed predose on the day of the first intranasal treatment session. 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 **documented**. ~~recorded in the subject's source documents and initialed by the investigator.~~
Rationale: To use the urine pregnancy test in order to allow the results to be available to the site prior to dosing, rather than waiting for the results of serum pregnancy test.	
4.1 Inclusion Criteria	Inclusion Criterion 5 revised as follows (strikethrough text deleted): A woman of childbearing potential must have a negative ~~serum (ß-human chorionic gonadotropin [ß-hCG])~~ urine pregnancy test predose on the day of the first intranasal treatment session.
Rationale: To provide consistency with the Phase 3 esketamine studies from which subjects can roll over into 54135419TRD3008, regarding the use of contraception for male subjects	
4.1 Inclusion Criteria	Inclusion Criterion 6 was revised as follows (strikethrough text deleted; **bold** text added): During the study (ie, from the first intranasal treatment session) and for a minimum of 1 spermatogenesis cycle (defined as approximately 90 days) after receiving the last dose of intranasal study medication, ~~in addition to the user independent highly effective method of contraception,~~ a man **who is sexually active with a woman of childbearing potential** • ~~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).** ~~agree to use a double-barrier method of contraception (eg, diaphragm or cervical/vault caps plus condom with spermicidal foam/gel/film/cream/suppository).~~ • ~~who is sexually active with a woman who is pregnant~~ must use a condom **if his partner is pregnant.** • must agree not to donate sperm ~~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

Applicable Section(s)	Description of Change(s)
	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.
Rationale: To decrease the burden on study sites and subjects in this open-label safety extension study, the sponsor removed the Mini Mental State Examination (MMSE) at study entry.	
Synopsis, Subject Population	Deleted the exclusion of subjects with a MMSE<25.
Time and Events Schedule (Induction Phase)	Deleted the row for MMSE.
4.2. Exclusion Criteria	In Exclusion Criteria 3, the following sentence was deleted: A Mini Mental *S*tate Examination (MMSE) <25 (only applicable to subjects entering the 54135419TRD3008 study at the Induction Phase).
9.5. Other Evaluations	The subsection (formerly numbered 9.5.1) on MMSE was deleted.
Rationale: To decrease the burden on study sites and subjects in this open-label safety extension study.	
9.2. Safety Evaluations, Clinical Laboratory Tests	Deleted the requirement that the glucose assessment be performed on subjects in a fasting state.
9.2. Safety Evaluations, Pulse Oximetry	The text in the second paragraph of this section was revised as follows (strikethrough text deleted; **bold** text added): On intranasal treatment session days, pulse oximetry will be recorded **predose and** every 15 minutes ~~from predose~~ to t=1 hour~~s~~ postdose **during the induction phase**. **During the optimization/ maintenance phase, pulse oximetry will be recorded predose and at 30 minutes and 60 minutes postdose on intranasal treatment session days.** If oxygen saturation levels are <93% at any time during the 1 hour postdose interval, pulse oximetry will be recorded every 5 minutes until levels return to ≥93% or until the subject is referred for appropriate medical care, if clinically indicated.
Rationale: To remove text that applies to study medication in pill form, which is not applicable for this study.	
14.5. Drug Accountability	The text in this section was revised as follows (strikethrough text deleted; **bold** text added): The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. ~~The dispensing of study drug to the subject, and the return of study drug from the subject (if applicable), must be documented on the drug accountability form. Subjects must be instructed to return all original containers, whether empty or containing study drug.~~ The study drug administered to the subject must be documented on the drug accountability form. ~~All~~ **The** study drug will be stored and disposed of according to the sponsor's instructions. ~~Study site personnel must not combine contents of the study drug containers.~~ Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug, ~~and study drug returned by the subject,~~ must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study drug, or used returned study drug for destruction, will be documented on the investigational product destruction form. When the study site is an authorized destruction unit and study drug

Applicable Section(s)	Description of Change(s)
	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/clinical study site 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.
Rationale: Clarifications made regarding the usage of certain concomitant medications (ADHD medications, anticonvulsants, clonidine, corticosteroids, lithium, and psychostimulants.)	
Attachment 1	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. For anticonvulsants, both episodic and continuous yes now allowed (previously prohibited); deleted text prohibiting use of these medications as adjunctive treatment for major depressive disorder. Added rows for clonidine (both episodic and continuous use for blood pressure control is allowed) and corticosteroids (systemic; both episodic and continuous use allowed). Removed lithium as a prohibited medication (ie, now allowed) For psychostimulants, allowed continuous use (previously prohibited); added that prescribed psychostimulants can be continued (or newly initiated) but must not be taken within 12 hours prior to the intranasal treatment session or for 2 hours after the intranasal treatment session.
Rationale: Revised the list of anticipated events to remove the terms that are on the adverse drug reactions (ADRs) list in the Investigator's Brochure (anticipated events should be events that are not on the ADR list).	
Attachment 2	Removed the terms "excessive happiness" and "feeling anxious/anxiety". Deleted one instance of the term "abnormal sleep" (was inadvertently listed twice).
Rationale: Minor changes were made throughout the protocol for compliance with updated protocol template text, for clarification, and to correct errors.	
Cover page	Deleted Janssen Infections Diseases BVBA from the sponsorship statement.
Time and Events Schedule (Induction Phase)	On Day 28, the visit window was changed to ±1 day (from -1 day) to be consistent with other visit windows during the induction phase. Footnote "c" was added to the rows "MADRS (7-day recall)", "computerized test battery and HVLT-R", "Hematology, chemistry", and "alcohol breath test".
Time and Events Schedule (Optimization/ Maintenance Phase)	Footnote "u" was added (to the row "Intranasal esketamine treatment session"). This footnote reads as follows: Subjects entering this phase from the induction phase of this study (54135419TRD3008) will be able to reduce the frequency of intranasal treatment sessions to weekly during Weeks 1 to 4 and subsequently (after Week 4) individualize and stabilize the treatment session frequency to weekly, every other week, or every 4 weeks based on the severity of depression during this phase (see Section 3.2.2).

Applicable Section(s)	Description of Change(s)
4.1. Inclusion Criteria	Inclusion Criterion 4 was modified to include the following statement: Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.
4.3 Prohibitions and Restrictions	Revised the first bullet as follows (strikethrough text deleted; **bold** text added): • **Agree to follow all requirements that must be met during the study as noted in** ~~Refer to~~ Section 4.1 (Inclusion Criteria) and Section 4.2 (Exclusion Criteria) **(eg.** for information regarding contraception requirements**)**.
12.3.1. All Adverse Events	Revised the text in the following paragraph (**bold** text added): 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). **For anticipated events reported as individual serious adverse events the sponsor will make a determination of relatedness in addition to and independent of the investigator's assessment. The sponsor will periodically evaluate the accumulating data and, when there is sufficient evidence and the sponsor has determined there is a reasonable possibility that the drug caused a serious anticipated event, they will submit a safety report in narrative format to the investigators (and the head of the investigational institute where required).** 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.
17.4. Source Documentation	Revised the last paragraph of this section as follows (strikethrough text deleted; **bold** text added): An **electronic source** ~~eSource~~ system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If **an electronic source** ~~eSource~~ is utilized, references made to the CRF in the protocol include the **electronic source** ~~eSource~~ system but information collected through **the electronic source** ~~eSource~~ may not be limited to that found in the CRF. **Data in this system may be considered source documentation.**
17.5 Case Report Form Completion	Deleted text stating "All data relating to the study must be recorded in CRF."
Attachment 2	Under the subheading Reporting of Adverse Events, revised the following paragraph (strikethrough text deleted; **bold** text added): ~~These~~ **All adverse** events will be captured on the CRF and in the database **regardless of whether considered to be anticipated events**, and will be reported to the sponsor as described in Section 12.3.1.
Investigator Agreement Page	Removed the "LAST PAGE" designation.

SYNOPSIS

An Open-label Long-term Extension Safety Study of Esketamine Nasal Spray in Treatment-resistant Depression

Major depressive disorder (MDD), a serious, recurrent, and disabling psychiatric illness, is the second leading cause of years lost to disability worldwide. Major depressive disorder is associated with excess mortality; and with years of potential life lost. About 30% of patients fail to achieve remission despite treatment with multiple antidepressant medications and are considered to have treatment-resistant depression (TRD). 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. 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.

Ketamine and esketamine (S-ketamine, the S enantiomer of ketamine) are approved in many countries 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 nasal spray as an antidepressant therapy. A higher NMDA receptor affinity of esketamine compared to ketamine, allows a lower volume of medication to be administered via the non-invasive and rapidly-absorbed intranasal route.

There is an ethical obligation to provide continued esketamine nasal spray treatment to subjects who participated in select Phase 3 studies and for whom the benefit versus risk has been favorable. This study provides an opportunity for subjects who have participated in select Phase 3 studies to receive open label esketamine nasal spray until:

- esketamine is approved in the respective country and accessible through the local healthcare system funding or until end of December 2022, whichever is earlier; or
- the subject no longer benefits from further treatment (based on the investigator's clinical judgment) or withdraws consent; or
- the company terminates clinical development of esketamine nasal spray for TRD in that country/region

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

Primary Objectives

The primary objective of this study is to assess the safety and tolerability of esketamine nasal spray in subjects with TRD, with special attention to the following:

- Potential long-term effects on cognitive function
- Treatment-emergent adverse events (TEAEs), including TEAEs of special interest
- Post dose effects on heart rate, blood pressure, respiratory rate and blood oxygen saturation
- Potential effects on suicidal ideation/behavior

Secondary Objective

The secondary objective is to assess long-term efficacy, including effects on:

- Depressive symptoms (clinician and self-reported),
- Overall severity of depressive illness,
- Functioning and associated disability,
- Health-related quality of life and health status,

Exploratory Objectives

The exploratory objectives are to assess:

- Medical resource utilization
- Response and remission rates to a second induction phase in eligible subjects who had relapsed in study ESKETINTRD3003
- Subject treatment satisfaction
- Subject tradeoff preferences for key benefit and harm outcomes associated with TRD treatment, using a stated-choice preference survey

Endpoints

Safety endpoints are listed below:

- Occurrence of TEAEs, including TEAEs of special interest
- Potential short-term effects observed on the day of intranasal treatment session with special attention to changes from baseline/predose over time for:
  - Blood pressure (systolic and diastolic) and heart rate
  - Blood oxygen saturation
  - 12-lead electrocardiogram
  - Alertness and sedation using Modified Observer's Assessment of Alertness/Sedation (MOAA/S)
- Long-term effects, with special attention to changes from baseline over time for:
  - Computerized cognitive battery and Hopkins Verbal Learning Test-Revised (HVLT-R), to assess potential effects on cognitive function
  - Columbia-Suicide Severity Rating Scale (C-SSRS), to assess potential effects on suicidal ideation and behavior
- Changes from baseline over time in clinical laboratory tests, including hematology, serum chemistry, and urinalysis
- Time to discharge readiness, using the Clinical Global Assessment of Discharge Readiness (CGADR)

Efficacy endpoints include changes from baseline over time for the following:

- Depressive symptoms, including response (≥50% improvement from baseline) and remission (MADRS total score ≤12, PHQ-9 total score <5); using the Montgomery Asberg Depression Rating scale (MADRS) and 9-item self-reported Patient Health Questionnaire (PHQ-9)
- Overall severity of illness, using the Clinical Global Impression Severity (CGI-S)

- Functioning and associated disability, using the Sheehan Disability Scale (SDS)
- Health related quality of life and health status, using the European Quality of Life (EuroQol) Group, 5-Dimension, 5-Level (EQ-5D-5L)
- Health related quality of life using the Quality of Life in Depression Scale (QLDS)

Exploratory endpoints include:

- Changes from baseline over time for:
  - Depression response and remission rates (as defined above) to a second induction phase in eligible subjects who had relapsed in study ESKETINTRD3003, assessed using the MADRS and PHQ-9
  - Subject treatment satisfaction
- Subject tradeoff preferences for key benefit and harm outcomes associated with TRD treatment, using a stated-choice preference survey

Hypothesis

There is no formal hypothesis for this study.

OVERVIEW OF STUDY DESIGN

This is a multicenter, open-label long term extension study to evaluate the safety, tolerability, and efficacy of esketamine nasal spray in subjects with TRD.

The table below describes the subjects who may be eligible to participate in this study based on the clinical judgment of the investigator and their point of entry into 54135419TRD3008:

Prior Study	Inclusion requirement	Point of entry for 54135419TRD3008
ESKETINTRD3001	Subject completed induction phase and the 2- week follow-up phase visit	Induction phase
	Subject completed the induction phase and was a responder and ESKETINTRD3003 is terminated.	Optimization/maintenance phase
ESKETINTRD3002	Subject completed induction phase and the 2- week follow-up phase visit	Induction phase
	Subject completed the induction phase and was a responder and ESKETINTRD3003 is terminated.	Optimization/maintenance phase
ESKETINTRD3003	Subject relapsed in maintenance phase	Induction phase
	Subject was in the induction phase at the time the study was terminated and, and, after completion of the induction phase, was determined to be a responder.	Optimization/maintenance phase
	Subject was in the optimization or maintenance phase at the time the study was terminated	Optimization/maintenance phase
	At Week 16 of Optimization, the subject was not eligible to proceed to the maintenance phase and sponsor has approved subject's entry into 54135419TRD3008	Induction phase or Optimization/maintenance phase
	Subject was in the induction phase and after completion of induction phase, was determined to not meet criteria for response and sponsor has approved subject's entry into 54135419TRD3008	Induction phase or Optimization/maintenance phase

Prior Study	Inclusion requirement	Point of entry for 54135419TRD3008
ESKETINTRD3004	Subject completed the optimization/maintenance phase	Optimization/maintenance phase
	Subject was in the induction phase at the time the study was terminated and, after completion of the induction phase, was determined to be a responder.	Optimization/maintenance phase
	Subject was in the optimization/maintenance phase at the time the study was terminated	Optimization/maintenance phase
	Subject was in the induction phase and did not meet criteria for response and sponsor has approved subject's entry into 54135419TRD3008	Induction phase or Optimization/maintenance phase
ESKETINTRD3005	Subject was in the induction phase of ESKETINTRD3005 study at the time enrollment into the ESKETINTRD3004 study was closed and, after completion of the induction phase, was determined to be a non-responder.	Induction phase
	Subject was in the induction phase of ESKETINTRD3005 study at the time enrollment into the ESKETINTRD3004 study was closed and, after completion of the induction phase, was determined to be a responder	Optimization/maintenance phase
ESKETINTRD3006 United States study sites only	Subject completed the induction phase and was a responder.	Optimization/maintenance phase
	Subject completed induction phase and did not meet the response criteria, and sponsor has approved subject's entry into 54135419TRD3008.	Induction phase or Optimization/Maintenance Phase

An Independent Data Monitoring Committee (IDMC) will meet approximately every 6 months to review select safety data through the end of 2020.

This study has 2 open label phases

- A 4-week induction phase (if applicable, per table above)
- A variable duration optimization/maintenance phase

The duration that a subject may participate in the study is variable and is based on the subject's point of entry into the study and the timing of when the predefined criteria (below) for ending study participation occurs.

Study participation will be stopped:

- when esketamine is approved in the respective country and accessible through the local healthcare system funding or until end of December 2022, whichever is earlier; or
- the subject no longer benefits from further treatment (based on the investigator's clinical judgment), or withdraws consent; or
- the company terminates clinical development of esketamine nasal spray for TRD in that country/region

Study Phases

All study subjects should be taking a permitted oral antidepressant (per clinical judgment) throughout the duration of study participation. Changes to the oral antidepressant medication(s) that a subject is taking at study entry is permitted per clinical judgment of the investigator. If subject may benefit from an additional

antidepressant medication (eg lithium, bupropion, adjunctive antipsychotic, etc.), the investigator should discuss with sponsor to determine whether continuing esketamine nasal spray still has a favorable benefit versus risk for the subject.

Induction Phase

Subjects will self-administer open-label esketamine nasal spray as a flexible dose regimen twice a week for 4 weeks as outlined in the "Dosage and Administration" section.

At the end of the induction phase, subjects may be eligible to proceed to the optimization/maintenance phase according to the investigator's clinical assessment of the benefit versus risk for the subject.

If a subject withdraws from the study before the end of the induction phase for reasons other than withdrawal of consent, an Early Withdrawal (EW) visit will be conducted within 1 week of the last intranasal dose.

Subjects who are currently in the induction phase at the time the 54135419TRD3008 study is completed will conduct an "End of Study" visit as their final study visit within 1 week of the last intranasal dose.

Optimization/Maintenance Phase:

During this phase, the dose and intranasal treatment session frequency can be adjusted based on the criteria outlined in the "Dosage and Administration" section.

If a subject withdraws from the study before the end of the optimization/maintenance phase for reasons other than withdrawal of consent, an EW visit will be conducted within 1 week of the last intranasal dose.

Subjects who are currently in the optimization/maintenance phase at the time the 54135419TRD3008 study is completed will conduct an "End of Study" visit as their final study visit within 1 week of the last intranasal dose.

SUBJECT POPULATION

The study population will include adult and elderly men and women who previously participated in studies ESKETINTRD3001, ESKETINTRD3002, ESKETINTRD3003, ESKETINTRD3004, ESKETINTRD3005 or ESKETINTRD3006 (US sites only) and will have met the inclusion/exclusion criteria for entry into those studies.

Potential subjects will be excluded from participating in the study if the evaluation of the risk versus benefit of continued esketamine nasal spray treatment is not favorable for the subject in the opinion of the investigator. Subjects reporting suicidal ideation with intent to act or suicidal behavior prior to the start of the study will be excluded. Subjects with a neurodegenerative disorder or evidence of mild cognitive impairment prior to the first intranasal treatment session will be excluded from participating in the study. In addition, any subject with uncontrolled hypertension, or a positive test result(s) for drugs of abuse (including barbiturates, methadone, opiates, cocaine, phencyclidine, and amphetamine/methamphetamine) prior to the first intranasal treatment session will be excluded from participating in the study.

DOSAGE AND ADMINISTRATION

Intranasal Study Medication

Induction Phase:

All eligible subjects will self-administer the intranasal study drug twice a week for 4 weeks at treatment sessions at the study site. Intranasal treatment sessions should not take place on consecutive days.

The esketamine nasal spray dose titration in the Induction Phase for subjects <65years of age is described in the table below:

Induction Phase Dose Titration of Esketamine nasal spray, Subjects <65 years of age

Day	Dose	Dose Titration Guidance
Day 1	56 mg	
Day 4	56 or 84 mg	The dose may remain at 56 mg or be increased to 84 mg, as determined by the investigator based on efficacy and tolerability.
Day 8, 11, 15, 18, 22, 25	56 or 84 mg	The dose may be increased to 84 mg (if previous dose was 56 mg), remain the same, or be reduced to 56 mg (if previous dose was 84 mg), as determined by the investigator based on efficacy and tolerability

The esketamine nasal spray dose titration in the Induction Phase for subjects ≥65years of age is described in the table below:

Induction Phase Dose Titration of Esketamine nasal spray, Subjects ≥65 years of age

Day	Dose	Dose Titration Guidance*
Day 1	28 mg	
Day 4	28 or 56 mg	The dose may remain at 28 mg or be increased to 56 mg, as determined by the investigator based on efficacy and tolerability
Day 8, 11, 15, 18, 22, 25	28, 56 or 84 mg	The dose may remain the same, or be increased or reduced by 28 mg from the previous dosing session, as determined by the investigator based on efficacy and tolerability.

Optimization/Maintenance Phase:

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.

For the first 4 weeks of the optimization/maintenance phase (Week 1 to Week 4):

- Subjects from the induction phase of study 54135419TRD3008, who enter the optimization/maintenance phase will continue on the same dose of esketamine nasal spray from the induction phase and have a weekly intranasal treatment session frequency (ie, reduced frequency from the twice-weekly frequency in the induction phase).
- Subjects who were responders at the end of the induction phase of ESKETINTRD3001, ESKETINTRD3002 or ESKETINTRD3006 (US sites only) who enter the optimization/maintenance phase will have a weekly intranasal treatment session frequency (ie, reduced frequency from the twice-weekly frequency in the induction phase). However, as the ESKETINTRD3001, 3002 and 3006 intranasal study medication is blinded at the time of entry into the current study, subjects entering the optimization/maintenance phase should start at 56 mg. The dose may remain at 56 mg or be increased to 84 mg, as determined by the investigator based on efficacy and tolerability.
- With sponsor approval, subjects from ESKETINTRD3003 and ESKETINTRD3004 entering directly from the induction phase who were determined to not meet the criteria for response in those studies may enter the optimization/maintenance phase of 54135419TRD3008 and will have a weekly intranasal treatment session frequency from week 1 to week 4 (ie, reduced frequency from the twice-weekly frequency in the induction phase). In addition, a one-time dose change will be allowed at study entry.

- With sponsor approval, subjects from ESKETINTRD3006 (US sites only) entering directly from induction phase and determined to not meet criteria for response in that study may enter the optimization/maintenance phase. However, as the ESKETINTRD3006 intranasal study medication is blinded at the time of entry into the current study, subjects entering the optimization/maintenance phase from study ESKETINTRD3006 will start at 56 mg. The dose may remain at 56 mg or be increased to 84 mg, as determined by the investigator based on efficacy and tolerability. Subjects will have a weekly intranasal treatment session frequency from week 1 to week 4 (ie, reduced frequency from the twice-weekly frequency in the induction phase).
- Subjects entering the optimization/maintenance phase from study ESKETINTRD3005 will also have a weekly intranasal treatment session frequency. However, as the ESKETINTRD3005 intranasal study medication is blinded at the time of entry into the current study, the dose of esketamine nasal spray will be administered as outlined in the table below.

Optimization/Maintenance Phase Week 1 to 4: Dose Titration of Esketamine nasal spray for Responder Subjects Entering from ESKETINTRD3005

Week	Dose	Dose Titration Guidance
Week 1	28 mg	
Week 2	28 or 56 mg	The dose may remain at 28mg or be increased to 56mg, as determined by the investigator based on efficacy and tolerability
Week 3 and 4	28, 56 or 84 mg	The dose may remain the same or be increased or reduced by 28mg from the previous dosing session, as determined by the investigator based on efficacy and tolerability. For those who have had a prior down titration from a higher dose, a dose increase by 28 mg is allowed based on clinical judgment.

- Subjects entering the optimization/maintenance phase from study ESKETINTRD3003 (Direct Entry) or ESKETINTRD3004 who were ongoing in the Optimization, Maintenance, or Optimization/Maintenance phase, respectively, will have the option to have their current intranasal dosing frequency adjusted at the time of entry into 54135419TRD3008 study and should remain on the selected frequency from week 1 to week 4 (inclusive). A one-time dose change will be permitted at study entry.
- Subjects entering the optimization/maintenance phase from study ESKETINTRD3003 (Transferred Entry) will start at 56 mg. The dose may remain at 56 mg or be increased to 84 mg, as determined by the investigator based on efficacy and tolerability. In addition, subjects will have the option to have their current intranasal dosing frequency adjusted at the time of entry into 54135419TRD3008 study and should remain on the selected frequency from week 1 to week 4 (inclusive).

After Week 4 (ie, starting at Week 5), based on the investigator's clinical judgment, the dose of esketamine for all subjects can be adjusted based upon efficacy and tolerability.

Starting at Week 4, the frequency for subsequent intranasal treatment sessions will be adjusted (if applicable) based on the algorithm outlined in the table below at fixed, 2-week intervals.

Current treatment session frequency	CGI-S score at current visit[a]	
	≤ 3	>3
Weekly	Change to every other week frequency	No change in frequency
Every other week	No change in frequency or change to every 4 weeks per clinical judgment	Change to weekly frequency
Every 4 weeks	No change in frequency	Change to weekly or every other week frequency per clinical judgment

[a] Note: The CGI-S is administered every 2 weeks from Week 4 through the end of the Optimization/Maintenance Phase, adjustment of the intranasal treatment session frequency is only permitted at the fixed 2-week interval (based on CGI-S performed at that visit), and every 4 weeks for subjects dosed at the 4 week interval.

For example, if at Week 4 a subject is currently at a weekly treatment session frequency and the CGI-S score at Week 4 is a 2, the intranasal treatment session frequency will be changed from weekly to every other week (ie, the next treatment session for this subject will be at Week 6).

MEDICAL RESOURCE UTILIZATION

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

STATISTICAL METHODS

Analysis Sets

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

- Full Analysis Set for Induction phase: will be defined as all subjects who receive at least one dose of esketamine nasal spray during this phase.
- Full Analysis Set for Optimization/Maintenance phase: will be defined as all subjects who receive at least one dose of esketamine nasal spray during this phase.

Sample Size Determination

No formal sample size calculation was performed as only subjects who have participated in the other Phase 3 studies may participate in this study.

Safety Analysis

Safety data for the induction phase and the optimization/maintenance phase will be analyzed separately for each phase as well as for the entire treatment period (induction and optimization/maintenance phase).

Computerized cognitive test battery and HVLT-R scores and their changes from baseline will be summarized at each scheduled time point using descriptive statistics.

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

Treatment emergent AEs of special interest will be examined separately grouped in the following categories: drug abuse, dependence and withdrawal, increased blood pressure, increased heart rate, transient dizziness/vertigo, impaired cognition, cystitis, anxiety, events potentially related to suicidality, hepatic adverse events, events related to renal disorders, and symptoms of dissociation persisting beyond the typical ≤2 hour post esketamine administration, as well as delirium, psychosis or mania.

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

Suicide-related thoughts and behaviors based on the C-SSRS will be summarized in incidence and shift tables. Separate endpoints for suicidal ideation and suicidal behavior will be defined and summarized descriptively.

Descriptive statistics of scores and their changes (and/or percent changes) from predose or baseline will be summarized for modified observer's assessment of alertness/sedation (MOAA/S) at each scheduled time point. In addition, CGADR responses will be summarized at each scheduled time point.

Efficacy Analysis

- Depression symptoms using the MADRS as well as a patient reported outcome (PHQ-9), global change in severity (CGI-S), social, occupational and family functioning related disability (SDS), depression specific health related quality of life (QLDS), and health related quality of life and health status (EQ-5D-5L) will be summarized descriptively at each scheduled visit for each phase, using both last observation carried forward and observed case data. The proportion of subjects who are responders (≥50% improvement from baseline) based on the MADRS total score and PHQ-9 total score and the proportion of subjects who remitted based on the MADRS total score (MADRS total score ≤12) and the PHQ-9 total score (PHQ-9 total score <5) will be provided over time for each phase.
- For subjects who had relapsed in ESKETINTRD3003 and participated in a second induction treatment phase, the proportion of responders (≥50% improvement from baseline) and remitters using the MADRS total score (MADRS total score ≤12) and PHQ-9 total score (PHQ-9 total score <5) at the end of the second induction phase will be provided.
- Subject treatment satisfaction questionnaire for medication (TSQM-9) will be summarized descriptively at each scheduled visit for each phase.

Medical Resource Utilization Analysis

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

Patient Stated-choice Preference Analysis

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

TIME AND EVENTS SCHEDULE (Induction Phase)

Phase	**Induction Phase[a)]**								
Visit number	**1.1[b)]**	**1.2**	**1.3**	**1.4**	**1.5**	**1.6**	**1.7**	**1.8**	**1.9**
Week	1		2		3		4		
Study day	1 (baseline)	4	8	11	15	18	22	25	28
Clinical Study Site visit window (in days)	-	±1	±1	±1	±1	±1	±1	±1	±1
Study Procedures									
Screening/Administrative									
Informed consent (ICF) – *performed prior to any study procedure*	X								
Inclusion/exclusion criteria-	X[c)]								
Study Drug									
Esketamine nasal spray[g)]	X	X	X	X	X	X	X	X	
Drug accountability (intranasal study medication)	X	X	X	X	X	X	X	X	
Safety Assessments (Site-completed)									
Physical examination	X[c)]								X
Nasal examination[c)]	X								X
Vital signs: blood pressure, pulse, respiratory rate, temperature [c),g)]	X	X	X	X	X	X	X	X	
Vital signs (postdose): blood pressure, pulse, respiratory rate [d),g)]	X	X	X	X	X	X	X	X	
Weight	X								X
12-lead ECG[e),g)]	X				X			X	
C-SSRS[c),g)]	X	X	X	X	X	X	X	X	X
MOAA/S and pulse oximetry[f),g)]	X	X	X	X	X	X	X	X	
CGADR[g),h)]	X	X	X	X	X	X	X	X	
Efficacy Assessments (Clinician)									
MADRS (7-day recall)[c]	X		X		X		X		X
CGI-S[c)]	X	X	X	X	X		X		X
Subject-completed Assessments									
PHQ-9	X				X				X
SDS	X								X
EQ-5D-5L	X				X				X
TSQM-9	X								X
MAGDA[j)]	X				X				X
QLDS	X				X				X
Patient Stated-choice Preference Survey[k)]									X[l)]
Cognition Testing									
Computerized test battery and HVLT-R[c]	X								X
Clinical Laboratory Assessments									
HbA1c[i)]	X								
Hematology, chemistry[c]	X								X
Urine drug screen[c)]	X								

Phase	**Induction Phase[a)]**								
Visit number	**1.1[b)]**	**1.2**	**1.3**	**1.4**	**1.5**	**1.6**	**1.7**	**1.8**	**1.9**
Week	1		2		3		4		
Study day	1 (baseline)	4	8	11	15	18	22	25	28
Clinical Study Site visit window (in days)	-	±1	±1	±1	±1	±1	±1	±1	±1
Alcohol breath test[c]	X								
Urinalysis[c)]	X								X
Urine pregnancy test[c)] (only for females of child bearing potential)	X				X				X
Ongoing Subject Review									
Concomitant Therapy	*Ongoing*								
Adverse Events	*Ongoing*								

Footnotes:

Abbreviations: CGADR = Clinical Global Assessment of Discharge Readiness; CGI-S = Clinical Global Impression – Severity; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EQ-5D-5L= EuroQol-5D, 5-level; HbA1C = glycosylated hemoglobin; HVLT-R = Hopkins Verbal Learning Test-Revised; ICF = informed consent form; MADRS = Montgomery-Asberg Depression Rating Scale; MAGDA = Magda Avatar Game Depression Implicit Association Scale; MOAA/S = Modified Observer's Assessment of Alertness/Sedation; PHQ-9 = Patient Health Questionnaire – 9; SDS = Sheehan Disability Scale; C-SSRS = Columbia Suicide Severity Rating Scale; QLDS = Quality of Life in Depression Scale

Note: On intranasal dosing days, time 0 is defined as the time of the first intranasal spray. Therefore, postdose time points are referenced from this.

a) If a subject withdraws before the end of the induction phase (ie, Visit 1.9, Day 28) for reasons other than withdrawal of consent, an "Early Withdrawal" visit (refer to Time and Events Schedule: Optimization/Maintenance Phase) should be conducted within 1 week of the last dose of esketamine nasal spray. If the early withdrawal visit is conducted on the same day as a scheduled visit, duplicate assessments are not required. Subjects who are currently in the induction phase at the time the 54135419TRD3008 study is completed will conduct an "End of Study" visit as their final study visit within 1 week of the last dose of esketamine nasal spray.
b) There is no maximum time limit between completing the prior study and enrolling into 54135419TRD3008. If a study procedure from the prior study has already been performed on the same day, duplicate predose assessments do not need to be repeated on Visit 1.1 (Day 1) of 54135419TRD3008 study.
c) Predose (if/when performed on intranasal dosing days).
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 on blood pressure monitoring on intranasal dosing days.
e) Twelve-lead ECG will be performed predose and t=1 hour postdose at Visit 1.1. Twelve-lead ECG will be performed at t=1 hour postdose only, at Visits 1.5 and 1.8. A time window of ±15 minutes will be permitted.
f) The MOAA/S will be performed every 15 minutes from predose to t=+1 hours postdose (please refer to Section 9.2 for further guidance on MOAA/S assessments). Pulse oximetry will be performed every 15 minutes from predose to t=1 hour postdose (please refer to Section 9.2 for further guidance on timing of pulse oximetry assessments).
g) If intranasal dosing is postponed (but occurs within the visit window) due to vital sign results (eg, blood pressure elevation), all assessment time points (including predose) must be performed on the actual dosing day.
h) CGADR to be performed at 30 mins; if the response is "No", 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. 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.
i) HbA1c to be performed only in those subjects with a documented medical history of diabetes.
j) In the event the MAGDA assessment is not available for use at the start of this trial, the procedure can be omitted until available for use.
k) Patient Stated-choice Preference Survey to be completed only by English-speaking subjects at United States, Canada, United Kingdom, and Australia sites. The survey will not be conducted in any other countries, regardless of whether the subjects in those other countries speak English. The survey is conducted only once per subject.
l) The survey should be completed during or shortly after Visit 1.9, or if a subject has completed this visit prior to when the survey becomes available, sites should have the subject complete the survey at the earliest possible opportunity or at early withdrawal. The survey should be administered predose (if/when performed on intranasal dosing days). See Section 9.5.1 in the protocol.

TIME AND EVENTS SCHEDULE (Optimization/Maintenance Phase)

Phase	Optimization/Maintenance Phase										
Visit Number	2.1[b),c)]	2.2	2.3	2.4	2.5 to 2.X						
					Study procedure frequency (following Week 4) through end of phase						
Week	1	2	3	4	5, 6, 7, 8, etc	6, 8, 10, etc	8, 12, 16, etc	12, 20, 28, etc	16, 28, 40 etc	28, 52, 76, etc	
Day	1	8	15	22	Every week	Every 2 Weeks	Every 4 Weeks	Every 8 Weeks	Every 12 Weeks	Every 24 Weeks	Early Withdrawal/ End of Study[e)]
Clinic (C) or Remote (R) Visit[a)]	C	C or R	C	C or R	C[s)]	C or R	C	C	C	C	C
Study Procedures											
Screening/Administrative											
Informed consent (prior to any procedure; except subjects entering phase from 54135419TRD3008 Induction Phase)	X										
Inclusion/exclusion criteria (predose; except subjects entering phase from 54135419TRD3008 Induction Phase)	X										
Study Drug											
Esketamine nasal spray treatment session[f),t)]	X	X[g)]	X	X[g)]		X[h)]					
Adjustment of intranasal treatment session frequency (if applicable) based on CGI-S				X		X	X				
Drug accountability (intranasal study medication)	X	X[i)]	X	X[i)]		X[i)]					
Efficacy Assessments (Clinician)[j)]											
MADRS	X		X				X				X
CGI-S	X	X	X	X		X					X
Subject-Completed Assessments[j)]											
PHQ-9	X		X						X		X
SDS	X		X						X		X
EQ-5D-5L	X		X						X		X
TSQM-9	X								X		X
QLDS[r)]	X		X						X		X
Patient Stated-choice Preference Survey[k)]				X[l)]							X[l)]
Safety Assessments (Clinician)											
Physical examination, weight	X								X[j)]		X
Vital signs (predose): blood pressure, pulse, respiratory rate, and temperature	X	X[i)]	X	X[i)]	X[i)]						
Vital signs (postdose): blood pressure, pulse, and respiratory rate only[m)]	X	X[i)]	X	X[i)]	X[i)]						
12-lead electrocardiogram[n)]	X						X				X
CSSRS[j)]	X	X[i)]	X	X[i)]		X					X
MOAA/S[o)]	X	X[i)]	X	X[i)]							

Phase	Optimization/Maintenance Phase										
Visit Number	2.1[b),c)]	2.2	2.3	2.4	2.5 to 2.X						
					Study procedure frequency (following Week 4) through end of phase						
Week	1	2	3	4	5, 6, 7, 8, etc	6, 8, 10, etc	8, 12, 16, etc	12, 20, 28, etc	16, 28, 40 etc	28, 52, 76, etc	
Day	1	8	15	22	Every week	Every 2 Weeks	Every 4 Weeks	Every 8 Weeks	Every 12 Weeks	Every 24 Weeks	Early Withdrawal/ End of Study[e)]
Clinic (C) or Remote (R) Visit[a)]	C	C or R	C	C or R	C[s)]	C or R	C	C	C	C	C
Pulse oximetry[d)]	X	X[i)]	X	X[i)]							
CGADR[p)]	X	X[i)]	X	X[i)]	X[i)]						
Cognitive Testing											
Computerized cognitive battery and HVLT-R[j)]			X						X		X
Clinical Laboratory Tests											
HbA1c[q)]	X									X	
Hematology and chemistry[j)]	X								X		X
Urinalysis[j)]	X								X		X
Urine drug screen[j)]	X								X		
Alcohol breath test[j)]	X										
Urine pregnancy test[j)] (only for females of child bearing potential)	X						X				X
Medical Resource Utilization											
HRUQ[j)]	X			X							
Ongoing Subject Review											
Concomitant therapy	*Ongoing*										
Adverse events	*Ongoing*										

Footnotes:

Abbreviations: 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; EW = Early Withdrawal; 7-item; HbA1c = Hemoglobin A1c; 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; SDS = Sheehan Disability Scale; QLDS=Quality of Life in Depression Scale

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) Visit window: ±3 days. Clinic visits will be conducted for all intranasal treatment sessions; a remote visit (ie, telephone contact) will be conducted for all other visits with a scheduled study procedure. Due to the variable clinic visit frequency, following Visit 2.4, visit numbers will continue sequentially (eg, 2.5, 2.6, etc) until the subject completes the phase. The frequency of study procedures following Week 4 to the end of the phase is provided within the respective column (ie, every week, 2 weeks, 4 weeks, 8 weeks, 12, and 24 weeks).

b) The Day 28 visit of 54135419TRD3008 (Visit 1.9) is expected to coincide with Visit 2.1. Results for all predose assessments performed on Day 28 of the induction phase of 54135419TRD3008 (ie, Visit 1.9) will not be repeated as part of Visit 2.1.

c) For subjects entering the 54135419TRD3008 Optimization/Maintenance Phase after completing the induction phase of the ESKETINTRD3003, ESKETINTRD3004, or ESKETINTRD3005 studies, the Day 28 visit of the prior study is expected to coincide with Visit 2.1 for this study. If so, results for all assessments performed on Day 28 of the induction phase of the prior study will not be repeated as part of Visit 2.1. If there is a gap between Day 28 and Visit 2.1, assessments listed for Visit 2.1 should be completed. If the MADRS is completed less than 1 week prior to Visit 2.1, it does not need to be repeated. Similarly, for subjects from the ESKETINTRD3003and ESKETINTRD3004 studies entering 54135419TRD3008 at the optimization/maintenance phase, if the visits occur the same day as the last visit of the parent study, duplicate predose assessments are not required.

d) Performed predose and at t = 30 minutes and 60 minutes postdose on all intranasal treatment session days.
e) If a subject withdraws during the induction or optimization/maintenance phase for reasons other than withdrawal of consent, an "Early Withdrawal" visit should be conducted within 1 week of the last intranasal dose. If the early withdrawal visit is conducted on the same day as a scheduled visit, duplicate assessments are not required. Subjects who are currently in the optimization/maintenance phases at the time the 54135419TRD3008 study is completed will conduct an "End of Study" visit as their final study visit within 1 week of the last intranasal dose.
f) If intranasal dosing is postponed (but occurs within the visit window) due to vital sign results (eg, blood pressure elevation), all assessment time points (including predose) must be performed on the actual dosing day.
g) Only applicable to subjects on a weekly intranasal treatment frequency.
h) Esketamine nasal spray frequencies include weekly, once every other week, or once every 4 weeks.
i) Only applicable for intranasal treatment session days
j) Predose (if performed on intranasal treatment session days). HRUQ will be completed until end of December 2020.
k) Patient Stated-choice Preference Survey to be completed only by English-speaking subjects at United States, Canada, United Kingdom, and Australia sites. The survey will not be conducted in any other countries, regardless of whether the subjects in those other countries speak English. The survey is conducted only once per subject.
l) Note for subjects whose point of entry for 54135419TRD3008 is the Optimization/maintenance phase, the survey should be completed during or shortly after Visit 2.4, or if a subject completed this visit prior to when the survey becomes available, the subject should complete the survey at the earliest possible opportunity or at early withdrawal. The survey should be administered predose (if/when performed on intranasal dosing days). Subjects who completed the Patient Stated-choice Preference survey while enrolled in a prior study (ESKETINTRD3001, ESKETINTRD3002, ESKETINTRD3003, ESKETINTRD3004, or ESKETINTRD3005) should not be issued the survey. See Section 9.5.1 in the protocol.
m) Postdose vital signs (if/when performed on intranasal dosing days) will be performed at t = +40 minutes, and 1 hours postdose. Please refer to Section 6.1 for guidance for blood pressure monitoring on intranasal dosing days.
n) 12-lead electrocardiogram will be performed predose at Visit 2.1 only, and at t= 1 hours postdose only for all other time points. A time window of ±15 minutes is permitted.
o) The MOAA/S will be performed every 15 minutes from predose to t = 1 hours postdose (please refer to Section 9.2 for further guidance on MOAA/S assessments).
p) CGADR to be performed at 30 mins; if the response is not "Yes", 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. 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.
q) HbA1c to be performed only in those subjects with a documented medical history of diabetes
r) Administration of the QLDS will be limited to sites where there are translations available in the local language(s)
s) The study procedures required at a weekly frequency are only associated with an intranasal treatment session day (ie, clinic visit).
t) Subjects entering this phase from the induction phase of this study (54135419TRD3008) will be able to reduce the frequency of intranasal treatment sessions to weekly during Weeks 1 to 4 and subsequently (after Week 4) individualize and stabilize the treatment session frequency to weekly, every other week, or every 4 weeks based on the severity of depression during this phase (see Section 3.2.2).

ABBREVIATIONS

ARC	Anticipated Event Review Committee
CGADR	Clinical Global Assessment of Discharge Readiness
CGI-S	Clinical Global Impression – Severity
C-SSRS	Columbia Suicide Severity Rating Scale
CRF	Case report form
CYP	Cytochrome P450
DBP	Diastolic blood pressure
ECG	Electrocardiogram
eDC	Electronic Data Capture
EQ-5D-5L	European Quality of Life (EuroQol) Group, 5-Dimension, 5-Level
EW	Early Withdrawal
GCP	Good Clinical Practice
HbA1c	Glycosylated hemoglobin
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
IEC	Independent Ethics Committee
IM	Intramuscular
IRB	Institutional Review Board
IV	Intravenous
MADRS	Montgomery-Asberg Depression Rating Scale
MDD	Major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MOAA/S	Modified Observer's Assessment of Alertness/Sedation
NMDA	N-methyl-D-aspartate
PCP	Primary care physician
PHQ-9	Patient Health Questionnaire, 9-Item
PK	Pharmacokinetics
PQC	Product quality complaint
QLDS	Quality of Life in Depression Scale
SBP	Systolic blood pressure
SDS	Sheehan Disability Scale
TEAE	Treatment emergent adverse events
TRD	Treatment-resistant depression
US	United States

DEFINITIONS OF TERMS

AUC	Area under the concentration-time curve
C_{max}	Maximum plasma concentration
T_{max}	Median time of Cmax

1. INTRODUCTION

Major depressive disorder (MDD), a serious, recurrent, and disabling psychiatric illness, is the second leading cause of years lost to disability worldwide. Major depressive disorder is associated with excess mortality; and with years of potential life lost.[73,74,78] About 30% of patients fail to achieve remission despite treatment with multiple antidepressant medications, and are considered to have treatment-resistant depression (TRD).[23,61] 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.[61,66] 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.[17,18]

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.[35] The desired analgesic-anesthetic effects of ketamine and esketamine are attributed to the blockade of ionotropic N-methyl-D-aspartate (NMDA) glutamate receptors.[44,55,81] Both ketamine and esketamine profoundly affects fast excitatory glutamate transmission, increases brain-derived neurotrophic factor (BDNF) release, and stimulates synaptogenesis.[18]

Most literature reports of the antidepressant effects of ketamine describe studies using IV administration of the racemate, with a few exceptions.[38] Janssen Research & Development (JRD) is developing esketamine nasal spray as an antidepressant therapy. A higher NMDA receptor affinity of esketamine compared to ketamine, allows a lower volume of medication to be administered via the non-invasive and rapidly-absorbed intranasal route.[42,53,56]

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

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Background

1.1.1. Summary of Nonclinical Findings

Safety Pharmacology

The following text is quoted from the United States (US) prescribing information for anesthetic Ketalar® (ketamine hydrochloride injection)[35] is provided below: Intravenous Ketalar produces a fall in arterial blood pressure in the Rhesus monkey and a rise in arterial blood pressure in the dog. In this respect the dog mimics the cardiovascular effect observed in man. The pressor response to Ketalar injected into intact, unanesthetized dogs is accompanied by a tachycardia, rise in cardiac output and a fall in total peripheral resistance. The pressor response to Ketalar is reduced or blocked by chlorpromazine (central depressant and peripheral α-adrenergic blockade), by β-adrenergic blockade, and by ganglionic blockade.

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

In a 3-month repeat-dose toxicity study with intranasally administered esketamine in dogs, no relevant electrocardiogram (ECG) changes were noted up to the highest dose tested, ie, 72 mg/day. Heart rate was slightly increased. The cardiovascular safety of racemic ketamine and esketamine in humans and animals is summarized in the Investigator's Brochure.[32]

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.[32]

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.[32]

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.[32]

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.[32]

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.[32]

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.[20] The inhibitory action on membrane currents may partly explain the species and tissue differences in inotropic responses to ketamine.

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

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

The dog would be considered the most predictive species in terms of ketamine's cardiovascular effects in humans, but the antidepressant effects of ketamine were studied only in rodent models. The myocardial contractility effects and blood pressure responses to ketamine vary between species.[32] 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.[32]

1.1.2. Clinical Studies

1.1.2.1. Pharmacokinetics and Product Metabolism

Metabolism

Ketamine (and esketamine) undergoes extensive metabolism by hepatic cytochrome P450 (CYP). In humans, N-demethylation to norketamine is the major route of metabolism, which can undergo

further metabolism to form hydroxynorketamine. Ketamine and norketamine are extensively hydroxylated to a series of 6 hydroxynorketamine metabolites and 2 hydroxyketamine metabolites.[77] Like ketamine, norketamine is a noncompetitive antagonist at the NMDA receptor.[19,29] Norketamine has a half-life in plasma of approximately 5 hours.[28] The major human hepatic CYPs that catalyze ketamine N-demethylation in vitro are CYP2B6 and CYP3A4.[57,80] The CYP enzymes responsible for the formation of norketamine metabolites include CYP2A6 and CYP2B6.[57] Published results of a clinical pharmacokinetics (PK) study indicate that esketamine does not invert to the R-enantiomer.[25]

Excretion

Racemic ketamine and its metabolites have been previously shown to be predominantly excreted in the urine. An average of 91% and 3% of a tritium-labeled dose (1 mg/kg) administered to 6 healthy subjects was recovered in urine and feces, respectively.[7] Less than 3% of an administered dose was excreted in urine as parent drug.[75]

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

Intravenous Esketamine

Subjects with TRD received 0.2 mg/kg or 0.4 mg/kg esketamine as a 40-minute IV infusion during Study ESKETIVTRD2001.[13] Maximum concentrations of esketamine were observed at the end of the infusion. Mean values for maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC) increased with an increase in the esketamine dose administered (80.9 and 135 ng/mL, respectively, and 150 and 218 ng*h/mL, respectively, for 0.2 mg/kg and 0.4 mg/kg esketamine). The mean plasma clearance of esketamine was high (109 L/h and 141 L/h for the 0.2 mg/kg and 0.4 mg/kg doses, respectively), as it was similar to or exceeded hepatic blood flow in humans.[13] The large volume of distribution suggests that esketamine distributes widely into tissues (236 L and 303 L, respectively). The half-life of esketamine in plasma was 2.14 and 2.65 hours, respectively, for the 2 doses.

Esketamine Nasal Spray

Plasma esketamine PK results from Studies ESKETINTRD1001, ESKETINTRD1002, ESKETINTRD1003, and the double blind phase of Panel A of the ESKETIVTRD2003 that inform dose selection for the Phase 3 program are described below. The results demonstrate that plasma esketamine concentrations produced by effective IV regimens (0.2 mg/kg and 0.4 mg/kg as 40-minute infusions) may be achieved by the intranasal route.

Study ESKETINTRD1001 included 3 cohorts of subjects who were healthy male and female subjects.[10] The esketamine nasal spray treatments were self-administered under the direct supervision of the investigator or designee.

Subjects in Cohorts 1 and 3 received esketamine doses that ranged from 28 to 112 mg. The regimens were self-administered in the upright position. No instructions were given with regards to sniffing after administration. The reported median time of C_{max} (T_{max}) of esketamine ranged

from 0.37 to 0.83 hours from the time the first spray was administered (ie, 0.33 to 0.5 hours after the last spray was administered). The doses of 28 to 112 mg produced mean C_{max} values ranging from 63.3 to 151 ng/mL, whereas mean AUC_{∞} values ranged from 164 to 565 ng*h/mL. Mean C_{max} and AUC values of esketamine increased in a less than dose-proportional manner across the dose regimens. Furthermore, there was substantial overlap in the range of individual C_{max} and AUC values among the 3 doses. The mean terminal half-life of esketamine ranged from 5.86 to 9.83 hours across all treatments.

Subjects in Cohort 2 received 84 mg in a semi-reclined position and were instructed to sniff after each spray. Higher mean C_{max} and AUC_{∞} values were observed in this cohort (174 ng/mL and 437 ng*h/mL, respectively) compared with the same esketamine dose self-administered by subjects in Cohort 1 (107 ng/mL and 363 ng*h/mL, respectively). The semi-reclined position of the head and the instruction to subjects to sniff following intranasal dosing are believed to be the cause for the increase in exposure observed in Cohort 2 compared with Cohort 1. As a result, the instructions for self-administration of esketamine nasal spray were adapted to include the semi-reclined position of the head and sniffing following dosing for all future studies.

During the Phase 1 study ESKETINTRD1002, healthy Japanese and Caucasian subjects received single intranasal doses of esketamine 28 mg, 56 mg, and 84 mg in a crossover manner.[11] On average, plasma esketamine C_{max} and AUC values were up to 48% higher in Japanese subjects compared with Caucasian subjects.

Study ESKETINTRD1003 compared the PK, safety, and tolerability of intranasally administered esketamine in healthy elderly (≥65 years of age) and younger adult subjects (18 to 55 years of age, inclusive).[12] Subjects received a single intranasal treatment of esketamine 28 mg. Median time to reach the maximum plasma concentration (t_{max}) of esketamine was approximately 30 minutes for both age groups. The geometric means of C_{max} and AUC from time 0 to infinite time, AUC_{∞}, for esketamine were approximately 21% and 17% higher, respectively, in the elderly compared with younger adult subjects.

Study ESKETINTRD1012 evaluated the pharmacokinetics and safety of a single intranasal 84-mg dose, which was self-administered by 8 healthy subjects who were ≥75 years of age and 8 healthy younger adults (18 to 55 years of age).[9] Preliminary data showed the median time to reach the maximum plasma concentration (t_{max}) of esketamine was 0.53 hours and 0.83 hours, in healthy elderly subjects ≥75 years of age and younger adults, respectively. The means of the C_{max} and area under the plasma concentration-time curve from time 0 to infinite time (AUC_{∞}), for esketamine were approximately 48% and 31% higher, respectively, in the elderly compared with younger adult subjects. Differences were greater based on median C_{max} and AUC_{∞} values (97% and 63% higher in the elderly, respectively).

Study ESKETINTRD1007 evaluated the effects of daily intranasal administration of mometasone on the pharmacokinetics of esketamine nasal spray in healthy subjects and in addition, the effects of a single pretreatment with oxymetazoline on the pharmacokinetics of esketamine in subjects with allergic rhinitis were assessed. Daily administration of mometasone did not affect the pharmacokinetics of esketamine. Pretreatment with oxymetazoline also did not affect the

pharmacokinetics of esketamine. These results indicate that subjects using a nasal decongestant or corticosteroid for the treatment of allergic rhinitis may receive esketamine nasal spray for the treatment of TRD.

Study ESKETINTRD2003 is a 2-panel, doubly randomized, double-blind, placebo-controlled, multicenter study.[59] Panel A was conducted in the United States and Belgium. Panel A assessed the efficacy and safety of 3 dose strengths of esketamine nasal spray (28, 56, and 84 mg) administered twice a week in subjects with TRD.[8] Results of a preliminary analysis of data from the double-blind phase of Panel A indicate mean (standard deviation) esketamine concentrations at 40 minutes postdose were 36.4 ng/mL (16.4), 58.1 ng/mL (24.5), and 72.5 ng/mL (34.2), respectively, for the 3 doses (data on file). The mean esketamine concentrations in plasma samples collected on Days 1 and 11 were similar, suggesting that the PK are consistent after repeated administration.

1.1.2.2. Pharmacodynamics and Efficacy

The efficacy of subanesthetic doses (0.5 mg/kg IV administered over 40 minutes) of IV ketamine has been evaluated in approximately 192 subjects with MDD (cases and controls), and 2 studies in bipolar depressed subjects (meta-analyses).[24] This recent meta-analysis of studies suggests that ketamine has a rapid onset (within 1 day) of antidepressant efficacy, including in those who have not benefitted from other antidepressants, used as monotherapy or in combination with oral antidepressants.

Esketamine (0.2 and 0.4 mg/kg administered over 40 minutes) has similar, rapid, and robust antidepressant effect as that seen with IV ketamine. A double-blind, double-randomization, placebo-controlled study (ESKETIVTRD2001) enrolled 30 adult subjects with TRD: 10 in the IV placebo group, 9 in the IV esketamine 0.20-mg/kg group, and 11 in the IV esketamine 0.40 mg/kg group (based on Day 1 randomization).[13] The intent-to-treat (ITT) analysis of the primary efficacy variable (change in Montgomery-Asberg Depression Rating Scale [MADRS] total score from baseline Day 1 to Day 2) indicated that the improvement in both esketamine dose groups was statistically significant (1-sided p=0.001 in both dose groups) compared with the placebo group. The mean (standard deviation) change from baseline Day 1 to Day 2 in MADRS total score was -4.9 (4.72) in the placebo group, -16.8 (10.12) in the esketamine 0.20-mg/kg group, and -17.8 (9.45) in the esketamine 0.40-mg/kg group.

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

The KETIVTRD2002 study assessed whether multiple doses of ketamine given twice a week would also maintain the antidepressant response; the data from this study suggest that ketamine (0.50 mg/kg IV over 40 minutes) administered twice a week was sufficient for maintaining the initial effect over a 4-week treatment period.[14]

As noted above, Study ESKETINTRD2003 is a 2-panel, doubly randomized, double-blind, placebo-controlled, multicenter study.[8] Panel A was conducted in the United States and Belgium and Panel B in Japan. Panel A assessed the efficacy and safety of 3 dose strengths of esketamine nasal spray (28, 56, and 84 mg) administered twice a week in subjects with TRD. Panel B (ongoing) is designed to assess the efficacy and safety of 14-mg and 56-mg dose strengths. In Panel A, subjects in period 1 (1-week duration) were randomly assigned in a 3:1:1:1 ratio to placebo (33 subjects), esketamine 28 mg (11 subjects), esketamine 56 mg (11 subjects), or esketamine 84 mg (12 subjects). An initial analysis of the data from the double-blind phase of Panel A indicates that of the 67 subjects randomized in Period 1, 63 entered Period 2 (1-week duration), in which 28 placebo subjects who were eligible for re-randomization at the end of Period 1, were randomly assigned in a 1:1:1:1 ratio to placebo (n=6), esketamine 28 mg (n=8), esketamine 56 mg (n=9), or esketamine 84 mg (n=5) (data on file). Subjects eligible for re-randomization had to have a Quick Inventory of Depressive Symptomatology - Self Report (QIDS-SR_{16}) total score >11 at the end of Period 1.

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

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

The effect sizes (95% CI) in Period 1 for esketamine, compared with placebo, were:

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

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

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

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.[27,36,60,70]

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

According to the SmPC for esketamine,[36] 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.[45]

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 esketamine nasal spray 28 mg in 14 healthy elderly subjects (≥65 years of age, with 3 subjects ≥75 years of age) and 20 healthy younger adult subjects (18 to 55 years of age, inclusive).[12] 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 esketamine nasal spray (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.[64] 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 the study agent was permanently withdrawn due to this event, which resolved on the same day. The investigator considered the event to be possibly related to the study agent. Another subject in the placebo/esketamine 56-mg group experienced a TEAE of headache of moderate intensity on Day 11 of Period 2 and the study agent was permanently withdrawn due to this event, which resolved on the same day. The

investigator considered the event to be very likely related to the study agent. A third subject in the esketamine group (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 and the study agent was permanently withdrawn due to the event of dissociative disorder, which resolved on the same day. The investigator considered the event to be very likely related to the study agent.[64]

Dissociative symptoms measured on the Clinician-Administered Dissociative Symptoms Scale (CADSS)[6] 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 esketamine nasal spray administration.

The mean (SD) peak systolic blood pressure (SBP) 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 (DBP) 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.[50] Eighty percent of the participants were retested at the end of 1 year. Cognitive deficits were mainly observed in frequent users and not with the infrequent users. Short-lasting, dose-dependent effects of psychosis were associated with ketamine users. There was no increase in symptoms over time, and symptoms were completely reversible upon stopping use of ketamine. As noted, these data should be interpreted with caution, as baseline data predating drug use were not available. Furthermore, in their recent review, Morgan and Curran report that there is little evidence of any link between chronic, heavy use of ketamine and diagnosis of a psychotic disorder.[48]

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.[16,47,49,52] Overall, infrequent or recreational ketamine use does not appear to be associated with long-term cognitive impairment.[52] The most robust findings are that frequent ketamine users (more than 5 times a week) exhibit impairments in both short- and long-term memory.[49] 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.[50]

Ketamine-induced ulcerative cystitis is a recently identified complication.[48] 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[31,33,46,54] but no large-scale studies, and so the incidence of ketamine dependence is largely unknown.[48] 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.[51] 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.[69] There is conflicting evidence of the existence of a "withdrawal syndrome" after cessation of ketamine use.[48] 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.[48] 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.[15,41] However, a specific ketamine withdrawal syndrome has not yet been described.[48]

Please refer to the Investigator's Brochure for a summary of the adverse events reported in ketamine and esketamine studies.[32]

1.2. Overall Rationale for the Study

Options for the treatment of TRD are limited. Esketamine nasal spray is a new medication being developed for TRD. There is an ethical obligation to provide continued esketamine nasal spray treatment to subjects who participated in select Phase 3 studies especially if the risk versus benefit to them has been favorable. This study provides an opportunity for subjects who have participated in select Phase 3 studies to receive open label esketamine nasal spray until:

- esketamine is approved in the respective country and accessible through the local healthcare system funding or until end of December 2022, whichever is earlier; or
- the subject does not benefit from further treatment (based on the investigator's clinical judgment) or withdraws consent; or
- the company terminates clinical development of esketamine nasal spray for TRD in that country/region

From a scientific/development perspective, this affords an opportunity to gain additional safety and efficacy information that can be helpful to clinicians, patients, and payers regarding esketamine's longer term use.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

2.1.1. Objectives

The primary objective of this study is to assess the safety and tolerability of esketamine nasal spray in subjects with TRD, with special attention to the following:

- Potential long-term effects on cognitive function
- Treatment-emergent adverse events (TEAEs), including TEAEs of special interest
- Post dose effects on heart rate, blood pressure, respiratory rate and blood oxygen saturation
- Potential effects on suicidal ideation/behavior

Secondary Objective

The secondary objective is to assess long-term efficacy, including effects on:

- Depressive symptoms (clinician and self-reported),

- Overall severity of depressive illness,
- Functioning and associated disability,
- Health-related quality of life and health status,

Exploratory Objectives

The exploratory objectives are to assess:

- Medical resource utilization
- Response remission rates to a second induction phase in eligible subjects who had relapsed in study ESKETINTRD3003
- Subject treatment satisfaction
- Subject tradeoff preferences for key benefit and harm outcomes associated with TRD treatment, using a stated-choice preference survey

2.1.2. Endpoints

Safety endpoints are listed below.

- Occurrence of TEAEs, including TEAEs of special interest
- Potential short-term effects observed on the day of intranasal treatment session with special attention to changes from baseline/predose over time for:
  - Blood pressure (systolic and diastolic) and heart rate
  - Blood oxygen saturation
  - 12-lead electrocardiogram
  - Alertness and sedation using Modified Observer's Assessment of Alertness/Sedation (MOAA/S)
- Long-term effects, with special attention to changes from baseline over time for:
  - Computerized cognitive battery and Hopkins Verbal Learning Test-Revised (HVLT-R), to assess potential effects on cognitive function
  - Columbia-Suicide Severity Rating Scale (C-SSRS), to assess potential effects on suicidal ideation and behavior
- Changes from baseline over time in clinical laboratory tests, including hematology, serum chemistry, and urinalysis
- Time to discharge readiness, using the Clinical Global Assessment of Discharge Readiness (CGADR)

Efficacy endpoints include changes from baseline over time for the following:

- Depressive symptoms, including response (≥50% improvement from baseline) and remission (MADRS total score ≤12, PHQ-9 total score <5); using the Montgomery Asberg Depression Rating scale (MADRS) and 9-item self-reported Patient Health Questionnaire (PHQ-9)
- Overall severity of illness, using the Clinical Global Impression Severity (CGI-S)

- Functioning and associated disability, using the Sheehan Disability Scale (SDS)
- Health related quality of life and health status, using the European Quality of Life (EuroQol) Group, 5-Dimension, 5-Level (EQ-5D-5L)
- Health related quality of life using the Quality of Life in Depression Scale (QLDS)

Exploratory endpoints include:

- Changes from baseline over time for:
  - Depression response and remission rates (as defined above) to a second induction phase in eligible subjects who had relapsed in study ESKETINTRD3003, assessed using the MADRS and PHQ-9
  - Subject treatment satisfaction
- Subject tradeoff preferences for key benefit and harm outcomes associated with TRD treatment, using a stated-choice preference survey

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

2.2. Hypothesis

There is no formal hypothesis for this study.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

- This is a multicenter, open-label long term extension study to evaluate the safety, tolerability, and efficacy of esketamine nasal spray in subjects with TRD.

The table (Table 1) below describes the subjects who may be eligible to participate in this study based on the clinical judgment of the investigator and their point of entry into 54135419TRD3008:

Table 1: Characterization of Study Population Entering 54135419TRD3008 from Different Phase 3 Studies

Prior Study	Inclusion requirement	Point of entry for 54135419TRD3008
ESKETINTRD3001	Subject completed induction phase and the 2-week follow-up phase visit	Induction phase
	Subject completed the induction phase and was a responder and ESKETINTRD3003 is terminated.	Optimization/maintenance phase
ESKETINTRD3002	Subject completed induction phase and the 2-week follow-up phase visit	Induction phase
	Subject completed the induction phase and was a responder and ESKETINTRD3003 is terminated.	Optimization/maintenance phase
ESKETINTRD3003	Subject relapsed in maintenance phase	Induction phase
	Subject was in the induction phase at the time the study was terminated and, after completion of the induction phase, was determined to be a responder.	Optimization/maintenance phase
	Subject was in the optimization or maintenance phase at the time the study was terminated	Optimization/maintenance phase

Table 1: Characterization of Study Population Entering 54135419TRD3008 from Different Phase 3 Studies

Prior Study	Inclusion requirement	Point of entry for 54135419TRD3008
	At Week 16 of Optimization, the subject was not eligible to proceed to the maintenance phase and sponsor has approved subject's entry into 54135419TRD3008	Induction phase or Optimization/maintenance phase
	Subject was in the induction phase and after completion of induction phase, was determined to not meet criteria for response, and sponsor has approved subject's entry into 54135419TRD3008	Induction phase or Optimization/maintenance phase
ESKETINTRD3004	Subject completed the optimization/maintenance phase	Optimization/maintenance phase
	Subject was in the induction phase at the time the study was terminated and, after completion of the induction phase, was determined to be a responder.	Optimization/maintenance phase
	Subject was in the optimization/maintenance phase at the time the study was terminated	Optimization/maintenance phase
	Subject was in the induction phase and did not meet criteria for response and sponsor has approved subject's entry into 54135419TRD3008	Induction phase or Optimization/maintenance phase
ESKETINTRD3005	Subject was in the induction phase of ESKETINTRD3005 study at the time enrollment into the ESKETINTRD3004 study was closed and, after completion of the induction phase, was determined to be a non-responder.	Induction phase
	Subject was in the induction phase of ESKETINTRD3005 study at the time enrollment into the ESKETINTRD3004 study was closed and, after completion of the induction phase, was determined to be a responder	Optimization/maintenance phase
ESKETINTRD3006 United States study sites only	Subject completed the induction phase and was a responder	Optimization/maintenance phase
	Subject completed induction phase and did not meet the response criteria, and sponsor has approved subject's entry into 54135419TRD3008	Induction phase or Optimization/maintenance phase

An Independent Data Monitoring Committee (IDMC) will meet approximately every 6 months to review select safety data through the end of 2020 (see Section 11.7, Independent Data Monitoring Committee, for details).

This study will have 2 open label phases

- A 4-week induction phase (if applicable, per Table 1 above)
- A variable duration optimization/maintenance phase

The duration that a subject may participate in the study is variable and is based on the subject's point of entry into the study and the timing of when the predefined criteria (below) for ending study participation occurs.

Study participation will be stopped:

- when esketamine is approved in the respective country and accessible through the local healthcare system funding or until end of December 2022, whichever is earlier; or
- the subject no longer benefits from further treatment (based on the investigator's clinical judgment), or withdraws consent; or
- the company terminates clinical development of esketamine nasal spray for TRD in that country/region

Subjects will have a final study visit within 1 week of the last dose of esketamine nasal spray.

All study subjects should be taking a permitted oral antidepressant (per clinical judgment) throughout the duration of study participation. Changes to the oral antidepressant medication(s) that a subject is taking at study entry is permitted per clinical judgment of the investigator. If subject may benefit from addition of an additional antidepressant medication (eg lithium, bupropion, adjunctive antipsychotic, etc.), the investigator should discuss with sponsor to determine whether continuing esketamine nasal spray still has a favorable benefit versus risk for the subject.

Induction Phase

Subjects will self-administer open-label esketamine nasal spray as a flexible dose regimen twice a week for 4 weeks as outlined in Section 6 (Dosage and Administration).

At the end of the induction phase, subjects may be eligible to proceed to the optimization/maintenance phase, according to the investigator’s clinical assessment of the benefit versus risk for the subject.

If a subject withdraws from the study before the end of the induction phase for reasons other than withdrawal of consent, or is not eligible to proceed to the optimization/maintenance phase, an Early Withdrawal (EW) visit will be conducted within 1 week of the last intranasal dose.

Subjects who are currently in the induction phase at the time the 54135419TRD3008 study is completed will conduct an “End of Study” visit as their final study visit within 1 week of the last intranasal dose.

Optimization/Maintenance Phase:

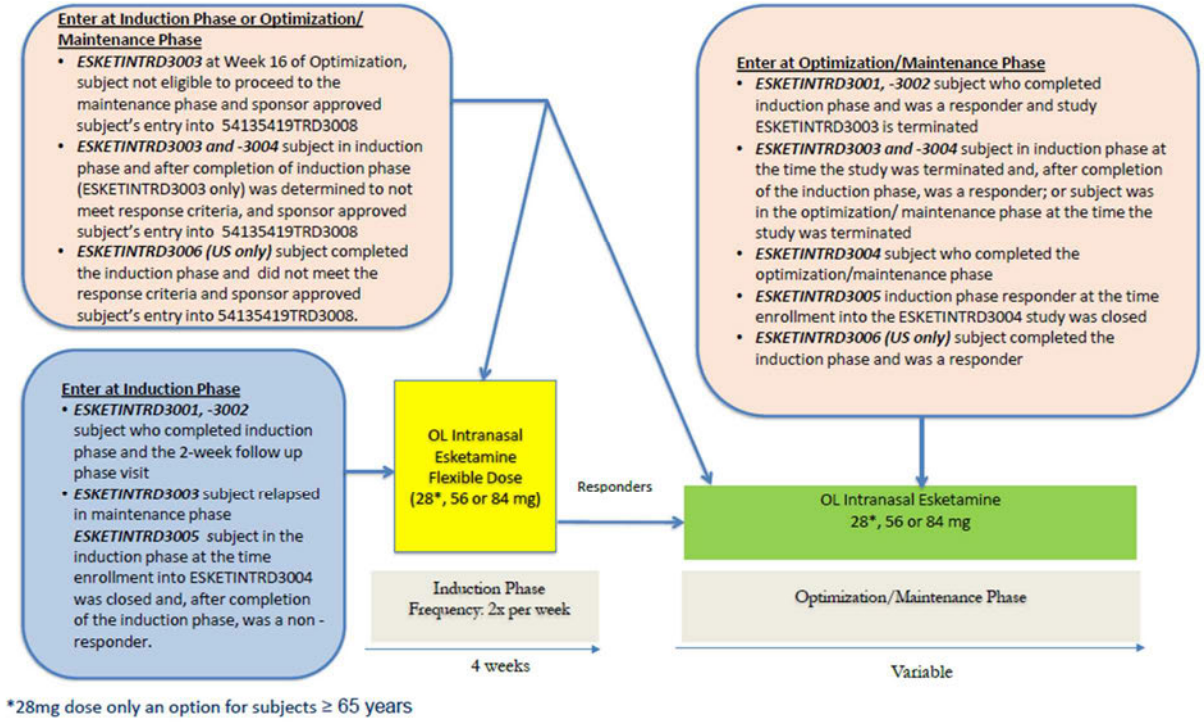
During this phase, the dose and intranasal treatment session frequency can be adjusted based on the criteria outlined in Section 6.1.2 (Dosage and Administration).

If a subject withdraws from the study before the end of the optimization/maintenance phase for reasons other than withdrawal of consent, an EW visit will be conducted within 1 week of the last intranasal dose.

Subjects who are currently in the optimization/maintenance phase at the time the 54135419TRD3008 study is completed will conduct an "End of Study" visit as their final study visit within 1 week of the last intranasal dose.

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

Figure 1: Schematic Overview of the 54135419TRD3008 Study



3.2. Study Design Rationale

3.2.1. Study Population

The study population will include adult and elderly men and women who previously participated in studies ESKETINTRD3001, ESKETINTRD3002, ESKETINTRD3003, ESKETINTRD3004, or ESKETINTRD3005, or ESKETINTRD3006 (US sites only).

Options for the treatment of TRD are limited. For subjects who have participated in studies ESKETINTRD3003, ESKETINTRD3004, ESKETINTRD3005 or ESKETINTRD3006 (US sites only) studies and have responded to esketamine nasal spray treatment, it is considered an ethical obligation to provide continued esketamine nasal spray treatment if the benefit/risk profile is favorable for the subject at the time of completion of the previous study. Subjects in the placebo-controlled, double blind ESKETINTRD3005 and who are non-responders at the end of the induction phase are eligible to enter the open label induction phase of ESKETINTRD3004, therefore if enrollment in the ESKETINTRD3004 is complete these subjects will be given the opportunity to enter this study, if clinically appropriate. For subjects who have completed the induction phase and 6-month follow up phase of the ESKETINTRD3001 or ESKETINTRD3002

study, this study provides an opportunity for subjects to have an induction phase with open-label esketamine nasal spray.

3.2.2. Study Phases

Induction Phase (4 week; if applicable)

The duration of the 4-week open-label phase was selected because this is the duration of the induction phase in the prior studies from which these subjects are entering. It is unknown whether a second, repeated induction phase may be efficacious in subjects who have relapsed following response to esketamine nasal spray treatment (ESKETINTRD3003), have not responded to intranasal treatment with esketamine or placebo (ESKETINTRD3001 and ESKETINTRD3002, ESKETINTRD3005 and ESKETINTRD3006 [US sites only]), or with sponsor's approval, subjects not meeting criteria for response from ESKETINTRD3003 and ESKETINTRD3004, therefore this study will implement the same duration of the subject's first induction phase.

Optimization/Maintenance Phase (Variable)

The duration of the optimization/maintenance phase is variable and based on the subject's individual efficacy and tolerability to esketamine nasal spray, or when esketamine is approved in the respective country and accessible through the local healthcare system funding or until end of December 2022, whichever is earlier.

Subjects entering this phase from the induction phase of this study (54135419TRD3008) will reduce the frequency of intranasal treatment sessions and subsequently individualize and stabilize the treatment session frequency to weekly, every other week, or every 4 weeks based on the severity of depression during this phase.

All other subjects will enter this phase at the same frequency of intranasal treatment sessions that they had in the prior study, and this phase will allow the frequency of intranasal treatment sessions to continue to be individualized to once weekly, once every other week, or once every 4 weeks based on the severity of depression in order to sustain antidepressant efficacy.

While there is not a separate follow up phase, to ensure subject safety, an End of Study visit will be planned to occur within 1 week of the last esketamine nasal spray treatment.

3.2.3. Blinding and Control Group

Blinding will not be used in this open-label study.

An open-label design has been selected for this study and is appropriate given the intention to provide a continued evaluation of the long term safety, tolerability, and efficacy of esketamine nasal spray in a TRD patient population with limited, effective treatment options and who have previously participated in a prior Phase 3 studies.

3.2.4. Intranasal Treatment Group and Dose Selection

Induction Phase

All subjects will receive open-label esketamine nasal spray during this phase.

The 56 mg and 84 mg doses 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, and is aligned with the induction phase of the prior study the subject is coming from.

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 induction phase. In addition, the 56-mg and 84 mg dosages were generally well tolerated by subjects.

To potentially improve tolerability, for those subjects that become ≥65 years of age at the time of signing the informed consent form (ICF; ie, the study populations in the ESKETINTRD3001, ESKETINTRD3002, and ESKETINTRD3003 were <65 years of age), a dose of 28 mg will be available. Based on PK data from ESKETINTRD1012 it is also possible that the 28 mg dose in the elderly may overlap with the 56 mg dose in younger patients, so addition of the 28 mg dose in the elderly may provide an efficacious dose while improving safety.

The use of flexible dosing for esketamine nasal spray 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/Maintenance Phase

Subjects from the induction phase of 54135419TRD3008, who enter the optimization/maintenance phase will continue on the same dose of esketamine nasal spray from the induction phase and have a weekly intranasal treatment session frequency (ie, reduced frequency from the twice-weekly frequency in the induction phase).

Subjects who were responders at the end of the induction phase of ESKETINTRD3001, ESKETINTRD3002 or ESKETINTRD3006 (US sites only) who enter the optimization/maintenance phase will have a weekly intranasal treatment session frequency (ie, reduced frequency from the twice-weekly frequency in the induction phase). However, as the ESKETINTRD3001, 3002 and 3006 intranasal study medication is blinded at the time of entry into the current study, subjects entering the optimization/maintenance phase should start at 56 mg. The dose may remain at 56 mg or be increased to 84 mg, as determined by the investigator based on efficacy and tolerability.

With sponsor approval, subjects from ESKETINTRD3003 and ESKETINTRD3004 entering directly from the induction phase who were determined to not meet the criteria for response in those studies may enter the optimization /maintenance phase of 54135419TRD3008 and will have a weekly intranasal treatment session frequency from week 1 to week 4 (ie, reduced from that in the induction phase (twice weekly) to weekly). In addition, a one-time dose change will be allowed at study entry.

With Sponsor approval subjects from ESKETINTRD3006 (US sites only) entering directly from induction phase and determined to not meet criteria for response in that study may enter the optimization/maintenance phase. However, as the ESKETINTRD3006 intranasal study medication is blinded at the time of entry into the current study, subjects entering the optimization/maintenance phase from study ESKETINTRD3006 will start at 56 mg. The dose may remain at 56 mg or be increased to 84 mg, as determined by the investigator based on efficacy and tolerability. Subjects will have a weekly intranasal treatment session frequency from week 1 to week 4 (ie, reduced frequency from the twice-weekly frequency in the induction phase).

Subjects entering the optimization/maintenance phase from study ESKETINTRD3003 (Direct Entry) or ESKETINTRD3004 who were ongoing in the Optimization, Maintenance, or Optimization/Maintenance phase respectively, will have the option to have their current intranasal dosing frequency adjusted at the time of entry into 54135419TRD3008 study and should remain on the selected frequency from week 1 to week 4 (inclusive). A one-time dose change will be permitted at study entry.

Subjects entering the optimization/maintenance phase from study ESKETINTRD3003 (Transferred Entry) will start at 56 mg. The dose may remain at 56 mg or be increased to 84 mg, as determined by the investigator based on efficacy and tolerability. In addition, subjects will have the option to have their current intranasal dosing frequency adjusted at the time of entry into 54135419TRD3008 study and should remain on the selected frequency from week 1 to week 4 (inclusive).

Subjects from the induction phase of ESKETINTRD3005 will have the intranasal treatment session frequency reduced to weekly. However, as the ESKETINTRD3005 study will be blinded at the time of entry into the current study, these subjects will start esketamine nasal spray with an initial dose of 28 mg (Week 1; Study Day 1) and have their dose adjusted over the following 3 weeks of the optimization/maintenance phase as described under the Section 6 Dosage and Administration.

Starting at Week 4, the frequency of intranasal treatment sessions will be individualized and subsequent intranasal treatment session frequency will be adjusted (if applicable) based on the algorithm below at fixed, 4-week intervals (starting at Week 4,) to once weekly, once every other week, or once every 4 weeks based on the severity of depression, as assessed by the CGI-S. This continued individualization of treatment session frequency is intended to allow subjects to sustain the antidepressant response while minimizing the frequency of intranasal treatment sessions required.

After Week 4 (ie, starting at Week 5), the dose can be adjusted based upon efficacy and tolerability, as determined by clinical judgment.

The rationale for allowing reduction in the frequency of intranasal treatment sessions from twice weekly to weekly, once every other week, or once every 4 weeks, is to individualize the treatment session frequency (weekly, every other week, or every 4 weeks) for a given subject (based on level of depressive symptoms). Open label data from Panel A of a recently completed study (ESKETINTRD2003), indicates that even with a reduction in dosing frequency from twice weekly to weekly for 3 weeks and then a reduction to every other week for an additional 4 week, the majority of patients were able to maintain their treatment response. Additional data from the 8-week follow up phase of ESKETINTRD2003 indicates that most patients who were responders when entering the follow up phase were able to maintain their response for up to 8 weeks after cessation of intranasal dosing. Therefor the current study will provide an opportunity to evaluate the impact of dosing every 4 weeks, which has not been studied in the other Phase 3 protocols to date. Similarly, anecdotal reports from clinical practice with IV ketamine, suggests patient may be able to maintain the antidepressant benefits achieved with less frequent dosing.

3.2.5. Safety Evaluations

Evaluation of TEAEs and concomitant therapies, clinical laboratory tests, vital signs (including blood pressure measurements), 12-lead ECG, pulse oximetry, physical examination, and body weight, will be performed throughout the study as per the Time and Events Schedule to monitor subject safety.

Treatment emergent AEs of special interest will be analyzed separately grouped in the following categories: drug abuse, dependence and withdrawal (standardized Medical Dictionary for Regulatory Activities [MedDRA]), increased blood pressure, increased heart rate, transient dizziness/vertigo, impaired cognition, cystitis, anxiety, events potentially related to suicidality, hepatic adverse events, events related to renal disorders, and symptoms of dissociation persisting beyond the typical ≤2 hour post esketamine administration, as well as delirium, psychosis or mania.

The effect of esketamine nasal spray on cognition will be assessed as per the Time and Events Schedule 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, and includes assessment of both immediate and delayed recall.

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 adverse events of cystitis, bladder pain, and interstitial cystitis during the study. If cystitis is considered to be associated with esketamine, subjects will be discontinued from the study and followed up with appropriate medical care.

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.

The Columbia Suicide Severity Rating Scale (C-SSRS) will be performed as per the Time and Events Schedule to assess suicidal ideation and behavior, the MOAA/S will be used to measure treatment-emergent sedation, and the CGADR will be used to measure the subject's readiness for discharge based on parameters including sedation, blood pressure, and adverse events.

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

All subjects must not drive a car or work with machines for 24 hours after receiving intranasal study drug.

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

3.2.6. Efficacy Measures

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

MADRS

The 10-item clinician-administered MADRS was designed to be used in subjects with MDD to measure the overall severity of depressive symptoms.[45] The MADRS scale is a validated, reliable scale and acceptable to regulatory health authorities as a primary scale to determine efficacy in major depression.

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

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.[26] Refer to Section 9.3.1.2 for additional information regarding CGI-S.

PHQ-9

The PHQ-9 will be used as a patient-reported measure of depressive symptomatology.[79] Refer to Section 9.3.1.3 for additional information regarding PHQ-9.

During the optimization/maintenance phase, the CGI-S will be used to measure severity of depressive symptoms to individualize intranasal treatment session frequency.

SDS

The Sheehan Disability Scale (SDS) is a patient reported measure included as an assessment of functional impairment and associated disability.[39,68] Refer to Section 9.3.1.4 for additional information regarding SDS.

EQ 5D-5L

The EQ-5D-5L is included as a standardized patient self-completed instrument for use as a measure of health-related quality of life and health status.[21,22] Refer to Section 9.3.1.5 for additional information regarding EQ-5D-5L.

QLDS

The QLDS is a disease specific PRO designed to assess health related quality of life in patients with Major Depressive Disorder.[30,43,72] The instrument has a recall period of "at the moment", contains 34-items with "yes"/"no" response options and takes approximately 5-10 minutes to complete. The score range is from 0 (good quality of life) to 34 (very poor quality of life).

3.2.7. Medical Resource Utilization

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

3.2.8. Patient Stated-choice Preference Survey

Stated-choice conjoint analysis is a method specifically designed to provide information about an individual's willingness to accept tradeoffs between treatments with multiple outcomes. It has been used in many therapeutic areas and with many types of patients, including patients with depression. The Patient Stated-choice Preference Survey will be used as an exploratory tool to assess the manner and degree to which the study subjects value or weigh the clinical outcomes associated with esketamine, allowing assessment of the maximum acceptable treatment-related risk that subjects would accept for various degrees of benefit.

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.

All the subjects entering 54135419TRD3008 study are coming from 1 of the following esketamine Phase 3 studies (ESKETINTRD3001, ESKETINTRD3002, ESKETINTRD3003, ESKETINTRD3004, ESKETINTRD3005, and ESKETINTRD3006 (US sites only) and will have met the inclusion/exclusion criteria for entry into those studies.

No formal sample size calculation was determined for this study as it is unknown how many subjects from the previous studies would participate.

4.1. Inclusion Criteria

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

1. Criterion modified per Amendment 1

   1.1 Based on the prior study the subject is entering 54135419TRD3008 from:

   a. *From ESKETINTRD3001 or ESKETINTRD3002 study*:

      i. Subject has completed the induction phase and the 2-week follow up phase visit; or

      ii. Subject completed the induction phase and was a responder and study ESKETINTRD3003 is terminated.

   b. *From ESKETINTRD3003 study*:

      i. Subject relapsed during the maintenance phase; or

      ii. Subject was in the induction phase of the ESKETINTRD3003 study when the study was terminated and, after completion of the induction phase, was determined to be a responder; or

      iii. Subject was in the optimization or maintenance phases at the time the study was terminated; or

      iv. At Week 16 of Optimization, the subject was not eligible to proceed to the Maintenance phase and sponsor has approved subject's entry into 54135419TRD3008; or

      v. Subject was in the induction phase and after completion of induction phase was determined to not meet response criteria, and sponsor has approved subject's entry into 54135419TRD3008.

   c. *From ESKETINTRD3004 study:*

      i. Subject completed ESKETINTRD3004 study optimization/maintenance phase; or

      ii. Subject was in the induction phase of the ESKETINTRD3004 study when the study was terminated and, after completion of the induction phase, was determined to be a responder; or

      iii. Subject was in the optimization/maintenance phase at the time the study was terminated; or

      iv. Subject was in the induction phase and did not meet criteria for response, and sponsor has approved subject's entry into 54135419TRD3008.

   d. From ESKETINTRD3005 study: Subject was in the induction phase of the ESKETINTRD3005 study at the time enrollment into the ESKETINTRD3004 study was closed and, after completion of the induction phase, was determined to be a responder or did not meet the criteria for response.

e. From ESKETINTRD3006 study (US Study sites only):

i. Subject completed the induction phase and was a responder; or

ii. Subject completed the induction phase and did not meet the response criteria and sponsor has approved subject's entry into 54135419TRD3008.

2. Subject must be medically stable on the basis of physical examination, vital signs (including blood pressure), pulse oximetry, and 12-lead ECG performed predose on the day of the first intranasal treatment session. 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.

3. Criterion modified per Amendment 1

   3.1 Subject must be medically stable according to the investigator's judgment and knowledge of the subject's medical stability in the parent study. This determination must be documented.

4. Criterion modified per Amendment

   4.1 Criterion modified per Amendment 2

   4.2 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. Note: FSH not required if post-menopausal status previously confirmed in either ESKETINTRD3001, ESKETINTRD3002, ESKETINTRD3003, ESKETINTRD3004 or ESKETINTRD3006. FSH is not required if subject is ≥ 65 years.

   – 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.

5. Criterion modified per Amendment 1

5.1 A woman of childbearing potential must have a negative urine pregnancy test predose on the day of the first intranasal treatment session.

6. Criterion modified per Amendment 1

6.1 During the study (ie, from the first intranasal treatment session) 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.

7. 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.

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

4.2. Exclusion Criteria

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

1. Criterion modified per Amendment 3

   1.1 The evaluation of the benefit versus risk of continued esketamine nasal spray treatment is not favorable for the subject in the opinion of the investigator.

2. Since the last study visit in the subject's prior study, subject has suicidal ideation with intent to act 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) in the suicidal ideation module of the C-SSRS] or suicidal behavior per the investigator's clinical judgment or based on the C-SSRS (corresponding to any score higher than 0 in the suicidal behavior module of the C-SSRS).

3. Criterion modified per Amendment 1

   3.1 Subject has:

   – A neurodegenerative disorder (eg, Alzheimer's disease, vascular dementia, Parkinson's disease), or evidence of mild cognitive impairment (MCI).

4. Subject has ongoing evidence of uncontrolled hypertension defined as a supine SBP >140 mmHg or DBP >90 mmHg predose on the day of the first intranasal treatment session. For those ≥65 years uncontrolled hypertension is defined as a supine SBP >150 mm Hg or DBP >90 mm Hg.

5. Subject has positive test result(s) for drugs of abuse (including barbiturates, methadone, opiates, cocaine, phencyclidine, and amphetamine/methamphetamine) predose on the day of the first intranasal treatment session.

6. 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.

7. Subject has taken any prohibited therapies that would not permit administration of the first intranasal treatment session, as noted in Section 8 (Pre study and Concomitant Therapy) and Attachment 1.

8. 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.

9. 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.
10. Subject is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.

NOTE: Investigators should ensure that all study enrollment criteria have been met. If a subject's status changes (including laboratory results or receipt of additional medical records) before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

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:

- Agree to follow all requirements that must be met during the study as noted in Section 4.1 (Inclusion Criteria) and Section 4.2 (Exclusion Criteria) (eg. for information regarding contraception requirements).
- Refer to Section 8 (Prestudy and Concomitant Therapy) and Attachment 1 (Prohibited Concomitant Medications for Intranasal Study Medication) for further information on prohibited therapies.
- 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) can continue these medications. Dose increases or new benzodiazepines are permitted during the study as long as dosages are equal to or less than the equivalent of 6 mg/day of lorazepam
- 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, MDMA, or cocaine 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 remain at the clinical study site until study procedures have been completed and the subject is ready for discharge and should be accompanied by a responsible adult when released from the clinical study site.
- Subjects must not drive a car or work with machines for 24 hours after study drug dosing.

- Electroconvulsive therapy, DBS, and vagal nerve stimulation are prohibited during the time of study participation.

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

Randomization will not be used in this study, all subjects will be allocated to open-label esketamine treatment.

Blinding

As this is an open study, blinding procedures are not applicable.

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, 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.

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 case report form (CRF).

All subjects will self-administer the intranasal study drug at treatment sessions at the study site.

Intranasal treatment sessions should not be given 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 be delayed (per the permitted visit window; see the Time and Events Schedule). The subjects must wait for at least 1 hour after using an intranasal decongestant or corticosteroid before self-administering esketamine.

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

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

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

- Prior to intranasal dosing, subjects must have a blood pressure ≤140/90 mm Hg
- If a subject's predose SBP is >140 mmHg and/or DBP is >90 mm Hg, it is recommended to repeat the blood pressure measurement after subject rests in sitting or recumbent position. If after rest and repeated measurements, predose SBP is >140 mmHg and/or DBP is >90 mm Hg, then dosing should be postponed and the subject scheduled to return on the following day or within the given visit window. If the blood pressure elevation still persists on the next visit, the subject will be scheduled for a consultation by a cardiologist, other specialist, or primary care physician (PCP) prior to further dosing.
- If at any post-dose time point on the dosing day the SBP is ≥180 mmHg but <200 mmHg and/or the DBP is ≥110 mmHg but <120 mmHg, further intranasal dosing should be interrupted and 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 PCP, if recommended by the referring doctor and considered appropriate according to the clinical judgment for the subject to continue in the study, the subject may continue with intranasal dosing provided the predose blood pressure at the next scheduled visit is within the acceptable range (see bullet point above).

- If at any post-dose time point on the dosing day the SBP is ≥200 mmHg and/or the DBP is ≥120 mmHg, the subject must discontinue from further dosing and the subject should be referred to a cardiologist, other specialist, or PCP for a follow up assessment.
- During the induction phase, at 1.5 hours postdose, if the SBP is ≥160 mm Hg and/or the DBP ≥100 mm Hg, blood pressure monitoring should continue every 30 minutes until:
  - the blood pressure is <160 mm Hg SBP and <100 mm Hg 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 ≥180 mmHg SBP and/or ≥110 mmHg DBP, 2 hours after dosing, the subject should be referred for immediate medical treatment.

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

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

- Prior to any dose escalation, subjects must have had a post-dose blood pressure, on the prior intranasal dosing day, of <180 mmHg systolic and <100 mm Hg diastolic blood pressure.

- If a subjects predose SBP is >150 mmHg and/or DBP is >90 mmHg, it is recommended to repeat the blood pressure measurement after subject rests in sitting or recumbent position. If after rest and repeated measurements, predose SBP is >150 mmHg and/or DBP is >90 mmHg, then dosing should be postponed and the subject scheduled to return on the following day or within the given visit window. If the blood pressure elevation still persists on the next visit, the subject will be scheduled for a consultation by cardiologist, other specialist, or a primary care physician, prior to further dosing.
- If at any postdose time point on the dosing day the SBP is ≥180 mm Hg but <190 mm Hg and/or the DBP is ≥100 mm Hg but <110 mm Hg, 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 of the investigator for the subject to continue in the study, the subject may continue with intranasal dosing if the predose blood pressure at the next scheduled visit is within the acceptable range (see bullet above).

- If at any postdose time point on a dosing day the SBP is ≥190 mm Hg and/or the DBP is ≥110 mm Hg, the subject must instead discontinue from further dosing and be referred to a cardiologist, other specialist, or primary care physician for a follow-up assessment.
- During the induction phase, at 1.5 hours postdose, if the SBP is ≥160 mm Hg and/or the DBP ≥100 mm Hg, blood pressure monitoring should continue every 30 minutes until:
  - the blood pressure is <160 mm Hg SBP and <100 mm Hg DBP, or
  - in the investigator's clinical judgment, the subject is clinically stable and can be discharged from the study site, or
  - the subject is referred for appropriate medical care if clinically indicated.

If the blood pressure remains ≥180 SBP and/or ≥110 mmHg DBP 2 hours after dosing, the subject should be referred for immediate medical treatment.

6.1.1. Induction Phase

All eligible subjects will self-administer the intranasal study drug twice a week for 4 weeks at treatment sessions at the study site. Intranasal treatment sessions should not take place on consecutive days.

The esketamine nasal spray dose titration in the Induction Phase for subjects <65years of age is described in Table 2:

Table 2: Induction Phase Dose Titration of Esketamine Nasal Spray, Subjects <65 Years

Day	Dose	Dose Titration Guidance
Day 1	56 mg	
Day 4	56 or 84 mg	The dose may remain at 56 mg or be increased to 84 mg, as determined by the investigator based on efficacy and tolerability.
Day 8, 11, 15, 18, 22, 25	56 or 84 mg	The dose may be increased to 84 mg (if previous dose was 56 mg), remain the same, or be reduced to 56 mg (if previous dose was 84 mg), as determined by the investigator based on efficacy and tolerability

The esketamine nasal spray dose titration in the Induction Phase for subjects ≥65years of age is described in Table 3:

Table 3: Induction Phase Dose Titration of Esketamine Nasal Spray, Subjects ≥65 Years

Day	Dose	Dose Titration Guidance*
Day 1	28 mg	
Day 4	28 or 56 mg	The dose may remain at 28mg or be increased to 56mg , as determined by the investigator based on efficacy and tolerability
Day 8, 11, 15, 18, 22, 25	28, 56 or 84 mg	The dose may remain the same, or be increased or reduced by 28mg from the previous dosing session, as determined by the investigator based on efficacy and tolerability.

6.1.2. Optimization/Maintenance Phase

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.

For the first 4 weeks of the optimization/maintenance phase (Week 1 to Week 4):

- Subjects from the induction phase of study 54135419TRD3008, who enter the optimization/maintenance phase will continue on the same dose of esketamine nasal spray from the induction phase and have a weekly intranasal treatment session frequency (ie, reduced frequency from the twice-weekly frequency in the induction phase).
- Subjects who were responders at the end of the induction phase of ESKETINTRD3001, ESKETINTRD3002 or ESKETINTRD3006 (US sites only) who enter the optimization/maintenance phase will have a weekly intranasal treatment session frequency (ie, reduced frequency from the twice-weekly frequency in the induction phase). However, as the ESKETINTRD3001, 3002 and 3006 intranasal study medication is blinded at the time of entry into the current study, subjects entering the optimization/maintenance phase should start at 56 mg. The dose may remain at 56 mg or be increased to 84 mg, as determined by the investigator based on efficacy and tolerability.
- With sponsor approval, subjects from ESKETINTRD3003 and ESKETINTRD3004 entering directly from the induction phase, who were determined to not meet the criteria for response in those studies may enter the optimization/maintenance phase of 54135419TRD3008 and will have a weekly intranasal treatment session frequency from week 1 to week 4 (ie, reduced frequency from the twice-weekly frequency in the induction phase). In addition, a one-time dose change will be allowed at study entry.

- With sponsor approval subjects from ESKETINTRD3006 (US sites only) entering directly from induction phase and determined to not meet criteria for response in that study may enter the optimization/maintenance phase. However, as the ESKETINTRD3006 intranasal study medication is blinded at the time of entry into the current study, subjects entering the optimization/maintenance phase from study ESKETINTRD3006 will start at 56 mg. The dose may remain at 56 mg or be increased to 84 mg, as determined by the investigator based on efficacy and tolerability. Subjects will have a weekly intranasal treatment session frequency from week 1 to week 4 (ie, reduced frequency from the twice-weekly frequency in the induction phase).
- Subjects entering the optimization/maintenance phase from study ESKETINTRD3005 will also have a weekly intranasal treatment session frequency. However, as the ESKETINTRD3005 intranasal study medication is blinded at the time of entry into the current study, the dose of esketamine nasal spray will be administered as outlined in Table 4.

Table 4: Optimization/Maintenance Phase Week 1 to 4: Dose Titration of Esketamine Nasal Spray for Responder Subjects Entering from ESKETINTRD3005

Week	Dose	Dose Titration Guidance
Week 1	28 mg	
Week 2	28 or 56 mg	The dose may remain at 28mg or be increased to 56mg, as determined by the investigator based on efficacy and tolerability
Week 3 and 4	28, 56 or 84 mg	The dose may remain the same or be increased or reduced by 28mg from the previous dosing session, as determined by the investigator based on efficacy and tolerability. For those who have had a prior down titration from a higher dose, a dose increase by 28 mg is allowed based on clinical judgment.

- Subjects entering the optimization/maintenance phase from study ESKETINTRD3003 (Direct Entry) or ESKETINTRD3004 who were ongoing in the Optimization, Maintenance, or Optimization/Maintenance phase, respectively, will have the option to have their current intranasal dosing frequency adjusted at the time of entry into 54135419TRD3008 study and should remain on the selected frequency from week 1 to week 4 (inclusive). A one-time dose change will be permitted at study entry.
- Subjects entering the optimization/maintenance phase from study ESKETINTRD3003 (Transferred Entry) will start at 56 mg. The dose may remain at 56 mg or be increased to 84 mg, as determined by the investigator based on efficacy and tolerability. In addition, subjects will have the option to have their current intranasal dosing frequency adjusted at the time of entry into 54135419TRD3008 study and should remain on the selected frequency from week 1 to week 4 (inclusive).

After Week 4 (ie, starting at Week 5), based on the investigator's clinical judgment, the dose of esketamine for all subjects can be adjusted based upon efficacy and tolerability.

Starting at Week 4, the frequency for subsequent intranasal treatment sessions will be adjusted (if applicable) based on the algorithm outlined in Table 5 at fixed, 2-week intervals.

Table 5: Algorithm for Adjusting Intranasal Treatment Session Frequency (if applicable) Starting Week 4

Current treatment session frequency	CGI-S score at current visit[a]	
	≤ 3	>3
Weekly	Change to every other week frequency	No change in frequency
Every other week	No change in frequency or change to every 4 weeks per clinical judgment	Change to weekly frequency
Every 4 weeks	No change in frequency	Change to weekly or every other week frequency per clinical judgment

[a] Note: The CGI-S is administered every 2 weeks from Week 4 through the end of the Optimization/Maintenance Phase, adjustment of the intranasal treatment session frequency is only permitted at the fixed, 2-week interval (based on CGI-S performed at that visit), and every 4 weeks for subjects dosed at the 4 week interval.

For example, if at Week 4 a subject is currently at a weekly treatment session frequency and the CGI-S score at Week 4 is a 2, the intranasal treatment session frequency will be changed from weekly to every other week (ie, the next treatment session for this subject will be at Week 6).

Missed Doses

If a subject missed a dose/s and the depression symptoms worsened, the investigator can go back to more frequent dosing if clinically applicable until the subject is stable.

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.

The investigator or designated study-site personnel will maintain a log of all intranasal study drug dispensed and returned. Drug supplies for each subject will be inventoried and accounted for throughout the study (see Section 14.5 Drug Accountability).

8. PRESTUDY AND CONCOMITANT THERAPY

All study subjects should be taking a permitted oral antidepressant (per clinical judgment) throughout the duration of study participation. Changes to the oral antidepressant medication(s) that a subject is taking at study entry is permitted per clinical judgment of the investigator. If subject may benefit from an additional antidepressant medication (eg lithium, bupropion, adjunctive antipsychotic, etc.), the investigator should discuss with sponsor to determine whether continuing esketamine nasal spray still has a favorable benefit versus risk for the subject.

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.

Concomitant therapies (including psychotherapy) 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, the morning dose should be taken prior to esketamine nasal spray on intranasal dosing days.

There is no restriction regarding psychotherapy in this study and subjects may continue or start psychotherapy (including cognitive behavioral therapy; CBT) during the study.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as psychotherapy, acupuncture, and special diets) different from the study drug must be recorded in the CRF. 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 esketamine nasal spray, the following rescue medications may be considered:

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

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedules summarize the frequency and timing of safety, efficacy, and medical resource utilization measurements applicable to this study.

Visit-specific predose 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/or CRF.

The total blood volume to be drawn from each subject over the first 1 year period will be approximately 42 mL (Table 6) and will not exceed the amount of blood donated by a volunteer for a single charitable blood donation in 1 day (about 500 mL). The amount of blood volume collected during optimization/maintenance phase will be variable due to the nature of the study design. 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 6: Volume of Blood to be Collected from Each Subject

Phase Type of Sample	Volume per Sample(s), mL	Number of Samples per Subject	Total Volume of Blood (mL)[a]
Baseline Tests			
HbA1C (if applicable)	2	1	2
Hematology	2	1	2
Serum chemistry[b]	5	1	5
Induction Phase			
Hematology	2	1	2
Serum Chemistry	2.5	1	2.5
Optimization/Maintenance Phase			
HbA1C (if applicable)	2	3	6
Hematology	2	5[c]	10[c]
Serum Chemistry	2.5	5[c]	12.5[c]
Approximate volume of blood collected during the study[d]			**42 mL**

[a] Calculated as number of samples multiplied by amount of blood per sample.
[b] Serum chemistry includes serum β-hCG pregnancy tests (for women of childbearing potential), and lipid panel.
[c] The number of samples per subject (5) is representative of the samples collected that will be collected in the optimization/maintenance phase in an year. The length of the optimization/maintenance phase is variable and would decide the total number of samples collected during this phase and in turn the total volume of blood collected.
[d] The approximate volume of blood (42 mL) collected during the study will vary as per the total volume of blood collected during the variable optimization/maintenance phase. The calculation shown is an estimate for a 1 year period.

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

9.1.2. Induction Phase

The following subjects are eligible to enter the study at the induction phase:

- Subjects who relapsed during the ESKETINTRD3003 maintenance phase, or
- Subjects who were in the induction phase of ESKETINTRD3005 study at the time enrollment into the ESKETINTRD3004 study was closed and, after completion of the induction phase, were determined to be a non -responder, or
- Subjects who completed the induction phase and the 2 week follow up phase visit in ESKETINTRD3001 or ESKETINTRD3002 studies

Prior to conducting any study procedure for 54135419TRD3008, the investigator (or designated study personnel) will review and explain the written ICF to each subject. The ICF will be signed at the start of this phase.

During this phase, all subjects will self-administer open-label treatment with esketamine nasal spray treatment twice a week for 4 weeks as a flexible dose regimen. Refer to Section 6, Dosage and Administration for details regarding intranasal study medication.

At the end of the induction phase of 54135419TRD3008, subjects may be eligible to proceed to the optimization/maintenance phase, according to the investigator's clinical assessment of the benefit versus risk for the subject.

Refer to Section 9.1.5 for information regarding early withdrawal subjects and subjects that are currently in this phase at the time the study is terminated.

9.1.3. Optimization/Maintenance Phase

The following subjects are eligible to enter the study at the optimization/maintenance phase:

- Subjects who completed the induction phase of ESKETINTRD3001 or ESKETINTRD3002 and were responders, and study ESKETINTRD3003 is terminated.
- Subjects who were in the induction phase of ESKETINTRD3003 and ESKETINTRD3004 studies at the time these studies were terminated and, after completion of the induction phase, were determined to be a responder.
- Subjects who completed the optimization/maintenance phase of ESKETINTRD3004
- Subjects who were in the optimization, maintenance or optimization/maintenance phase of ESKETINTRD3003 and ESKETINTRD3004 studies, respectively, at the time these studies were terminated
- Subjects who were in the induction phase of ESKETINTRD3005 study at the time enrollment into the ESKETINTRD3004 study was closed and, after completion of the induction phase, were determined to be responders.
- Subjects (US only) who completed the induction phase of ESKETINTRD3006 and were responders.

The duration that a subject may participate in the study is variable and is based on the subject's point of entry into the study and the timing of when the predefined criteria (below) for ending study participation occurs.

Study participation will be stopped:

- when esketamine is approved in the respective country and accessible through the local healthcare system funding or until end of December 2022, whichever is earlier; or
- the subject no longer benefits from further treatment (based on the investigator's clinical judgment), or withdraws consent; or

- the company terminates clinical development of esketamine nasal spray for TRD in that country/region

Refer to Section 6 Dosing and Administration for further details regarding intranasal study medication.

Refer to Section 9.1.5 for information regarding early withdrawal subjects and subjects that are currently in this phase at the time the study is terminated.

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

9.1.4. Induction Phase and Optimization/Maintenance Phase - Study Entry

The following subjects are eligible to enter the study at either the Induction Phase or the Optimization/Maintenance Phase:

- Subjects in ESKETINTRD3003, who at Week 16 of Optimization were not eligible to proceed to the maintenance phase and the sponsor has approved subject's entry into 54135419TRD3008; or
- Subjects in ESKETINTRD3003 and ESKETINTRD3004, who were in the induction phase and (for ESKETINTRD3003, after completion of the induction phase) were determined to not meet response criteria, and sponsor has approved subject's entry into 54135419TRD3008; or
- Subjects in ESKETINTRD3006 (US sites only) who completed the induction phase but did not meet the response criteria, and sponsor has approved subject's entry into 54135419TRD3008.

9.1.5. Early Withdrawal/End of Study Visit

Early Withdrawal

If a subject withdraws before the end of the induction or optimization/maintenance phase for reasons other than withdrawal of consent, an early withdrawal visit should be conducted within 1 week of the last intranasal dose.

If the early withdrawal visit occurs on the same day as a scheduled visit, duplicate assessments are not required.

End of Study Visit

Subjects in the induction phase or optimization/maintenance phase at the time of study termination will have an End of Study visit conducted as the final visit within 1 week of the last intranasal dose.

If the End of Study visit occurs on the same day as a scheduled visit, duplicate assessments are not required.

9.2. Safety Evaluations

Details regarding the IDMC are provided in Section 11.7.

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

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

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

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

Adverse Events

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

Treatment emergent AEs of special interest will be examined separately (please refer to Section 3.2.5 and Section 11.3).

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology and urine samples for urinalysis will be collected. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the CRF. The laboratory reports must be filed with the source documents.

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

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

- **Hematology panel:**

  - hemoglobin
  - hematocrit
  - red blood cell count
  - white blood cell count with differential
  - platelet count

- **Serum chemistry panel:**

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

- **Urinalysis:**

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

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

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

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

- Serum and urine pregnancy testing (for women of childbearing potential only)
- Urine drug screen: barbiturates, methadone, opiates, cocaine, phencyclidine, and amphetamine/methamphetamine
- Alcohol breath test
- Glycosylated hemoglobin (HbA1c) will be monitored only in those subjects with a documented medical history of diabetes
- Serum follicle stimulating hormone (FSH) level test if applicable

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

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

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

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

Tympanic temperature is recommended.

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

Electrocardiogram (ECG)

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

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

The investigator's review of the machine read ECG tracing (provided by the central reader) is considered acceptable in determining if it is appropriate in determining eligibility in cases where initiation of treatment or safety follow-up is time-critical, and where the central cardiology results are not expected to be available before the need to begin dosing, or if actions need to be taken for safety reasons.

All ECG tracings will be sent to the central ECG vendor, where it will be used to determine whether it is appropriate to proceed with dosing.

Pulse Oximetry

Pulse oximetry will be used to measure arterial oxygen saturation. On each dosing day, the device will be attached to the finger, toe, or ear before the first nasal spray and then, after the first spray it will be monitored and documented. Any arterial oxygen saturation (SpO_2) <93% and lasting for more than 2 minutes, and confirmed by an additional measurement on another part of the body, will be reported as an adverse event.

On intranasal treatment session days, pulse oximetry will be recorded predose and every 15 minutes to t=1 hour postdose during the induction phase. During the optimization/maintenance phase, pulse oximetry will be recorded predose and at 30 minutes and 60 minutes postdose on intranasal treatment session days. If oxygen saturation levels are <93% at any time during the

1 hour postdose interval, pulse oximetry will be recorded every 5 minutes until levels return to ≥93% or until the subject is referred for appropriate medical care, if clinically indicated.

Physical Examination and Body Weight

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

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 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.[58] It is a clinical interview providing a summary of both suicidal ideation and behavior that can be administered during any evaluation or risk assessment to identify the level and type of suicidality present. The C-SSRS can also be used during treatment to monitor for clinical worsening.

The 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.

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

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

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 specified days in the T&E, the MOAA/S will be performed every 15 minutes from predose to t=+1 hours postdose.

- If the score is ≤3 at any time during the 1 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 hours post dose).
- If a subject does not have a score of at least 5 at t=+1 hours postdose, they should continue to be monitored. For subjects with a score of 4, the assessment should be repeated every 15 minutes. And for subjects with a score of ≤3, the assessment should be repeated every 5 minutes until the score returns to 5 or the subject is referred for appropriate medical care, if clinically indicated.

Clinical Global Assessment of Discharge Readiness (CGADR)

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

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

On 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.

Cognition Testing

Computerized Cognitive Battery

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

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

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

Hopkins Verbal Learning Test-Revised (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).[4] 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.

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

9.3. Efficacy

9.3.1. Efficacy Evaluations

9.3.1.1. Montgomery-Asberg Depression Rating Scale (MADRS)

The MADRS is a clinician-rated scale designed to measure depression severity and detects changes due to antidepressant treatment.[45] The scale consists of 10 items, each of which is scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), for a total

possible score of 60. Higher scores represent a more severe condition. The MADRS evaluates apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, inability to feel (interest level), pessimistic thoughts, and suicidal thoughts. The test exhibits high inter-rater reliability. The structured interview guide for the MADRS (SIGMA) will be used for each administration.

The typical recall period for the MADRS is 7 days.

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

9.3.1.2. Clinical Global Impression - Severity (CGI-S)

The CGI-S provides an overall clinician-determined summary measure of the severity of the subject's illness that takes into account all available information, including knowledge of the subject's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the subject's ability to function.[26] 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.

The CGI-S will be used to determine intranasal treatment session frequency in the optimization/maintenance phase.

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

The PHQ-9 is a 9-item, patient-reported outcome measure to assess depressive symptoms.[79] The scale scores each of the 9 symptom domains of the DSM-5 MDD criteria and it has been used both as a screening tool and a measure of response to treatment for depression. Each item is rated on a 4-point scale (0=not at all, 1=several days, 2=more than half the days, and 3=nearly every day). The subject's item responses are summed to provide a total score (range of 0 to 27) with higher scores indicating greater severity of depressive symptoms. The recall period is 2 weeks.

9.3.1.4. Sheehan Disability Scale (SDS)

The Sheehan Disability Scale will be used to assess the secondary objective of functional impact and associated disability. The SDS, a patient-reported outcome measure, is a 5 item questionnaire which has been widely used and accepted for assessment of functional impairment and associated disability.[39,67] The first three items assess disruption of (1) work/school, (2) social life, and (3) family life/home responsibilities using a 0-10 rating scale. The score for the first three items are summed to create a total score of 0-30 where a higher score indicates greater impairment. It also has one item on days lost from school or work and one item on days when underproductive. The recall period for this study is 7 days.

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

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome, primarily designed for self-completion by respondents. It consists of the EQ-5D-5L descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each of the 5 dimensions is divided into 5 levels of perceived problems (Level 1 indicating no problem, Level 2 indicating slight problems, Level 3 indicating moderate problems, Level 4 indicating severe problems, and Level 5 indicating extreme problems).[21,22]

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 visual analogue scale self-rating records the respondent's own assessment of his or her overall health status at the time of completion, on a scale of 0 to 100.

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

9.3.1.6. Subject Treatment Satisfaction Scale

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

9.3.1.7. QLDS

The QLDS is a disease specific PRO designed to assess health related quality of life in patients with Major Depressive Disorder.[30,43,72] The instrument has a recall period of "at the moment", contains 34-items with "yes"/"no" response options and takes approximately 5-10 minutes to complete. The score range is from 0 (good quality of life) to 34 (very poor quality of life).

9.4. Medical Resource Utilization

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

9.5. Other Evaluations

9.5.1. Patient Stated-choice Preference Survey

Stated-choice conjoint analysis is a method specifically designed to provide information about an individual's willingness to accept tradeoffs between treatments with multiple outcomes.[34,37,62,63] Preference studies have been performed with patients with depression and other mental

illnesses.[76,71,40] The Patient Stated-choice Preference survey will be used as an exploratory tool to assess the manner and degree to which subjects value or weigh the benefit and harm clinical outcomes associated with Esketamine.

The intent is to have subjects complete the survey after having some experience with Esketamine. The survey will be administered once and only at sites in the United States, Canada, United Kingdom and Australia and only for English speakers. Subjects at any other site, regardless of whether they speak English, will not be surveyed. It is expected that subjects will require 20 to 25 minutes to complete the survey. Since subjects may be in different stages of the trial when the survey becomes available, trial sites should have subjects complete the survey as noted in the T&E schedule. Specifically, the survey should be completed during or shortly after Visit 1.9, or if subjects completed this visit prior to when the survey becomes available, trial sites should have the subject complete the survey at the earliest possible opportunity. Note, for subjects whose point of entry for 54135419TRD3008 is the Open-label Optimization/maintenance phase, the survey should be completed during or shortly after Visit 2.4, or if the subject completed this visit prior to when the survey becomes available, the subject should complete the survey at the earliest possible opportunity. Subjects who completed the Patient Stated-choice Preference survey while enrolled in a prior study (ESKETINTRD3001, ESKETINTRD3002, ESKETINTRD3003, ESKETINTRD3004, or ESKETINTRD3005) should not be issued the survey. The survey should be performed predose (if/when performed on intranasal dosing days).

If the subject indicates a desire to discontinue the study, the subject should be asked to complete the survey by his or her last visit if, in the study coordinator's judgment, the subject will give the survey the required time and attention.

9.6. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the CRF or laboratory requisition form.

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

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

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

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

10.1. Completion

A subject will be considered to have completed the study if he/she is actively participating in the induction or optimization/maintenance phase when one of the following is reached:

- esketamine is approved in the respective country and accessible through the local healthcare system funding or until end of December 2022, whichever is earlier
- the company terminates clinical development of esketamine nasal spray for TRD in that country/region

10.2. Withdrawal from the Study

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

- Lost to follow-up
- Withdrawal of consent (Note: See "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 further study assessments or procedures, another reason for withdrawal should be selected.) Lack of efficacy
- The investigator or sponsor believes (eg, that for safety or tolerability reasons such as an adverse event) it is in the best interest of the subject to discontinue the study. The subject does not meet criteria for continuing into the optimization/maintenance phase at the end of the 54135419TRD3008 induction phase.
- Violation of protocol procedures (determined on a case-by-case basis)
- The subject becomes pregnant
- Death

If a subject discontinues study drug and withdraws from the study before the end of the study, assessments should be obtained. Refer to Section 9.1.5 for further information on the EW or End of Study Visit.

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

If 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 prior to dosing. In addition, the study site should emphasize the importance of follow-up information to the subject prior to dosing. The measures taken to follow up must be documented.

When a subject withdraws, the reason for withdrawal is to be documented in the CRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject.

Withdrawal of Consent

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

Subjects who wish to withdraw from the study should be asked if they are agreeable to be contacted for further follow up (eg, early withdrawal visit, adverse event follow up). 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 are agreeable to be contacted for follow up will be withdrawn from the study 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).

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

11.1. Subject Information

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

- Full Analysis Set for Induction phase: will be defined as all subjects who receive at least one dose of esketamine nasal spray during this phase.
- Full Analysis Set for Optimization/Maintenance phase: will be defined as all subjects who receive at least one dose of esketamine nasal spray during this phase.

11.2. Sample Size Determination

No formal sample size calculation was performed as only subjects who have participated in the other Phase 3 studies may participate in this study.

11.3. Safety Analyses

Safety data for the induction phase and the optimization/maintenance phase will be presented separately for each phase as well as for the entire treatment period (induction and optimization/maintenance phase). The baseline for safety assessments will be defined in the Statistical Analysis Plan.

Cognitive Function

Computerized cognitive test battery and HVLT-R: Descriptive statistics of each of the cognitive domain scores and changes from baseline will be provided at each scheduled time point.

Adverse Events

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

Treatment emergent AEs of special interest will be examined separately grouped in the following categories: drug abuse, dependence and withdrawal, increased blood pressure, increased heart rate, transient dizziness/vertigo, impaired cognition, cystitis, anxiety, events potentially related to suicidality, hepatic adverse events, events related to renal disorders, and symptoms of dissociation persisting beyond the typical ≤2 hour post esketamine administration, as well as delirium, psychosis or mania.

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

Vital Signs

Descriptive statistics of body weight, temperature, pulse/heart rate, respiratory rate, pulse oximetry and supine blood pressure (systolic and diastolic) values and changes from baseline will be provided at each scheduled time point. Any treatment-emergent abnormalities will be listed.

Clinical Laboratory Tests

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

Electrocardiogram (ECG)

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

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

The ECG variables that will be analyzed are heart rate, PR interval, QRS interval, QT interval, and QT interval corrected (QTc) according to Bazett's formula (QTcB) and Fridericia's formula (QTcF).[3,65]

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).

C-SSRS

Suicide-related thoughts and behaviors based on the C-SSRS will be summarized in incidence and shift tables. Separate endpoints for suicidal ideation and suicidal behavior will be defined and summarized descriptively.

Other Safety and Tolerability Questionnaires and Assessments

CGDAR and MOAA/S: Descriptive statistics of scores and their changes (and/or percent changes) from predose or baseline will be summarized at each scheduled time point.

11.4. Efficacy Analyses

Depression symptoms using the MADRS as well as a patient reported outcome (PHQ-9), global change in severity (CGI-S), social, occupational and family functioning related disability (SDS), depression specific health related quality of life (QLDS), and health related quality of life and health status (EQ-5D-5L) will be summarized descriptively at each scheduled visit for each phase, using both last observation carried forward and observed case data. The proportion of subjects who are responders (≥50% improvement from baseline) based on the MADRS total score and PHQ-9 total score and the proportion of subjects who remitted based on the MADRS total score (MADRS total score ≤12) and the PHQ-9 total score (PHQ-9 total score <5) will be provided over time for each phase.

For subjects who had relapsed in ESKETINTRD3003 and participated in a second induction treatment phase, the proportion of responders (≥50% improvement from baseline) and remitters using the MADRS total score (MADRS total score ≤12) and PHQ-9 total score (PHQ-9 total score <5) at the end of the second induction phase will be provided. Subject treatment satisfaction

questionnaire for medication (TSQM-9) will be summarized descriptively at each scheduled visit for each phase.

11.5. Medical Resource Utilization Analysis

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

11.6. Patient Stated-choice Preference Survey

The stated-choice preference survey will be used as an exploratory tool to assess the manner and degree to which esketamine study subjects value or weigh the clinical outcomes associated with Esketamine.

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

11.7. Independent Data Monitoring Committee

An IDMC will be established to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study. The committee will meet approximately every 6 months to review select safety data through the end of 2020. After the reviews, the IDMC will make recommendations regarding the continuation of the study. The details will be provided in a separate IDMC charter.

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

12. ADVERSE EVENT REPORTING

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

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

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

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

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

Serious Adverse Event

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

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

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

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis), the event must be

reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

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

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

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

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.

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. 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 CRF. 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 CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

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

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

12.3.2. Serious Adverse Events

All SAEs, as well as PQC, 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.

Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

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 CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.
- For convenience the investigator may choose to hospitalize the subject for the duration of the treatment period.

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

12.3.3. Pregnancy

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

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

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

12.4. Contacting Sponsor Regarding Safety

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

13. PRODUCT QUALITY COMPLAINT HANDLING

Definition

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, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system. 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.

A sample of the suspected product should be maintained under the correct storage conditions until a shipment request is received from the sponsor.

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

13.2. Contacting Sponsor Regarding Product Quality

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

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drugs

14.1.1. Intranasal Study Drug

The esketamine supplied for this study is formulated 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 mcl spray. Each individual nasal spray pump (device) contains a total of 28 mg (ie, 2 sprays).

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

14.2. Packaging

Intranasal Study Drug

Study drug (ie, esketamine nasal spray) will be supplied by the sponsor in a bi-dose nasal spray device. The devices will contain 230 µL (of which ~30µL is the residual volume). Each device delivers 16.14 mg esketamine hydrochloride (14 mg esketamine base).

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.

14.3. Labeling

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

14.4. Preparation, Handling, and Storage

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

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

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

14.5. Drug Accountability

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

The study drug administered to the subject must be documented on the drug accountability form. The study drug will be stored and disposed of according to the sponsor's instructions.

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 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.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinical study site pharmacist. Study drug will be supplied only to subjects participating in the study. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator's Brochure for esketamine
- Investigational Product (IP) Binder, including the IP Procedures investigational product procedures manual
- Laboratory manual and materials
- Clinician-administered and subject-completed/patient-reported outcomes assessments
    - Paper versions, as applicable
    - Electronic devices and associated materials
- IWRS Manual
- ECG equipment and associated materials (eg, manual)
- Instructions for Use documents (subject and healthcare provider versions) for intranasal study medication
- Computerized cognitive battery and HVLT-R, and all associated equipment and materials
- Device to measure respiratory rate
- Guidance on recommended order of study procedures
- Guidance on required equipment for supportive ventilation and resuscitation will be provided in a separate document.

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Clinical Study in Treatment-resistant Major Depression

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

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

Selection of Subjects

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

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which

they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

All subjects will be from Phase 3 studies ESKETINTRD3001, ESKETINTRD3002, ESKETINTRD3003, ESKETINTRD3004, ESKETINTRD3005, and ESKETINTRD3006 (US Sites only).

For subjects who have participated in the ESKETINTRD3003, ESKETINTRD3004, and ESKETINTRD3005 studies and have responded to esketamine nasal spray treatment or did not meet the study criteria for response but per clinical judgment have benefitted, it is considered an ethical obligation to provide continued esketamine nasal spray treatment if the benefit/risk profile is favorable for the subject at the time of completion of the previous study.

For subjects who have completed the induction phase of ESKETINTRD3005 or ESKETINTRD3006 (US sites only) and did not meet the study criteria for response, or for subjects who have completed the induction phase and 2-week follow up phase visit of the ESKETINTRD3001 or ESKETINTRD3002 study, as the double-blind treatment (esketamine nasal spray or placebo) in these studies will be blinded, the second induction phase of this study provides the following:

- Subjects who are non-responders to intranasal placebo and oral antidepressant in the prior study have the potential of receiving esketamine in this study, and
- Subjects who are non-responders to esketamine nasal spray in the prior study who decide to participate in this study may not benefit from additional treatment with esketamine nasal spray. The benefit of additional treatment with esketamine remains unknown. In case of no perceived benefit of esketamine nasal spray to the subject during this study, the subject and/or investigator may choose to discontinue study participation.

Subjects from ESKETINTRD3001, ESKETINTRD3002, and ESKETINTRD3005 who were responders to intranasal placebo and oral antidepressant but did not participate in the subsequent available study (eg, ESKETINTRD3003 and ESKETINTRD3004 study, respectively): may or may not benefit from additional treatment with esketamine nasal spray. Any additional benefit of treatment with esketamine nasal spray remains unknown. In case of no perceived benefit of esketamine nasal spray to the subject during this study, the subject and/or investigator may choose to discontinue study participation. At any time during the study, subjects may discontinue and appropriate follow-up care will be arranged.

Precautions to Ensure Subject Safety in the Study

Subjects may participate in the study only if they have adequate capacity to give consent and after fully understanding the potential risks and giving an informed consent. Determination of capacity will be made by the study investigator. Subjects may discontinue the study at any time. Potential disadvantages and adverse events of participating in the study and alternative treatment options will be discussed. For subjects who do not meet predefined response criteria during the study, clinical care will be arranged between the subject and the study investigator and/or the subject's physician.

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

Subjects will be carefully monitored during the study and subjects who are unable to tolerate study drugs will be discontinued from the study. If the investigator judges it to be necessary to immediately stop study drug, he or she has the option to do so. Specific guidance is provided regarding blood pressure monitoring on dosing days (see Section 6.1).

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 throughout the study participation is variable due to the nature of the study design and 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, unless required locally), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

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

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

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

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

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

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. It also denotes that the subject agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, 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.

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.

16.2.5. 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/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 listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

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

17.2.2. Required Prestudy Documentation

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

- Protocol and amendment(s), if any, signed and dated by the principal investigator

- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

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

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.3. Subject Identification, Enrollment, and Screening Logs

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

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

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

17.4. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care, must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

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

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

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

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

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries
- Antidepressant treatment in the current episode of depression

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by subject interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If an electronic source is utilized, references made to the CRF in the protocol include the electronic source system but information collected through the electronic source may not be limited to that found in the CRF. Data in this system may be considered source documentation.

17.5. Case Report Form Completion

Case report forms are provided by the sponsor 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.

The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

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

If necessary, queries will be generated in the electronic data capture (eDC) tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done 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 CRF completion will be provided and reviewed with study-site personnel before the start of the study.

The sponsor will review CRFs 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 CRFs 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 CRFs with the source documents (eg, hospital/clinic/physician's office medical records); a sample will be reviewed. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data in the CRF are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, the monitor may contact the site by telephone for an update on study progress. It is expected that study -site personnel will be available to provide an update on the progress of the study at the site.

17.9. Study Completion/Termination

17.9.1. Study Completion

The end of the study will occur based on the subject's individual efficacy and tolerability to esketamine nasal spray, and/or until esketamine is approved in the respective country and accessible through the local healthcare system funding or until end of December 2022, whichever is earlier.

Study participation will be stopped:

- when esketamine is approved in the respective country and accessible through the local healthcare system funding or until end of December 2022, whichever is earlier; or
- the subject no longer benefits from further treatment (based on the investigator's clinical judgment), or withdraws consent; or
- the company terminates clinical development of esketamine nasal spray for TRD in that country/region

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

17.9.2. Study Termination

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

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

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

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

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding esketamine or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of esketamine, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which

state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

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Attachment 1: Prohibited Concomitant Medications with Esketamine Nasal Spray Study Medication

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 non-study medications 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 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
Anorexiants (eg, phentermine, phendimetrazine)	N	N		Safety
Anticholinesterase inhibitors	N	N		Subject population is excluded
Anticonvulsants	Y	Y	– Subjects with seizures are excluded. Note: Anticonvulsants used for indications other than seizures may be allowed (eg valproate for migraine; pregabalin)	Safety and PD interaction
MAO-I Antidepressants	N	N	There must be a minimum washout interval of 2 weeks prior to the first dose of intranasal study medication and MAO-I antidepressants are prohibited throughout the study.	Safety
Antipsychotics	N	Y		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

Drug Class	Episodic Use (as needed)	Continuous Use	Comments	Reason for Prohibition
Benztropine	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	Inhaled, intranasal, topical, and ophthalmic steroids are not prohibited. Intermittent IM/IV/PO corticosteroids are permitted with sponsor approval (chronic use prohibited).	PD interaction
Cough/cold preparations/nasal solutions containing vasoconstrictors, decongestants	Y	Y	Intranasally-administered decongestants (vasoconstrictors) should not be used from 1 hour prior to each intranasal study medication administration. Pseudoephedrine- containing products should not be used within 12 hours prior to an intranasal treatment session.	Safety and PD interaction
CYP3A4 inducers - Potent	N	N	Subjects may not take a known potent inducer of hepatic CYP3A activity within 2 weeks of the first administration of intranasal study medication until at least 24 hours after the last intranasal dose of study medication. Examples (not all-inclusive): Efavirenz, nevirapine, barbiturates, carbamazepine, glucocorticoids, modafinil, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort	PK
Dextromethorphan	N	N		PD interaction
Diphenhydramine	Y	N	Prohibited within 12 hours prior to the start of each intranasal treatment session	Safety
Ketanserin	N	N		Safety
Memantine	N	N		PD interaction
Methyldopa	N	N		Safety and PD Interaction
Metyrosine	N	N		Safety and PD interaction

Drug Class	Episodic Use (as needed)	Continuous Use	Comments	Reason for Prohibition
Non-vitamin K antagonist oral anticoagulation agents (eg, dabigatran, rivaroxaban, apixaban)	N	N		Safety
Opioids	N	N	With Sponsor approval, brief treatment with opiates may be allowed for treatment of acute injuries, etc.	PD interaction
Psychostimulants (eg, amphetamines, methylphenidate)	N	Y	Prescribed psychostimulants can be continued or newly initiated 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
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: ADHD, attention deficit hyperactivity disorder; N, Prohibited; PD, pharmacodynamics; PK, pharmacokinetics; Y, Permitted, with restrictions (please refer to the column labeled “Comments” for additional guidance).

INVESTIGATOR AGREEMENT

JNJ-54135419 (esketamine)
Clinical Protocol 54135419TRD3008 Amendment 4

INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

Signature: PPD Date: PPD
(Day Month Year)

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

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Janssen Research & Development *

Clinical Protocol

COVID-19 Appendix

Protocol Title
An Open-label Long-term Extension Safety Study of Esketamine Nasal Spray in Treatment-resistant Depression

Safety and Sustenance of Esketamine Treatment Response With Repeated Doses at Intervals Determined by Symptom Severity

SUSTAIN-3

Protocol 54135419TRD3008; Phase 3

JNJ-54135419 (esketamine)

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

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

Status: Approved
Date: 19 June 2020
Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-RIM-37289, 2.0

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL

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

COVID-19 APPENDIX

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

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

In alignment with recent health authority guidance, the sponsor is providing temporary options for study-related subject management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of subjects and site staff. If, at any time, a subject's safety is considered by the investigator to be at risk, study treatment may be discontinued after discussion with the sponsor, and study follow-up will be conducted according to GUIDANCE SPECIFIC TO THIS PROTOCOL.

Re-consenting of subjects will be performed (including remote consenting by phone or video consultation) as applicable for the measures taken and according to local guidance for informed consent applicable during the COVID-19 pandemic.

Every effort should be made to adhere to protocol-specified assessments for subjects on study treatment. Modifications to protocol-required assessments may be permitted in accordance with this Appendix after consultation with the subject, investigator, and the sponsor. Missed assessments/visits will be captured in the clinical trial management system (CTMS) for protocol deviations.

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a subject has tested positive for COVID 19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic will be summarized in the clinical study report.

GUIDANCE SPECIFIC TO THIS PROTOCOL

These provisions are meant to minimize the risk of exposure to COVID-19 and to safely maintain subjects on study treatment while site capabilities are compromised by COVID-19-related restrictions. As restrictions are lifted and the acute phase of the COVID-19 pandemic resolves, sites should revert to original protocol conduct as soon as feasible.

At each contact, subjects will be interviewed to collect safety data. Subjects will also be questioned regarding general health status to fulfill any physical examination requirement.

Evaluate the subject's situation on a case by case basis and contact the study responsible physician for discussion and decision if necessary. Certain measures, such as those listed below, may be necessary and should be instituted in accordance with applicable (including local) laws, regulations, guidelines, and procedures.

- The safety of study subjects is priority; investigators may make the decision to provide other available therapy to patients on the study. Please discuss any decision to provide other therapy outside of the protocol with the study responsible physician and ensure that this is recorded in the source document and the case report form (CRF) along with reason for administration.
- Dosing frequency can change based upon the Clinical Global Impression-Severity (CGI-S) score, or investigator's clinical judgement after discussion with the study responsible physician. Please refer to the "Regular Dosing Visits" section for additional information.

Reminder: missed esketamine dosing of itself does not result in withdrawal from the study, and treatment can resume if considered beneficial per clinical judgement.

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

Regular Dosing Visits

In the event that it is not feasible for the subject to be assessed and dosed at the study site (eg, due to temporary site closure), the following options may be used on a temporary basis after consultation with the sponsor and with the agreement of the subject and investigator:

- Administer at an alternative location (to include the equipment/supplies needed for the care/treatment of a subject post dose) in the vicinity of the site, with the subject remaining there during post dose observation period, after consultation with the sponsor and under the supervision of site staff;
- Continue administering study treatment within the study site, with adjustments for temporary changes in dates/hours site is open for study subjects;
- Administer at alternative TRD3008 study site (data to stay with primary study site) after consultation with the sponsor (at which time specific guidance on the process will be provided) and if permitted by local regulations;

- Complete clinical and subject rating scales the day prior to dosing via phone or video conference.

Missed doses should be documented in the CRF in accordance with the CRF completion guidelines.

Non-dosing Days

- Rating scales/ safety assessments can be completed remotely (via phone or video conference).
- Missed/ out of window assessments should be documented with "COVID-19-related" in the comment section of the CRF.
- It is recommended that close contact be maintained with study subjects and remote contact arranged consistent with the subject's regularly scheduled visit interval.
  - If the subject is on weekly dosing, attempt to contact the subject weekly.
  - If the subject is on dosing every other week or every 4 weeks, attempt to contact the subject every other week.

Study subjects who show worsening or who are at high risk for relapse may require more frequent monitoring as per investigator discretion.

Laboratory Assessments

If laboratory samples cannot be collected by Covance, sample collection and analysis can be performed using the site's local laboratory at the discretion of the investigator.

- Local laboratory results should be reviewed to confirm if any significant changes should be added as AEs in the eCRF.
- If the investigator does not feel laboratory assessments are required at this time, and subject(s) want to avoid any risk to COVID-19 exposure, this rationale should be documented in the source documents.

Exposure to COVID-19

- If a subject develops COVID-19 infection (or suspected), the PI should contact the sponsor's Medical Monitor to discuss the best course of action based on individual symptoms/ subject setting and risk benefit relationship.

Data Collection

- For clinician-completed (MADRS, C-SSRS, CGI-S, PWC-20 [(France only], HRUQ) and subject-completed (PHQ-9, SDS, EQ-5D-5L, TSQM-9, QLDS)[a] scale assessments conducted by a telephone contact, the data should be entered directly onto the paper assessment. Ensure that the correct date is present on the assessment form in the CRF, or enter remote assessments as Unscheduled if the assessments were performed on another day as the visit day.
- For missed doses, the dosing form should be inactivated and a "COVID-19 related" comment entered on the Comments form.
- All COVID-19-related deviations from the main study protocol will be documented according to the CRF completion guidelines.

Statistical Analysis

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

[a] C-SSRS= Columbia Suicide Severity Rating Scale; CGI-S= Clinical Global Impression – Severity; EQ-5D-5L= European Quality of Life (EuroQol) Group, 5-Dimension, 5-Level; HRUQ= Healthcare Resource Use Questionnaire; MADRS= Montgomery-Asberg Depression Rating Scale; PHQ-9= Patient Health Questionnaire, 9-Item; PWC= Physician Withdrawal Checklist; QLDS= Quality of Life in Depression Scale; SDS= Sheehan Disability Scale; TSQM-9= Treatment Satisfaction Questionnaire for Medication, 9-item.

INVESTIGATOR AGREEMENT

COVID-19 Appendix
JNJ-54135419 (esketamine)
Clinical Protocol 54135419TRD3008

INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

Signature: PPD Date: PPD

(Day Month Year)

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