**Janssen EMEA***

**Clinical Protocol**

# Open-label Long-Term Extension Study for Participants With Treatment-Resistant Major Depressive Disorder Who are Continuing Esketamine Nasal Spray Treatment From Study 54135419TRD3013

## ESCAPE-LTE

## Open-label Extension Study to Assess Long-term Safety of Esketamine Nasal Spray

**Protocol 54135419TRD4010; Phase 4**
**Amendment 1**

**JNJ-54135419 (esketamine)**

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

## PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

| DOCUMENT HISTORY | |
|---|---|
| **Document** | **Date** |
| Amendment 1 | 2 September 2022 |
| Original Protocol | 20 January 2021 |

Changes implemented in the current amendment are summarized in the table below.

### Amendment 1 (2 September 2022)

**Overall Rationale for the Amendment:** To indicate that the bicarbonate assay (one of the protocol-required clinical laboratory safety tests) is optional, to reduce patient burden. In addition, the window during which the additional assessment of MADRS total score can be evaluated to confirm relapse is widened (from '14 to 28 days' to '5 to 31 days) to allow greater patient flexibility with undertaking this additional assessment and to align with the parent study (54135419TRD3013) and a previous relapse prevention study.

| | **Section Number and Name** | **Description of Change** |
|---|---|---|
| 1 | 1.3 Schedule of Activities (SoA); 10.8 Appendix 8 Clinical Laboratory Tests. | Added text to Footnote k of the SoA and the table of clinical chemistry tests in Appendix 8 to indicate that the bicarbonate assay is optional. |
| | **Brief Rationale:** From a clinical perspective, missing the bicarbonate assay in this long-term extension study does not significantly alter the evaluation of clinical safety.<br>Participants have been receiving esketamine within the parent study, in which no clinically meaningful changes in bicarbonate test have been noted. Additionally, there were no clinically meaningful changes observed in mean laboratory analytes after esketamine treatment in any of the completed esketamine Phase 1 to 4 studies. Furthermore, the bicarbonate assay is not part of routine clinical lab testing, and some countries in which sites are active do not have the capability to perform this test locally.<br>Therefore, to reduce the burden for patients and address the challenges with nonavailability of the bicarbonate assay at some sites, it is considered reasonable for this test to be optional for all patients. | |
| 2 | 1.1 Synopsis; 1.3 Schedule of Activities (SoA) (footnote j); 3 Objectives and Endpoints; 8.1.1.1 Montgomery-Asberg Depression Rating Scale (MADRS). | Increased the window during which the additional assessment of MADRS total score can be evaluated to confirm relapse from 'within the next 14 to 28 days' to 'within the next 5 to 31 days. |
| | **Brief Rationale:** The widening of the window for additional assessment of MADRS total score to confirm relapse is introduced to allow greater patient flexibility with undertaking this additional assessment. This change also aligns with the parent study and a previous relapse prevention study, in which the 2 consecutive MADRS assessments should be separated by 5 to 15 days, as well as accommodating the 3-day visit window around the scheduled efficacy assessment. There is no clinical reason why this extension to the window should affect the likelihood of a higher or lower MADRS score. | |
| | Throughout the protocol. | Minor edits and formatting changes made. |

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# 1. PROTOCOL SUMMARY

## 1.1. Synopsis

Open-label Long-Term Extension Study for Participants With Treatment-Resistant Major Depressive Disorder Who are Continuing Esketamine Nasal Spray Treatment From Study 54135419TRD3013

Open-label Extension Study to Assess Long-term Safety of Esketamine Nasal Spray

Esketamine hydrochloride (HCl) is referred to as JNJ-54135419-AAC. Esketamine is a nonselective, noncompetitive antagonist of the N-methyl-D-aspartate receptor (NMDAR), an ionotropic glutamate receptor. Through NMDAR antagonism, esketamine produces a transient increase in glutamate release leading to increases in α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR) stimulation and subsequently to increases in neurotrophic signaling that restore synaptic function in these mood regulatory brain regions. Esketamine nasal spray is indicated for use in combination with a selective serotonin reuptake inhibitor (SSRI)/ serotonin-norepinephrine reuptake inhibitor (SNRI) to treat adults with treatment-resistant major depressive disorder (MDD). Esketamine nasal spray has also been approved by the United States Food and Drug Administration for MDD with acute suicidal ideation or behavior.

**OBJECTIVES AND ENDPOINTS**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| To assess the long-term safety and tolerability of esketamine nasal spray in combination with an SSRI/SNRI in participants who have completed 32 weeks of esketamine nasal spray treatment in Study TRD3013. | Intervention-emergent adverse events (AEs), including intervention-emergent AEs of special interest<br><br>Suicidal ideation and behavior: Columbia-Suicide Severity Rating Scale (C-SSRS) |
| **Secondary** | |
| • To assess the long-term efficacy of esketamine nasal spray in combination with an SSRI/SNRI based on the proportion of participants being relapse-free at Week 104 (or end-of-study). | No relapse until the end of the prospective observation period at Week 104 visit (or end-of-study).<br><br>A relapse is defined by any of the following:<br><br>a) Worsening of depressive symptoms as indicated by Montgomery-Asberg Depression Rating Scale (MADRS) total score ≥22 confirmed by 1 additional assessment of MADRS total score ≥22 within the next 5 to 31 days. The date of the second MADRS assessment will be used for the date of relapse.<br>b) Any psychiatric hospitalization for<br>– worsening of depression<br>– suicide prevention or due to a suicide attempt<br>for any of these events, the start date of hospitalization will be used for the date of relapse.<br>c) Suicide attempt, completed suicide, or any other clinically relevant event determined per the investigator's clinical judgment to be indicative |

| Objectives | Endpoints |
|---|---|
| | of a relapse of depressive illness, but for which the participant was not hospitalized. The onset of the event will be used for the date of relapse.<br>In case more than 1 of the relapse criteria are met, the earliest date will be defined as the date of relapse for that participant. |
| To assess the effect of esketamine nasal spray in combination with an SSRI/SNRI on:<br>• Clinician-rated overall severity of depressive illness<br>• Participant-reported depressive symptoms<br>• Participant-reported health-related quality of life and health status | Change from baseline in Study TRD3013 at all visits for the following scale scores:<br>• Clinician-rated MADRS:<br>– Overall severity of depressive illness (total score)<br>– Depressive symptoms (individual items)<br>• Clinician-rated overall severity of depressive illness:<br>– Clinical Global Impression – Severity (CGI-S)<br>• Participant-reported depressive symptoms: Patient Health Questionnaire 9-item (PHQ-9)<br>• Participant-reported European Quality of Life (EuroQoL) Group, 5-Dimension, 5-Level (EQ-5D-5L) questionnaire |
| **Exploratory** | |
| To assess the impact of switching the oral antidepressant (AD) with another compound from the SSRI/SNRI classes, in cases where the oral AD is switched due to tolerability | • Reason for switching the oral AD<br>• Impact on adverse events present at the time of the switch<br>• Adverse events starting after the switch<br>• Impact on MADRS and CGI-S |

**Hypothesis**

Due to the design of the study (single-arm, long-term extension) and the objective (exploratory nature) no hypothesis is described for this study.

## OVERALL DESIGN

This study is a single-arm, 2-year open-label extension to Study TRD3013, which is an open-label, randomized, active-controlled study to evaluate the efficacy, safety, and tolerability of flexibly dosed esketamine nasal spray compared with quetiapine extended release, both in combination with a continuing SSRI/SNRI, in participants 18 to 74 years of age, inclusive, with treatment-resistant MDD. Participants who were randomly assigned to the esketamine arm in Study TRD3013, had esketamine nasal spray administered through Week 30 (every 2 week dosing) or Week 31 (once weekly dosing), completed the maintenance phase at Week 32, continue to benefit from esketamine nasal spray in combination with a continuing SSRI/SNRI in the opinion of the investigator, and commercial esketamine nasal spray is not accessible to them in their country, will be eligible to enter this open-label extension study (Study TRD4010). The end of study is considered as the last visit for the last participant in the study.

Informed consent may be obtained from participants at any time in the 4 weeks before Day 1 (ie, at or after Week 28 visit in Study TRD3013). It is the investigator's responsibility to contact the sponsor to request esketamine nasal spray supply for participants who will enroll in the long-term extension study. On Day 1 (Week 32 visit of Study TRD3013), participants who consented and are eligible will enter the 2-year open-label extension study. If a participant cannot receive the esketamine nasal spray dose on the same day as the Week 32 visit in Study TRD3013, the participant may be enrolled in this study (TRD4010) as long as they continue their current SSRI/SNRI and receive their first dose of esketamine nasal spray within 14 days of the Study TRD3013 Week 32 visit date; Day 1 of this study will be the day of the esketamine nasal spray dose.

Participants will attend site visits once weekly or every 2 weeks, depending on their dosing frequency, for administration of esketamine nasal spray. All participants will have a safety follow-up visit 2 weeks (±2 days) after the last nasal treatment session.

Safety, efficacy, and other assessments will be performed according to the Schedule of Activities, with additional assessments to be added at the discretion of the investigator as deemed necessary, per usual clinical practice.

At any point during the long-term extension study, participants who, in the opinion of the investigator, are no longer benefiting from treatment with esketamine nasal spray in combination with an SSRI/SNRI should be discontinued from the study; these participants will complete the early study withdrawal visit and then return for the safety follow-up visit 2 weeks (±2 days) after their last dose of esketamine nasal spray, unless they withdraw consent, are lost to follow-up, or have died.

Participants will have access to esketamine nasal spray for a maximum of 2 years during this study. If esketamine nasal spray becomes accessible locally before the 2 year endpoint, then participants will be considered as having completed the open-label extension study and will be switched to a commercially available supply if in the opinion of the treating physician, the participant continues to benefit from treatment and the participant wishes to continue the esketamine nasal spray treatment. Once esketamine nasal spray becomes accessible in a given country, all participants in the long-term extension study will be discontinued at all sites in that country. Study site personnel will notify participants of study termination and schedule an end-of-study visit with each participant.

**NUMBER OF PARTICIPANTS**

The total number of participants to be enrolled will depend on the number of countries that participate in the study and the number of participants receiving esketamine nasal spray who complete through Week 32 in Study TRD3013. It is expected that from 100 to 200 participants will be enrolled in this study.

**INTERVENTION GROUPS AND DURATION**

Study intervention: The dosage of esketamine nasal spray in this long-term extension study will be determined based on the participant's dose (28 mg [elderly participants ≥65 years of age and adults of Japanese ancestry], 56 mg, or 84 mg) and frequency (once weekly or every 2 weeks) at completion of the maintenance phase (Week 32) of Study TRD3013. Investigators will be allowed to change the dose and frequency during the open-label extension study based on clinical judgment.

Background medication: The continuing SSRI/SNRI dose should have been optimized up to the maximum tolerated dose during Study TRD3013 as per the respective Summary of Product Characteristics (SmPC; or local equivalent, if applicable). During the long-term extension study, a stable dose should be maintained; however, dose modifications to the continuing SSRI/SNRI may be made, if necessary, at the investigator's discretion. Additionally, during the long-term extension study, the SSRI/SNRI may be switched for individual participants by the investigator for tolerability issues. The newly prescribed SSRI/SNRI must be labeled for treatment of depression/MDD in their country of participation and the dosage being taken should be according to the respective SmPC (or local equivalent, if applicable). Off-label use of an SSRI/SNRI is

not permitted. The switch of a participant's SSRI/SNRI should occur at an "every 4 week visit" so that clinician-rated scales and patient-reported outcomes (PROs) are captured prior to the switch; the reason for the switch must be documented in the electronic case report form. If the SSRI/SNRI is discontinued at any time during the study, the esketamine nasal spray must also be discontinued and the participant will be withdrawn from the study.

Study participation will continue for up to a maximum of 2 years (104 weeks), or until esketamine nasal spray becomes accessible in the participant's local country, whichever occurs first.

**EFFICACY EVALUATIONS**

Efficacy will be assessed using clinician-rated scales (MADRS and CGI-S) and PROs (PH-9 and EQ-5D-5L). The MADRS will be performed by a qualified rater who has sufficient qualifications as documented by experience or training. If possible, for individual participants, the independent rater from Study TRD3013 may continue performing the MADRS in this study. To avoid interrater variability, all efforts should be made to have the same rater rating the same study participants as much as possible.

**SAFETY EVALUATIONS**

Safety assessments include the monitoring of adverse events, measurement of body weight, vital sign measurements, clinical laboratory tests, and pregnancy testing. Suicide risk will also be assessed throughout the study using the C-SSRS.

**STATISTICAL METHODS**

As no hypothesis is specified for this study, no sample size estimation is performed. Sample size will be driven by pragmatic considerations. It is expected that 100 to 200 participants will be enrolled in this study.

Descriptive analyses will be performed on the Safety/Efficacy analysis set.

All continuous variables will be summarized using descriptive statistics, which will include the number of participants, mean, standard deviation, median, minimum, maximum, and 95% confidence interval. All categorical variables will be summarized using frequencies and percentages. Distribution of time-to-event variables will be estimated using standard survival analysis methods, including Kaplan-Meier product-limit survival curves. The median time to event with 2-sided 95% confidence intervals will be estimated.

For continuous/ordinal parameters (eg, MADRS, CGI-S, PHQ-9, EQ-5D-5L) descriptive statistics of the observed values and change from Study TRD3013 baseline will be provided for each study visit. For categorical/dichotomous parameters descriptive statistics of the observed score will be provided for each study visit.

**Primary Endpoint Analyses**

All reported intervention-emergent adverse events will be included in the analysis. For each adverse event, the percentage of participants who experience at least 1 occurrence of the given event will be summarized.

Intervention-emergent AEs of special interest will be summarized separately grouped by category (sedation, dissociation, events suggestive of abuse potential, cystitis, hepatic impairment, and suicidality (including suicidal ideation and behavior).

The 10 items of the C-SSRS and the derived endpoints (Suicidal ideation, Suicidal behavior, Suicidal ideation or behavior, Suicidal ideation score) will be summarized as frequency distributions for each assessment during treatment.

**Secondary Endpoint Analyses**

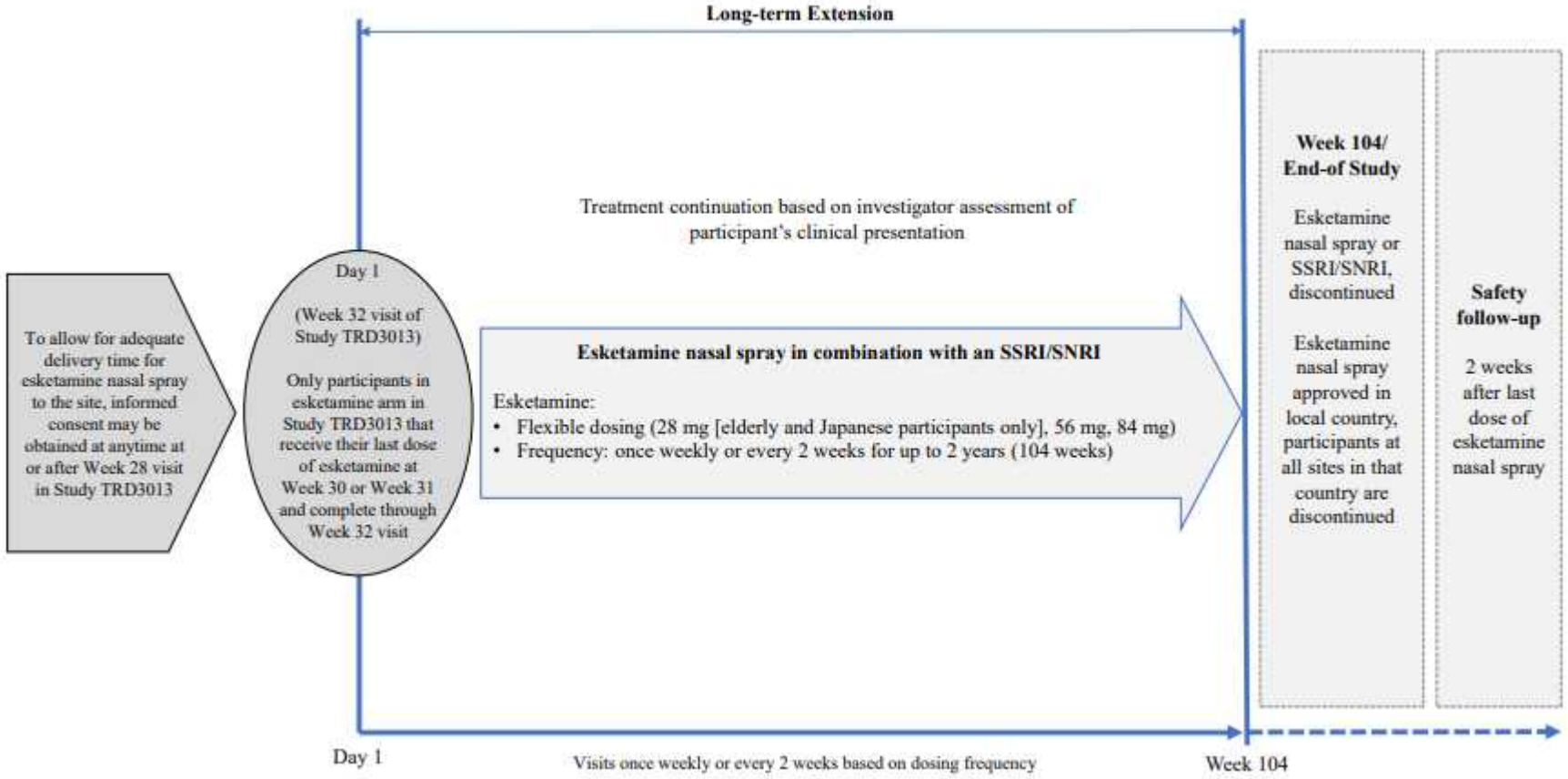
For the MADRS (total and individual scores), CGI-S, and the PHQ-9 (total score), the scale score and changes from Study TRD3013 baseline will be analyzed by study visit.

Frequency of relapse and time to relapse will be described.

For the EQ5D-Health-Utility and the EQ5D-VAS, the score and changes from Study TRD3013 baseline will be analyzed by study visit.

## 1.2. Schema

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



## 1.3. Schedule of Activities (SoA)

| | | Long-term Extension Phase | | | | |
|---|---|---|---|---|---|---|
| | Day 1[a] | ESK Dosing: Once Weekly or Every 2 Weeks | Every 4 Weeks | Every 24 Weeks | Week 104/ End-of-Study[b,c,d]/ Early Study Withdrawal Visit[e] | Safety follow-up visit[f] |
| **Visit Window (Days)** | +14 | ±3 | ±3 | ±3 | ±3 | ±2 |
| **Administrative Procedures** | | | | | | |
| Informed consent | X[g] | | | | | |
| Inclusion/exclusion criteria | X | | | | | |
| **Patient-reported outcomes[h]** | | | | | | |
| PHQ-9 | | | X | | X | |
| EQ-5D-5L | | | X | | X | |
| **Clinician-rated scales and questionnaires[i]** | | | | | | |
| MADRS: efficacy assessment | | | X[j] | | X | |
| CGI-S | | | X | | X | |
| C-SSRS (Since Last Visit version) | | | X | | X | |
| **Safety assessments** | | | | | | |
| Hematology/chemistry, urinalysis (local)[k] | | | | X | X | X |
| Pregnancy testing[l] | | | X | | X | X |
| Body weight | | | | | X | |
| Nasal examination predose[m] | X | X | | | X[n] | |
| Vital signs predose[o] | X | X | | | X[n] | |
| Vital signs postdose[o,p] | X | X | | | X[n] | |
| Vital signs[o,q] | | | | | X[r] | X |
| **Study intervention procedures** | | | | | | |
| Nasal treatment sessions[s,t] | X | X[u] | | | X[c] | |
| Drug accountability: esketamine | X | X | | | X[c] | |
| Medication compliance counseling (SSRI/SNRI)[v] | X | X | | | | |
| **Ongoing** | | | | | | |
| Concomitant therapy/psychotherapy | X | X | | | X | X |
| Adverse events | X | X | | | X | X |

Abbreviations: C-SSRS=Columbia-Suicide Severity Rating Scale; CGI-S= Clinical Global Impression – Severity; eCRF=electronic case report form; EQ-5D-5L=European Quality of Life Group, 5 dimension, 5-level (questionnaire); MADRS=Montgomery-Asberg Depression Rating Scale; MDD=major depressive disorder; PHQ-9=Patient Health Questionnaire – 9; PRO=patient-reported outcome; SmPC=Summary of Product Characteristics; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor.

[a] Day 1 **should** be the same day as Week 32 visit from Study TRD3013. If a participant cannot receive the esketamine nasal spray dose on the same day as the Week 32 visit in Study TRD3013, the participant may be enrolled in this study (TRD4010) as long as they continue their current SSRI/SNRI and receive their first dose of esketamine nasal spray within 14 days of the Study TRD3013 Week 32 visit date; Day 1 of this study will be the day of the esketamine nasal spray dose. The sponsor will use the PROs, clinician-rated scales, and safety assessments, including clinical laboratory tests, from Week 32 in Study TRD3013 in the database for Day 1 in this study; these procedures do not need to be repeated for participants who return for esketamine nasal spray dosing within 14 days after the Week 32 visit in TRD3013.

[b] This study will continue for up to a maximum of 2 years (104 weeks) for each individual participant, or until esketamine nasal spray becomes accessible in the participant's local country, whichever occurs first. If esketamine nasal spray becomes accessible locally before the 2-year endpoint, then participants will be considered as having completed the open-label extension study and will have an end-of-study visit performed. Participants will be switched to a commercially available supply if in the opinion of the treating physician, the participant continues to benefit from treatment and the participant wishes to continue the esketamine nasal spray treatment.

[c] The dose of esketamine at the end-of-study visit (ie, esketamine becomes accessible locally) is not mandatory, this dose may be administered to allow time for transition to commercially available esketamine nasal spray. For subjects who receive a dose of esketamine nasal spray at the end-of-study visit, they will return for a safety follow-up visit 2 weeks after this visit.

[d] For subjects who complete through end-of-study and do not administer a dose of esketamine nasal spray at this visit: 1) if participant's last dose was 2 weeks before this visit (ie, every 2 week dosing), then this visit is also considered the safety follow-up visit; or 2) if participant's last dose was 1 week before this visit (ie, once-weekly dosing), then the participant will return for the safety follow-up visit 1 week after this visit.

[e] Participants who withdraw early from the study (ie, before Week 104/end-of-study) must have the early study withdrawal visit performed and then return for the safety follow-up visit 2 weeks after their last dose of esketamine nasal spray, unless they withdraw consent, are lost to follow-up, or have died. If the early study withdrawal visit is conducted on the same day as a scheduled visit, duplicate assessments are not required. If the early study withdrawal visit is performed 2 weeks or more after their last dose of esketamine nasal spray, this visit is also considered the safety follow-up visit.

[f] The safety follow-up visit will be performed 2 weeks after the last nasal treatment session. For participants who withdraw early from the study, all safety follow-up visit assessments will be performed 2 weeks after their last dose of esketamine nasal spray unless they withdraw consent, are lost to follow-up, or have died. If the safety follow-up visit is conducted on the same day as a scheduled visit (eg, early withdrawal visit performed 2 weeks after last dose of esketamine nasal spray), duplicate assessments are not required.

[g] Informed consent may be obtained from participants at any time in the 4 weeks before Day 1 (ie, at or after Week 28 visit in Study TRD3013).

[h] Visit-specific PRO assessments should be conducted/completed before clinician-rated assessments, any tests, procedures, other consultations, or esketamine nasal spray administration to prevent influencing participant perceptions.

[i] Must be performed prior to esketamine dosing.

[j] In case of worsening of depressive symptoms and MADRS increase to ≥22, an additional assessment should be performed within the next 5 to 31 days to confirm the relapse criteria.

[k] Blood samples should be collected in fasting condition (at least 8 hours fasting, water is permitted). If clinically relevant abnormal results are found in hematology, chemistry, or urinalysis tests, tests should be repeated more frequently at the discretion of the investigator. Additionally, required laboratory tests as recommended in the respective SSRI/SNRI SmPC (or local equivalent, if applicable) should be performed. The investigator must record any clinically relevant changes occurring during the study in the Adverse Event section of the eCRF. Protocol-required safety laboratory assessments are listed in Appendix 8 (bicarbonate assay is optional, based on availability of the test at the local laboratory).

[l] Urine pregnancy testing (at site/local) for women of childbearing potential. Counseling on pregnancy prevention will be provided at all visits, if applicable. 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 participation in the study.

[m] Visual inspection of nostrils, nasal mucosa, and throat for nasal erythema, rhinorrhea, rhinitis, capillary/blood vessel disruption, and epistaxis.

[n] Only if participant receives a dose of esketamine at this visit (see footnote c).

[o] Vital signs: blood pressure, pulse/heart rate, respiratory rate.

[p] Vital signs will be measured at approximately 40 minutes after esketamine nasal spray dose and subsequently as clinically warranted until blood pressure values decline. Participants must be monitored by a healthcare professional until the participant is considered clinically stable and ready to leave the study site. If blood pressure remains elevated for a prolonged period of time, assistance should promptly be sought from practitioners experienced in blood pressure management. Participants who experience symptoms of a hypertensive crisis should be referred immediately for emergency care.

[q] At an early study withdrawal visit or the safety follow-up visit (no esketamine nasal spray dose), vital signs will be performed according to usual practice.

[r] Vital signs performed for participants not administrating esketamine nasal spray at this visit.

[s] If the participant has nasal congestion on the dosing day, a nasal decongestant can be used to reduce congestion (but not within 1 hour before esketamine dosing) or the dosing day can be delayed (per the permitted visit window).

[t] Esketamine nasal spray dosing and related safety-monitoring procedures MUST be performed LAST at all visits. Esketamine nasal spray must NOT be administered before all other visit assessments are completed.

[u] The frequency of nasal treatment sessions may be individualized on even week visits from once weekly to every 2 weeks based on severity of depressive symptoms and at the discretion of the investigator. If participants show early signs of worsening of depressive symptoms after reduced treatment frequency, the treatment frequency can be changed back to once weekly at any visit.

[v] A stable dose should be maintained; however, dose modifications to the continuing SSRI/SNRI may be made, if necessary, at the investigator's discretion. Additionally, during the long-term extension study, the SSRI/SNRI may be switched for individual participants by the investigator for tolerability issues. The newly prescribed SSRI/SNRI must be labeled for treatment of depression/MDD in their country of participation and the dosage being taken should be according to the respective SmPC (or local equivalent, if applicable). Off-label use of an SSRI/SNRI is not permitted. The switch of a participant's SSRI/SNRI should occur at an "every 4 week visit" so that clinician-rated scales and PROs are captured prior to the switch; the reason for the switch must be documented in the eCRF. If the SSRI/SNRI is discontinued at any time during the study, the esketamine nasal spray must also be discontinued and the participant will be withdrawn from the study.

# 2. INTRODUCTION

Esketamine hydrochloride (HCl) is referred to as JNJ-54135419-AAC. Ketamine is known as a noncompetitive, receptor subtype nonselective, activity-dependent N-methyl-D-aspartate receptor (NMDAR) antagonist. Among ketamine enantiomers and their metabolites, esketamine is the most potent NMDAR antagonist.

Janssen Research & Development (JRD) is developing intranasal esketamine for 2 populations with major depressive disorder (MDD): patients with treatment-resistant depression (TRD) and patients with MDD who have active suicidal ideation with intent (MDSI).

Esketamine nasal spray was approved by the United States Food and Drug Administration (FDA) on 05 March 2019 for use in conjunction with an oral antidepressant (AD) to treat adult patients with TRD and on 31 July 2020 for MDD with acute suicidal ideation or behavior. Marketing authorizations for the TRD indication have also been granted in a number of other regions and countries including the European Union (18 December 2019), Switzerland, New Zealand, Israel, and Canada. Applications are currently under review or planned in several other countries. Marketing authorization applications for the treatment of adults with MDSI for esketamine nasal spray are also under review in the European Union and other countries.

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

The term “study intervention” throughout the protocol, refers to esketamine nasal spray as defined in Section 6.1, Study Interventions Administered. Esketamine nasal spray will be taken in combination with background medication consisting of a continuing selective serotonin reuptake inhibitor (SSRI) or a serotonin-norepinephrine reuptake inhibitor (SNRI) at study entry (see Section 6.1.5 regarding switching SSRI/SNRI for tolerability issues during this long-term extension study).

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.

The term “participant” throughout the protocol refers to the common term “subject”.

In the text of this document, Studies ESKETINTRDxxxx (eg, ESKETINTRD3001) and 54135419TRDxxxx (eg, 54135419TRD3013) are abbreviated as TRDxxxx.

## 2.1. Study Rationale

The main rationale for this open-label extension study is to collect long-term safety, tolerability, and efficacy data with esketamine nasal spray in combination with an SSRI/SNRI and to provide access to esketamine nasal spray for participants with treatment-resistant MDD who have previously been treated in an open-label, randomized, active-controlled study (Study TRD3013). Participants from Study TRD3013 who complete 32 weeks of treatment with esketamine nasal spray in combination with a continuing SSRI/SNRI and continue to benefit from use of the

combination in the opinion of the investigator will be eligible to enter the current study in countries where esketamine nasal spray is not yet accessible, and will be provided the esketamine nasal spray component of the combination by the sponsor during the 2-year open-label extension. Participants must continue the same SSRI/SNRI as they were taking in Study TRD3013. This study will be continued for up to a maximum of 2 years (104 weeks) for each individual participant, or until esketamine nasal spray becomes accessible in a participant's local country, whichever occurs first. If esketamine nasal spray becomes accessible locally before the 2-year endpoint, then participants will be considered as having completed the open-label extension study at the time of their last dose and subsequent 2-week safety follow-up. Participants will be switched to a commercially available supply if in the opinion of the treating physician, the participant continues to benefit from treatment and the participant wishes to continue esketamine nasal spray treatment after the end of the study; the sponsor will not provide esketamine nasal spray once it becomes accessible in a participant's local country.

## 2.2. Background

The following sections detail the nonclinical and clinical profile of esketamine. Further details on pharmacologic profile and safety of racemic ketamine can be found in the IB (IB 2020).

### 2.2.1. Pharmacologic Profile

Esketamine is a nonselective, noncompetitive antagonist of the NMDAR, an ionotropic glutamate receptor. Through NMDAR antagonism, esketamine produces a transient increase in glutamate release leading to increases in α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR) stimulation and subsequently to increases in neurotrophic signaling that restore synaptic function in these mood regulatory brain regions.

### 2.2.2. Nonclinical Studies

In repeat-dose toxicity studies, no adverse effects were noted with nasal esketamine up to the highest dose tested in rats (9 mg/day) and in dogs (72 mg/day). Although heart rate was slightly increased in dogs, no relevant electrocardiogram changes were observed. Minor, non-adverse histologic findings were observed in the nasal cavity. Following nasal administration, a fraction of the dose is orally absorbed. Two in vivo assays (rat bone marrow and liver cells), conducted with esketamine HCl at dose levels up to the maximum tolerated dose, showed no evidence of genotoxic potential. The potential formation of N-nitroso-esketamine in simulated gastric fluid was evaluated. The equivalent of a full human dose orally ingested did not lead to the formation of N-nitroso-esketamine. Consequently, the (partial) oral absorption of esketamine following intranasal dosing does not pose a genotoxic risk. Esketamine was not carcinogenic in rat and mouse bioassays. Repeated-dose neurotoxicity studies in juvenile rats and dogs did not cause brain lesions even at high exposures. Intranasally administered esketamine did not affect fertility (rat), early embryonic development (rat) and pre- and postnatal development (rat). The offspring of ketamine-treated pregnant rabbits showed skeletal malformations at maternally toxic dose levels. Based on published data on the developmental neurotoxicity potential of ketamine in animals during pregnancy and in early postnatal rodent pups, a similar risk of developmental neurotoxicity cannot

be excluded for esketamine. Therefore, the use of esketamine during pregnancy is not recommended.

In summary, currently available nonclinical safety studies support chronic nasal administration of esketamine in human participants up to a dosage of 84 mg/day. Further details on the nonclinical profile of esketamine and nasal esketamine can be found in the IB (IB 2020).

### 2.2.3. Clinical Studies

The clinical program for esketamine in participants with TRD includes: a comprehensive clinical pharmacology program in healthy volunteers and special populations to fully characterize the product's pharmacokinetic and pharmacodynamic activity, including Phase 2 studies with intravenous (IV) esketamine and ketamine; a Phase 2 dose response study in adults with TRD; and data from 5 completed Phase 3 studies establishing efficacy and safety in adults with TRD, including 2 studies establishing safety in those 65 years and older. Results from 2 ongoing Phase 3 studies in adults with TRD are not available at the time of finalization of this protocol.

Information on the completed Phase 2 and Phase 3 studies in participants with MDSI is provided in the IB.

#### 2.2.3.1. Metabolism and Excretion

Esketamine undergoes extensive metabolism by human hepatic cytochrome P450 (CYP). In all species, the most important primary metabolic pathway was N-demethylation at the secondary amine (M10, noresketamine). In human and mouse microsomes, M10 was the most important metabolite. Minor secondary pathways in human microsomes were the result of oxidation on the cyclohexanone moiety (M2, M4, and M5), oxidative deamination (M11), and keto-reduction (M12) of M10. Traces of a primary pathway, oxidation of the cyclohexanone moiety of esketamine (M6) were observed in human microsomes. The main CYP enzymes responsible for esketamine N-demethylation are CYP2B6 and CYP3A4.

Following oral administration of radiolabeled esketamine, approximately 86% and 2% of administered radioactivity was recovered in urine and feces, respectively. The recovered radioactivity consisted primarily of esketamine metabolites. Very low levels of unchanged drug were present in urine (<1% of the dose), indicating that esketamine is metabolically cleared.

#### 2.2.3.2. Pharmacokinetics

Esketamine can be measured in plasma within 7 minutes following a 28-mg nasal dose. Maximum plasma concentrations ($t_{max}$) are reached approximately 20 to 40 minutes after the last nasal spray. The mean absolute bioavailability of 84 mg esketamine nasal spray is 48%.

The maximum concentrations ($C_{max}$) and area under the plasma concentration-time curve (AUC) from time 0 to the last measurable concentration ($AUC_{last}$) of esketamine increase with dose from 28 mg to 84 mg. The increases were less than dose proportional between 28 mg and 56 mg or 84 mg, but nearly dose proportional between 56 mg and 84 mg. Esketamine does not accumulate in plasma when administered nasally once or twice weekly.

The pharmacokinetic results of Janssen sponsored clinical studies for nasally-administered esketamine are summarized below:

- **Studies in Asian populations:** In Study TRD1008, mean plasma esketamine $C_{max}$ and AUC from time 0 to infinity ($AUC_{\infty}$) values produced by a 56 mg dose administered as a nasal spray were approximately 14% and 33% higher, respectively, in Chinese participants compared with Caucasian participants. Both parameters were approximately 40% higher in Japanese participants, compared with Caucasian participants. On average, esketamine $C_{max}$ was 10% lower and $AUC_{\infty}$ was 17% higher in Korean participants, relative to Caucasian participants. In Study TRD1002, the mean plasma esketamine $C_{max}$ and $AUC_{\infty}$ values produced by 28 mg, 56 mg, and 84 mg of intranasal esketamine were higher in Japanese participants as compared with Caucasian participants, consistent with results from Study TRD1008. The mean plasma esketamine concentrations at 40 minutes to 6 hours postdose in Japanese participants in Study TRD2003 were higher relative to the corresponding concentrations following the same esketamine dose self-administered by non-Japanese participants from the United States and Belgium, consistent with results from the Phase 1 studies. In addition, the exposure to esketamine after nasal administration of a 14 mg dose of esketamine in Japanese participants was comparable to administration of a 28 mg dose in non-Japanese participants.
- **Elderly (≥65 years of age [TRD1003]; ≥75 years of age [TRD1012]) and younger adults (18 to ≤55 years of age):** In single, self-administered dose studies using 28 mg (TRD1003) and 84 mg (TRD1012) of esketamine, the geometric means of $C_{max}$ and $AUC_{\infty}$ were approximately 21% and 18% higher, respectively, for the 28 mg dose and approximately 67% and 38% higher, respectively, for the 84 mg dose, in the elderly compared with the younger adult participants. In both studies, the decline in the esketamine concentrations was similar in the elderly and young adult participants. Mean plasma esketamine $C_{max}$ and $AUC_{\infty}$ values following 28 to 84 mg of intranasal esketamine were higher in elderly Japanese participants as compared with younger adult Japanese participants (TRD1018).
- **Hepatic impairment:** In Study TRD1011, the mean $C_{max}$ and $AUC_{\infty}$ of esketamine following a 28 mg nasal dose were 8% and 14% higher, respectively, in participants with mild hepatic impairment (Child-Pugh score 5 and 6, Class A), compared with healthy participants. In moderately hepatically impaired participants (Child-Pugh score 7 to 9, Class B), the $C_{max}$ and $AUC_{\infty}$ of esketamine were 8% and 103% higher, respectively, compared to healthy participants. Small differences with no clear trend were observed in the apparent terminal half-life of esketamine across the 3 cohorts (13.1 to 18.7 hours). The pharmacokinetics of esketamine in participants with severe hepatic impairment was not investigated.
- **Renal impairment:** In Study TRD1014, no clinically meaningful effect on pharmacokinetics of esketamine (28 mg nasal dose) was observed in participants with mild to severe renal impairment relative to the participants with normal renal function (creatinine clearance [$CL_{CR}$], 88 to 140 mL/min).
- **Allergic rhinitis:** The pharmacokinetic profiles of nasal esketamine in participants with allergic rhinitis who were exposed to grass pollen prior to dosing and in healthy participants were similar (Study TRD1007).
- **Participants with TRD or MDSI:** A limited pharmacokinetic sampling strategy was included in various Phase 2 and 3 studies. At corresponding esketamine nasal doses and

timepoints, the mean plasma esketamine concentrations were similar to the range of mean esketamine concentrations in samples collected in Phase 1 studies. These results demonstrate that the PK of esketamine is similar in participants with TRD, MDSI, and healthy participants.

- **Effects of potent inducers and inhibitors of hepatic CYP:** On average, the $C_{max}$ and $AUC_{\infty}$ of an intranasal dose of esketamine were approximately 17% and 28% lower, respectively, when participants were pretreated with rifampin (an inducer of CYP3A4 and CYP2B6 activity) (Study TRD1008). On average, the $C_{max}$ and $AUC_{\infty}$ of an intranasal dose of esketamine were increased by <11% when participants were pretreated with clarithromycin (a potent inhibitor of hepatic CYP3A activity), and the decline in plasma concentrations (ie, half-life) of esketamine was not affected by clarithromycin pretreatment (Study TRD1009). Pretreatment with oral ticlopidine, an inhibitor of hepatic CYP2B6 activity, had no effect on the $C_{max}$ of nasally administered esketamine, the $AUC_{\infty}$ of esketamine was increased by approximately 29%, and there was no effect on terminal half-life of esketamine (Study TRD1020).
- **Intranasal drug-drug interactions:** Daily administration of intranasal mometasone furoate (with the last dose given 1 hour prior to intranasal esketamine) did not affect the pharmacokinetics of esketamine in healthy participants (Study TRD1007). In addition, pretreatment with intranasal oxymetazoline HCl (1 hour prior to intranasal esketamine) did not affect the pharmacokinetics of esketamine in participants with allergic rhinitis. These results indicate that participants should wait for at least 1 hour after using an intranasal decongestant or corticosteroid before self-administering esketamine.

#### 2.2.3.3. Pharmacodynamics and Efficacy

The efficacy of intranasal esketamine in the treatment of participants with TRD was investigated in 2 completed Phase 2 studies (TRD2003 and TRD2005) and 5 completed Phase 3 studies (3 short-term studies [TRD3001, TRD3002, TRD3005] and 2 long-term studies [TRD3003 and TRD3004]). The 2 long-term studies are summarized below; refer to the IB for information on the Phase 2 and short-term studies (IB 2020).

In the long-term relapse-prevention Study TRD3003 (using a randomized withdrawal design in the context of newly initiated SSRI/SNRI treatment), the efficacy of intranasal esketamine at flexible doses (56 mg or 84 mg) was assessed in adult participants with TRD. Results demonstrated that a statistically significantly longer time to relapse was observed with continued esketamine treatment relative to discontinuation of esketamine in participants who had achieved stable remission (or stable response) of their depression symptoms during 16 weeks of treatment with esketamine in combination with a newly initiated SSRI/SNRI. Relapse events occurred during the maintenance phase for 26.7% of participants in the esketamine in combination with a newly initiated SSRI/SNRI group and 45.3% of participants in the newly initiated SSRI/SNRI in combination with placebo group; this result indicated that relapse was, on average, 51% less likely for stable remitters who continued treatment with esketamine than for those who switched to placebo.

Data from the long-term safety and efficacy Study TRD3004 showed long-term symptom improvements during up to 1 year of treatment with esketamine in combination with a newly

initiated SSRI/SNRI in participants with TRD, although interpretation of the efficacy results from this study is limited since this was an unblinded and uncontrolled study.

#### 2.2.3.4. Safety Studies

In 6 completed Phase 2 and 3 studies in TRD as of 04 March 2020 (TRD2003, TRD3001, TRD3002, TRD3005, TRD3003, and TRD3004), a total of 1,708 participants received esketamine (611 patient-years of exposure) and 486 participants received placebo (107 patient-years of exposure). Study TRD2005 was completed after this cutoff date; in this study an additional 122 participants received at least 1 dose of esketamine nasal spray for a median duration of exposure of 24 to 25 days across the 3 dose groups (28 mg, 56 mg, and 84 mg). In one of the ongoing studies (open-label Phase 3 extension safety study TRD3008), 1,148 participants have received at least 1 dose of esketamine for a median duration of exposure (including exposure in previous controlled trials) of 143 weeks through 20 May 2020; 991 participants had at least 12 months of exposure, and 850 participants had at least 24 months of exposure.

- Over the therapeutic dose range for use in a TRD population (28 to 84 mg), most intervention-emergent adverse events (AEs) with esketamine were mild to moderate in severity, occurred shortly after dosing, were transient, and resolved the same day.
- In the short-term TRD studies, the most common intervention-emergent AEs (reported by ≥10% of participants who received esketamine in combination with a newly initiated SSRI/SNRI and observed more frequently compared with participants who received placebo in combination with a newly initiated SSRI/SNRI) were nausea, dissociation, dizziness, vertigo, headache, dysgeusia, somnolence, paresthesia, hypoesthesia, and hypoesthesia oral in Studies TRD3001 and TRD3002, and dizziness, nausea, headache, fatigue, blood pressure increased, dissociation, and vertigo in Study TRD3005.
- Across the Phase 3 studies in TRD, esketamine had a consistent, well-characterized, and tolerable safety profile. Most reported intervention-emergent AEs during induction and maintenance esketamine treatment, including those that were most common, were reported postdose on the day of dosing and resolved the same day. Only a minority of the reported intervention-emergent AEs were assessed as severe. There were no new intervention-emergent AEs considered associated with the use of esketamine reported with longer-term repeated dosing of esketamine in combination with a newly initiated SSRI/SNRI of up to 1 year.
- Among the 1,708 participants treated with esketamine across the completed Phase 2 and 3 studies in TRD, there were 4 deaths, including 2 completed suicides. Through 04 March 2020, in the ongoing long-term open-label safety extension Phase 3 study (TRD3008, 1,148 participants), 3 deaths (completed suicide, myocardial infarction, and death due to multiple injuries from car accident) were reported in esketamine-treated participants.
- Discontinuation of esketamine treatment due to intervention-emergent AEs was uncommon across all clinical studies and tended to be highest early in the course of treatment. With long-term treatment of up to 1 year, <10% of treated participants in the open-label long-term safety study (TRD3004) experienced intervention-emergent AEs that necessitated discontinuation of esketamine.

- Overall, across Phase 2 and 3 TRD studies, suicidality-related events were reported at a frequency of ~1% to 5%, and most of the reported cases were those of suicidal ideation. Severe suicidality-related intervention-emergent AEs were reported at a low incidence (<1% for individual preferred terms) in each of the Phase 2 and 3 studies. Clinical review of suicidality-related intervention-emergent AEs indicated that most of these events were likely associated with the underlying disease.
- The most common psychological effects of esketamine have been transient dissociative/perceptual changes (including distortion of time and space and illusions), derealization and depersonalization. The majority of participants who were administered esketamine experienced dissociative symptoms as assessed by the Clinician-Administered Dissociative States Scale (CADSS). The symptoms peaked at around 40 minutes from the time of esketamine nasal spray administration and typically resolved by 1.5 to 2 hours after dosing. The severity of dissociative symptoms tended to reduce over time with repeated treatments. Dissociation reported as severe in intensity at the incidence of less than 4% across studies, was not considered serious for any participants in completed Phase 2 and 3 studies, and infrequently led to discontinuation of study intervention. Transient dissociative/perceptual changes (based on the CADSS scores, the overall intervention-emergent AE incidence rates, and the severe intervention-emergent AE incidence rates) were more pronounced in participants receiving the esketamine 84 mg dose than in those receiving the esketamine 56 mg dose.
- Transient, primarily asymptomatic, increases in systolic and diastolic blood pressure (SBP and DBP) were observed following administration of esketamine nasal spray, with maximum mean changes typically observed within 40 minutes of dosing (consistent with peak plasma elevations) and mean blood pressure values subsequently returning to, or close to, predose values within the 1.5-hour postdose timepoint. The blood pressure elevations did not appreciably attenuate over time with continued administration. Few participants (<2% across studies/study phase) discontinued esketamine treatment due to increased blood pressure.
  - In clinical trials, increases in SBP and DBP over time were about 7 to 9 mm Hg in SBP and 4 to 6 mm Hg in DBP at 40 minutes post dose and 2 to 5 mm Hg in SBP and 1 to 3 mm Hg in DBP at 1.5 hours post dose in participants receiving esketamine nasal spray plus oral ADs. The frequency of markedly abnormal blood pressure elevations of SBP (≥40 mm Hg increase) ranged from 8% (<65 years) to 17% (≥65 years) and DBP (≥25 mm Hg increase) ranged from 13% (<65 years) to 14% (≥65 years) in participants receiving esketamine nasal spray plus oral AD. The incidence of increased SBP (≥180 mm Hg) was 3% and DBP (≥110 mm Hg) was 4%.
- Intranasal esketamine 84 mg was associated with an early, transient decline in cognitive function compared with placebo, which was restored to comparable levels in participants receiving either esketamine or placebo by 2 hours postdose. Transient reductions with esketamine were associated with early postdose sedation, as assessed by the Karolinska Sleepiness Scale, and the greater level of effort required to complete the test battery, as assessed using the Mental Effort Scale. The increases in sleepiness (at 40 minutes and 2 hours postdose) and the mental effort required (at 40 minutes postdose) returned to levels comparable to placebo by 4 and 2 hours postdose, respectively (Phase 1 study TRD1005).
- Treatment with esketamine nasal spray had no clinically meaningful effects on oxygen saturation as measured by pulse oximetry or on respiratory rate. There were no cases of

respiratory depression or intervention-emergent AEs that required cardiopulmonary resuscitation or other medical intervention reported in the Phase 2 or 3 studies.

- Results of the Phase 2 and Phase 3 studies indicate that there is no clinically meaningful effect of esketamine on body weight over short- or long-term administration.
- No evidence of QT interval prolongation (based on a study-specific power model and Fridericia's correction methods) was found in participants treated with intranasal or IV esketamine in a thorough corrected QT interval (QTc) study. Moxifloxacin demonstrated QTc prolongation and established assay sensitivity.
- Treatment with intranasal esketamine does not appear to be associated with development of potential psychotic-like symptoms. No intervention-emergent AEs of psychosis were reported across the Phase 2 and 3 studies in TRD. Mania was reported in 2 esketamine-treated participants (1 report after first dose of esketamine and oral AD [duloxetine] and second report during the follow-up phase), and hypomania was not reported in any participant.
- No cases of interstitial cystitis or ulcerative cystitis have been reported with esketamine use in any of the completed or ongoing studies, including the ongoing long-term open-label TRD study TRD3008, where over 700 participants were treated for at least 2 years. There was a higher rate of cystitis-related intervention-emergent AEs (eg, pollakiuria, dysuria, micturition urgency) with esketamine compared to placebo.
- No cases of newly elevated total serum bilirubin to >2x the upper limit of normal associated with esketamine treatment were identified. No cases in any Phase 1, 2, or 3 esketamine studies across indications met the criteria for severe drug-induced hepatocellular injury as defined by Hy's law. No new hepatic safety signal was observed in the ongoing long-term open-label TRD study TRD3008, where over 700 participants were treated for at least 2 years.
- Nasal tolerability in participants self-administering esketamine nasal spray, including that following long-term treatment, was good. There were no nasal examination findings or Nasal Symptom Questionnaire evidence to support an impact on nasal anatomy or function including the sense of smell.
- Ketamine, the racemic mixture of arketamine and esketamine, has been reported as a drug of abuse. The potential for abuse, misuse, and diversion of intranasal esketamine is minimized due to the product's design and the administration taking place under the supervision of a healthcare professional. Evidence of abuse, misuse, and diversion was not observed in clinical studies of intranasal esketamine.

## 2.3. Benefit-Risk Assessment

A structured approach was applied to the selection and analysis of all the endpoints in the Phase 3 esketamine program in TRD that have an important effect on the benefit-risk balance. Proportions of beneficial events were compared to proportions of harmful events. While some of the dichotomous endpoints (remission and response rates) that underlay these comparisons are not associated with formal statistical testing, they do characterize clinically significant differences and provide an overall picture of the benefit-risk balance for esketamine. More detailed information about the known and expected benefits and risks of esketamine nasal spray may be found in the IB (IB 2020).

The totality of evidence supports a positive benefit-risk balance for esketamine nasal spray as a new treatment for adults with TRD. The extensive clinical study program for esketamine in TRD demonstrates the rapid, robust, and sustained efficacy for improving depression symptoms in this difficult-to-treat population. Benefit-risk assessments estimate that between 6 and 18 more patients per 100 treated achieve remission of depression symptoms after 4 weeks of treatment with esketamine in combination with a newly initiated SSRI/SNRI compared to initiating treatment with an SSRI/SNRI alone. Further, once remission has been achieved on esketamine, continued maintenance treatment with esketamine nasal spray in combination with an SSRI/SNRI is estimated to result in 19 to 32 fewer relapses per 100 patients relative to those who discontinue esketamine. The safety experience with esketamine nasal spray indicated that most of the adverse reactions seen with the drug, including those of common events such as dissociative symptoms, dizziness/vertigo, increased blood pressure, and sedation, occur shortly after dosing while the patient is under the supervision of a health care provider, and resolve the same day. In addition, certain AEs such as dissociation, dizziness/vertigo, and nausea/vomiting tend to lessen in frequency with continued dosing.

While the potential for abuse exists with esketamine nasal spray, there were no intervention-emergent AEs of drug abuse or overdose and no reports of confirmed diversion in clinical trials. Several risk mitigation initiatives to lessen the potential for abuse and misuse are in place in regions where esketamine nasal spray has been launched and will be in place at the time of product launch in other regions. Patient preference study findings indicate that patients with TRD, both with and without esketamine treatment experience, place a higher value on improved depression symptoms over those of short-term unusual postdose sensations and drug administration logistics or hypothesized extreme safety risks associated with ketamine abuse.

The benefits of esketamine nasal spray are considered to outweigh the risks of the infrequent severe or treatment-limiting side effects in the treatment-resistant MDD population.

## 3. OBJECTIVES AND ENDPOINTS

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| To assess the long-term safety and tolerability of esketamine nasal spray in combination with an SSRI/SNRI in participants who have completed 32 weeks of esketamine nasal spray treatment in Study TRD3013. | Intervention-emergent AEs, including intervention-emergent AEs of special interest<br><br>Suicidal ideation and behavior: Columbia-Suicide Severity Rating Scale (C-SSRS) |

| Objectives | Endpoints |
|---|---|
| **Secondary** | |
| • To assess the long-term efficacy of esketamine nasal spray in combination with an SSRI/SNRI based on the proportion of participants being relapse-free at Week 104 (or end-of-study). | No relapse until the end of the prospective observation period at Week 104 visit (or end-of-study).<br>A relapse is defined by any of the following:<br>d) Worsening of depressive symptoms as indicated by Montgomery-Asberg Depression Rating Scale (MADRS) total score ≥22 confirmed by 1 additional assessment of MADRS total score ≥22 within the next 5 to 31 days. The date of the second MADRS assessment will be used for the date of relapse.<br>e) Any psychiatric hospitalization for<br>– worsening of depression<br>– suicide prevention or due to a suicide attempt<br>for any of these events, the start date of hospitalization will be used for the date of relapse.<br>f) Suicide attempt, completed suicide, or any other clinically relevant event determined per the investigator's clinical judgment to be indicative of a relapse of depressive illness, but for which the participant was not hospitalized. The onset of the event will be used for the date of relapse.<br>In case more than 1 of the relapse criteria are met, the earliest date will be defined as the date of relapse for that participant. |
| To assess the effect of esketamine nasal spray in combination with an SSRI/SNRI on:<br>• Clinician-rated overall severity of depressive illness<br>• Participant-reported depressive symptoms<br>• Participant-reported health-related quality of life and health status | Change from baseline in Study TRD3013 at all visits for the following scale scores:<br>• Clinician-rated MADRS:<br>– Overall severity of depressive illness (total score)<br>– Depressive symptoms (individual items)<br>• Clinician-rated overall severity of depressive illness:<br>– Clinical Global Impression – Severity (CGI-S)<br>• Participant-reported depressive symptoms: Patient Health Questionnaire 9-item (PHQ-9)<br>• Participant-reported European Quality of Life (EuroQoL) Group, 5-Dimension, 5-Level (EQ-5D-5L) questionnaire |

| Objectives | Endpoints |
|---|---|
| **Exploratory** | |
| To assess the impact of switching the oral AD with another compound from the SSRI/SNRI classes, in cases where the oral AD is switched due to tolerability | • Reason for switching the oral AD<br>• Impact on adverse events present at the time of the switch<br>• Adverse events starting after the switch<br>• Impact on MADRS and CGI-S |

Refer to Section 8, Study Assessments and Procedures for evaluations related to endpoints.

**HYPOTHESIS**

Due to the design of the study (single-arm, long-term extension) and the objective (exploratory nature) no hypothesis is described for this study.

# 4. STUDY DESIGN

## 4.1. Overall Design

This study is a single-arm, 2-year open-label extension to Study TRD3013, which is an open-label, randomized, active-controlled study to evaluate the efficacy, safety, and tolerability of flexibly dosed esketamine nasal spray compared with quetiapine extended release, both in combination with a continuing SSRI/SNRI, in participants 18 to 74 years of age, inclusive, with treatment-resistant MDD. Participants who were randomly assigned to the esketamine arm in Study TRD3013, had esketamine nasal spray administered through Week 30 (every 2 week dosing) or Week 31 (once weekly dosing), completed the maintenance phase at Week 32, continue to benefit from esketamine nasal spray in combination with a continuing SSRI/SNRI in the opinion of the investigator, and commercial esketamine nasal spray is not accessible to them in their country, will be eligible to enter this open-label extension study (Study TRD4010).

The total number of participants to be enrolled will depend on the number of countries that participate in the study and the number of participants receiving esketamine nasal spray who complete through Week 32 in Study TRD3013. It is expected that from 100 to 200 participants will be enrolled in this study.

Informed consent may be obtained from participants at any time in the 4 weeks before Day 1 (ie, at or after Week 28 visit in Study TRD3013). It is the investigator's responsibility to contact the sponsor to request esketamine nasal spray supply for participants who will enroll in the long-term extension study. On Day 1 (Week 32 visit of Study TRD3013), participants who consented and are eligible will enter the 2-year open-label extension study. See Section 5.5, Criteria for Temporarily Delaying Enrollment or Administration of Study Intervention, for requirements if a participant cannot receive first esketamine nasal spray dose for the long-term extension study at the Week 32 visit of Study TRD3013.

The dosage of esketamine nasal spray in this long-term extension study will be determined based on the participant's dose and frequency at completion of the maintenance phase (Week 32) of

Study TRD3013. Investigators will be allowed to change the dose and frequency during the open-label extension study based on clinical judgment. Participants will attend site visits once weekly or every 2 weeks, depending on their dosing frequency, for administration of esketamine nasal spray. The SSRI/SNRI dose should have been optimized up to the maximum tolerated dose during Study TRD3013 as per the respective Summary of Product Characteristics (SmPC; or local equivalent, if applicable). During the long-term extension study, a stable dose should be maintained; however, dose modifications to the continuing SSRI/SNRI may be made, if necessary, at the investigator's discretion. Additionally, during the long-term extension study, the SSRI/SNRI may be changed for individual participants by the investigator for tolerability issues; see Section 6.1.5, Background Medication -SSRI/SNRI for additional information on changing the SSRI/SNRI during the study. If the SSRI/SNRI is discontinued at any time during the study, the esketamine nasal spray must also be discontinued and the participant will be withdrawn from the study.

Safety, efficacy, and other assessments will be performed according to the Schedule of Activities in Section 1.2, with additional assessments to be added at the discretion of the investigator as deemed necessary, per usual clinical practice.

At any point during the long-term extension study, participants who, in the opinion of the investigator, are no longer benefiting from treatment with esketamine nasal spray in combination with an SSRI/SNRI should be discontinued from the study; these participants will complete the early study withdrawal visit and then return for the safety follow-up visit 2 weeks (±2 days) after their last dose of esketamine nasal spray, unless they withdraw consent, are lost to follow-up, or have died.

Study participation will continue for up to a maximum of 2 years (104 weeks), or until esketamine nasal spray becomes accessible in the participant's local country, whichever occurs first. Participants will have access to esketamine nasal spray for a maximum of 2 years during this study. If esketamine nasal spray becomes accessible locally before the 2-year endpoint, then participants will be considered as having completed the open-label extension study and will be switched to a commercially available supply if in the opinion of the treating physician, the participant continues to benefit from treatment and the participant wishes to continue the esketamine nasal spray treatment. Once esketamine nasal spray becomes accessible in any given country, all participants in the long-term extension study will be discontinued at all sites in that country. Study site personnel will notify participants of study termination and schedule an end-of-study visit with each participant.

A diagram of the study design is provided in Section 1.2, Schema (Figure 1).

**Day 1 Through Week 104**

Efficacy will be assessed using clinician-rated scales (MADRS and CGI-S) and patient-reported outcomes (PROs) (PH-9 and EQ-5D-5L). The MADRS will be performed by a qualified rater who has sufficient qualifications as documented by experience or training. If possible, for individual participants, the independent rater from Study TRD3013 may continue performing the MADRS in

this study. To avoid interrater variability, all efforts should be made to have the same rater rating the same study participants as much as possible.

All visit-specific PRO assessments (PHQ-9 and EQ-5D-5L) should be conducted/completed before clinician-rated assessments, any tests, procedures, other consultations, or esketamine nasal spray administration to prevent influencing participant perceptions.

All clinician-rated scales, the MADRS and C-SSRS, must be completed before the nasal treatment session at each visit. Esketamine nasal spray dosing and related safety-monitoring procedures MUST be performed LAST at all visits.

Safety assessments include the monitoring of AEs, measurement of body weight, vital sign measurements, clinical laboratory tests, and pregnancy testing. Suicide risk will also be assessed throughout the study using the C-SSRS.

The dose of esketamine at the end-of-study visit (ie, esketamine becomes accessible locally) is not mandatory, this dose may be administered to allow time for transition to commercially available esketamine nasal spray. For subjects who receive a dose of esketamine nasal spray at the end-of-study visit, they will return for a safety follow-up visit 2 weeks after this visit.

For subjects who complete through end-of-study and do not administer a dose of esketamine nasal spray at this visit: 1) if participant's last dose was 2 weeks before this visit (ie, every 2 week dosing), then this visit is also considered the safety follow-up visit; or 2) if participant's last dose was 1 week before this visit (ie, once-weekly dosing), then the participant will return for the safety follow-up visit 1 week after this visit.

Refer to Section 6.6, for information regarding access to esketamine nasal spray following completion of the study.

**Early Study Withdrawal Visit**

If a participant withdraws from the study, an early study withdrawal visit should be conducted unless they withdraw consent, are lost to follow-up, or have died. If the early study withdrawal visit is conducted on the same day as a scheduled visit, duplicate assessments are not required.

If the early study withdrawal visit is performed 2 weeks or more after their last dose of esketamine nasal spray, this visit is also considered the safety follow-up visit.

**Safety Follow-Up Visit**

For participants who complete the study, the safety follow-up visit will be performed 2 weeks after the last nasal treatment session.

For participants who withdraw early from the study, all safety follow-up visit assessments as specified in the Schedule of Activities will be performed 2 weeks after their last dose of esketamine nasal spray unless they withdraw consent, are lost to follow-up, or have died.

If the safety follow-up visit is conducted on the same day as a scheduled visit (eg, early withdrawal visit performed 2 weeks after last dose of esketamine nasal spray), duplicate assessments are not required.

## 4.2. Justification for Dose

All participants will receive flexible doses (either 28 mg [elderly participants and adults of Japanese ancestry only], 56 mg, or 84 mg) of esketamine nasal spray, based on their tolerability and response to esketamine in Study TRD3013.

The dose selections used in this study are in line with previous Phase 2 and Phase 3 studies where esketamine was administered at doses of 28 mg, 56 mg, or 84 mg. Phase 1 and 2 studies in elderly and Japanese participants, which indicated higher mean plasma esketamine $C_{max}$ and $AUC_{\infty}$ values at studied doses, support the dose of 28 mg in these 2 populations. A flexible dosing schedule was used in Phase 3 studies (TRD3002, TRD3004, and TRD3005) to facilitate improved tolerability by gradually increasing the dose higher and to align with clinical practice, as many clinicians prefer to gradually increase the dose of AD medication and then adjust as clinically required. Based on the approved SmPC for esketamine nasal spray, this study is being conducted with a flexible dosing scheme.

In the longer-term Phase 3 studies (TRD3003 and TRD3004), the frequency of nasal dosing after the induction phase was individualized to once weekly or every other week to achieve the lowest dosing frequency for an individual participant that could sustain initial improvements in depressive symptomatology. Data from the up-to-9-week open-label phase of Study TRD2003 showed that reducing the dosing frequency from twice-weekly to weekly or every other week did not impact the ability to maintain the AD activity of esketamine.

**Background Medication: SSRI/SNRI**

All participants must be continuing their same SSRI/SNRI as during Study TRD3013 on Day 1 to be eligible for the study. Participants must be taking an SSRI/SNRI that is approved for use in depression in their country of participation; off-label use of any SSRI/SNRI is not permitted. The continuing SSRI/SNRI dosage may be optimized throughout the study, at the investigator's discretion and based on the SmPC (or local equivalent, if applicable). During this long-term extension study, investigators will be allowed to switch individual participant's SSRI/SNRI for tolerability issues (see Section 6.1.5 for additional details).

## 4.3. Scientific Rationale for Study Design

**Participant selection criteria**

This study will recruit adult participants (men and women) with treatment-resistant MDD who were randomly assigned to the esketamine arm in Study TDR3013, had esketamine nasal spray administered through Week 30 (every 2 week dosing) or Week 31 (once weekly dosing), completed the maintenance phase at Week 32, continue to benefit from esketamine nasal spray in combination with a continuing SSRI/SNRI in the opinion of the investigator, and do not have commercial esketamine nasal spray accessible to them in their country. Participants must continue

to be willing to receive esketamine nasal spray during the open-label extension study. Participants will be required to meet selection criteria (see Section 5, Study Population) and must voluntarily consent and be able and willing to fulfill all study requirements.

Participants were not included in Study TRD3013 if they had a current or prior Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) diagnosis of a psychotic disorder or MDD with psychotic features or bipolar or related disorders (confirmed by the Mini International Neuropsychiatric Interview [MINI]). If, during the course of Study TRD3013, a participant was diagnosed with psychosis, mania, or bipolar disorder or has presence of at Day 1 in this long-term extension study, treatment with esketamine nasal spray could be continued with caution. These participants should be carefully assessed before entering this long-term extension study and treatment with esketamine nasal spray should be continued only if the benefit outweighs the risk.

**Study design**

This is a single-arm, open-label study in which all participants will receive esketamine nasal spray in combination with an SSRI/SNRI. Open-label treatment design is considered suitable for the collection of long-term safety and tolerability data and is more consistent with real-world clinical practice. As such, this study will strive to be pragmatic, with minimal mandated assessments.

During this study, participants will attend site visits once weekly or every 2 weeks for administration of esketamine nasal spray. Participants will continue their current SSNR/SSRI throughout the study, dose modifications may be made, if necessary, at the investigator's discretion. Additional study visits may be added at the discretion of the investigator, as deemed necessary, per usual practice.

**Selection of efficacy and safety evaluations**

The full lists of efficacy and safety assessments for this study are described in Section 8, Study Evaluations.

The objective of this study is to collect long-term safety, tolerability, and efficacy information for esketamine nasal spray and to provide access to esketamine nasal spray for participants who successfully completed the 32-week maintenance phase of Study TRD3013 in countries where commercial esketamine nasal spray is not yet accessible.

Efficacy of esketamine nasal spray will be assessed as a secondary objective, and will be evaluated based on an assessment of relapse. The MADRS was chosen to assess efficacy as it is a well-known and widely accepted scale to assess the severity of depression. The relapse criteria used in this study are listed in Section 3.

At each study visit, adverse events will be assessed and investigators will evaluate the participant's mental status (including an assessment of suicidality). Clinical laboratory values, pregnancy testing, and body weight will be assessed at limited time points during the study, with additional assessments to be added at the discretion of the investigator. If clinically warranted, investigators may perform additional evaluations as needed during the study.

### 4.3.1. Study-Specific Ethical Design Considerations

The safety profile of esketamine nasal spray indicates that it is considered safe to use in the current study population based on the pre-clinical and clinical data noted earlier (Section 2.2, Background).

Participants must be taking an SSRI/SNRI that is approved for use in depression in their country of participation. Off-label use of SSRIs/SNRIs is not allowed.

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants 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 participants who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study.

## 4.4. End of Study Definition

**End of Study Definition**

The end of study is considered as the last visit for the last participant in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant visit at that study site, in the time frame specified in the Clinical Trial Agreement.

**Study Completion Definition**

A participant will be considered to have completed the study if he or she has completed assessments at Week 104 of the long-term extension study, or is discontinued from the study and completes end-of-study assessments when commercial esketamine nasal spray becomes accessible in the participant's local country and the study is terminated in the local country.

# 5. STUDY POPULATION

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

## 5.1. Inclusion Criteria

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

1. completed the maintenance phase (Week 32) of Study TRD3013 and had esketamine nasal spray in combination with continuing SSRI/SNRI administered through Week 30 (every 2 week dosing) or Week 31 (once weekly dosing) of Study TRD3013, and continues to be willing to be treated with esketamine nasal spray.

2. must, in the opinion of the investigator, be benefiting from continuation of esketamine nasal spray in combination with their current SSRI/SNRI based on efficacy and tolerability assessed on Day 1 of this study.

3. must be medically stable based on the investigator's judgment.

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

5. a woman of childbearing potential must have a negative urine pregnancy test on Day 1.

6. a woman must be (as defined in Appendix 2, Contraceptive and Barrier Guidance)

    a. Not of childbearing potential

    b. Of childbearing potential and

        - Practicing a highly effective, preferably user-independent method of contraception (failure rate of <1% per year when used consistently and correctly) and agrees to remain on a highly effective method while receiving study intervention and until at least 6 weeks after last dose - the end of relevant systemic exposure. The investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first dose of study intervention. Examples of highly effective methods of contraception are located in Appendix 2, Contraceptive and Barrier.

7. male participants who are sexually active with a woman of childbearing potential must agree to the following during the intervention period and for at least 1 spermatogenesis cycle (defined as approximately 90 days) after receiving the last dose of study intervention (ie, esketamine nasal spray), must fulfill the following criteria:

    - must be practicing a highly effective method of contraception with his female partner.
    - 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 participant, must begin a highly effective method of birth control, as described above. Contraceptive use by men or women should be consistent with local regulations

regarding the use of contraceptive methods for participants participating in clinical studies.

8. willing and able to adhere to the lifestyle restrictions specified in this protocol.

## 5.2. Exclusion Criteria

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

1. has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

2. completed Study TRD3013 while presenting adverse events deemed clinically relevant by the investigator, and which may interfere with safety and well-being of the participant.

3. has developed during participation in Study TRD3013 any of the following cardiovascular-related conditions where an increase in blood pressure or intracranial pressure poses a serious risk:

   - cerebrovascular disease following stroke or transient ischemic attack.
   - aneurysmal vascular disease (including intracranial, thoracic, or abdominal aorta, or peripheral arterial vessels).
   - intracerebral hemorrhage.
   - coronary artery disease following myocardial infarction, unstable angina, or revascularization procedure (eg, coronary angioplasty or bypass graft surgery).
   - uncontrolled brady- or tachyarrhythmias that lead to hemodynamic instability.
   - hemodynamically significant valvular heart disease such as mitral regurgitation, aortic stenosis, or aortic regurgitation or heart failure (NYHA Class III-IV) of any etiology.

   Significant pulmonary insufficiency, including chronic obstructive pulmonary disease

4. has homicidal ideation or intent, per the investigator's clinical judgment; or has suicidal ideation with some intent to act within 1 month prior to Day 1, per the investigator's clinical judgment; or based on the C-SSRS performed at Week 32 visit of Study TRD3013, corresponding to a response of "Yes" on Item 4 (active suicidal

ideation with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent) for suicidal ideation.

5. pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study or within 90 days after the last dose of study intervention

**NOTE:** Investigators should ensure that all study enrollment criteria have been met. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) before the first dose of study intervention is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. The required source documentation to support meeting the enrollment criteria are noted in Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

## 5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the course of the study to be eligible for participation:

1. refer to Section 6.8, Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

2. agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

3. agree to remain at the study site after administration of esketamine nasal spray until the investigator determines clinically (ie, based on vital signs) that the participant is ready for discharge; the expected duration is up to 2 hours.

4. agree to not to engage in potentially hazardous activities requiring complete mental alertness and motor coordination, such as driving a vehicle or operating machinery, after receiving esketamine nasal spray until the next day following a restful sleep.

### 5.3.1. Meals and Dietary Restrictions

1. participants must agree to fast (water is permitted) for 8 hours before visits when clinical laboratory tests are required (Day 1, every 24 weeks visits, Week 104/end-of-study, 2-week safety follow-up visit).

2. participants will have food restricted for at least 2 hours before each administration of esketamine nasal spray. Drinking of any fluids will be restricted for at least 30 minutes before the first nasal spray at each session.

### 5.3.2. Alcohol

1. participants must agree to abstain from alcohol consumption for 24 hours before and after esketamine nasal treatment sessions.

## 5.4. Screen Failures

**Participant Identification, Enrollment, and Screening Logs**

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

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent for this long-term extension study. In cases where the participant is not enrolled into the study, the date seen and age at initial informed consent for this long-term extension study will be used.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

## 5.5. Criteria for Temporarily Delaying Enrollment or Administration of Study Intervention

If a participant cannot receive the esketamine nasal spray dose on the same day as the Week 32 visit in Study TRD3013, the participant may be enrolled in this study (TRD4010) as long as they continue their current SSRI/SNRI and receive their first dose of esketamine nasal spray within 14 days after the Week 32 visit date in Study TRD3013; Day 1 of this study will be the day of the esketamine nasal spray dose.

Administration of study intervention may be delayed if the participant has nasal congestion on the dosing day as described in Section 6.1.1, Esketamine Nasal Spray, or if the participant requires adjustment of blood pressure medication.

Appendix 4 provides guidance related to study conduct during the Coronavirus Disease 2019 (COVID-19) pandemic.

# 6. STUDY INTERVENTION AND CONCOMITANT THERAPY

## 6.1. Study Intervention Administered

The interactive web response system (IWRS) will assign a unique intervention code, which will dictate the study intervention kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant participant details to uniquely identify the participant.

Study intervention (ie, esketamine nasal spray) administration must be captured in the source documents and the electronic case report form (eCRF). Refer to Section 6.1.5, for information on the SSRI/SNRI background medication.

Esketamine nasal spray is an Investigational Medicinal Product (IMP). The background medication (SSRI/SNRI) is a Non-Investigational Medicinal Product /Auxiliary Medicinal Product (NIMP/AxMP) in this study.

Refer to Section 6.6 for information regarding standard of care treatment following completion of the study or early discontinuation of the study intervention.

For a definition of study intervention overdose, refer to Section 6.7, Treatment of Overdose.

### 6.1.1. Combination Products

- The combination product comprises a drug constituent (esketamine) fill-finished in a vial which is then assembled with a container holder and the actuator subassembly to prepare the complete single-use nasal spray device.
- The nasal spray device components and sub-assemblies, including the primary container glass vial and stopper, are sourced from third parties. The combination product is filled (with the drug constituent) and assembled by a third party on behalf of the sponsor.
- Instructions for use (participant and healthcare provider versions) for esketamine nasal spray administration will be provided as separate documents.
- All combination product deficiencies (including failure, malfunction, improper or inadequate design, manufacturer error, use error, and inadequate labeling) shall be documented and reported by the investigator throughout the study. For studies in combination product, these deficiencies will be reported as product quality complaints (PQC) (see Appendix 5: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting and appropriately managed by the sponsor.

### 6.1.2. Esketamine Nasal Spray

Esketamine is provided as a nasal spray solution (eq. 140 mg/mL nasal spray) and is an aqueous solution of esketamine hydrochloride in water for injection, at a concentration of 161.4 mg/mL and an esketamine base equivalent concentration of 140 mg/mL, provided in a disposable single-use nasal spray device. The device dispenses 2 sprays delivering a total volume of 0.2 mL of drug product containing a total of 32.3 mg of esketamine hydrochloride (equivalent to 28 mg of esketamine).

Esketamine nasal spray will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.

Each nasal spray device will be individually packaged in a blister tray and subsequently put into a carton box. Each carton box constitutes 1 non-child-resistant participant kit, labeled with a unique

medication kit number. Study intervention labels will contain information to meet the applicable regulatory requirements.

Food will be restricted for at least 2 hours before each administration of esketamine nasal spray. Drinking of any fluids will be restricted for at least 30 minutes before the first nasal spray at each session. Participants should abstain from alcohol consumption for 24 hours before and after esketamine nasal treatment sessions.

Nasal treatment sessions should not take place on 2 consecutive days. Dosing will be in an outpatient setting, or inpatient setting if participants are currently hospitalized. If the participant has nasal congestion on the dosing day, a nasal decongestant can be used to reduce congestion or the dosing day can be delayed (per the permitted visit window; see the Schedule of Activities in Section 1.3). Participants who require a nasal corticosteroid or nasal decongestant on a dosing day should be advised not to administer these medicinal products 1 hour prior to esketamine nasal spray dosing.

Postdosing, participants' vital signs will be measured at approximately 40 minutes after esketamine nasal spray dose and subsequently as clinically warranted until blood pressure values decline. Participants must be monitored by a healthcare professional until the participant is considered clinically stable and ready to leave the study site. If blood pressure remains elevated for a prolonged period of time, assistance should promptly be sought from practitioners experienced in blood pressure management. Participants who experience symptoms of a hypertensive crisis should be referred immediately for emergency care.

On all nasal dosing days, participants must remain at the study site until study procedures have been completed and they are ready for discharge. Participants must not engage in potentially hazardous activities requiring complete mental alertness and motor coordination, such as driving a vehicle or operating machinery, after receiving esketamine nasal spray until the next day following a restful sleep.

For a definition of esketamine nasal spray overdose, refer to Section 6.7, Treatment of Overdose.

### 6.1.3. Esketamine Nasal Spray Dosing Recommendations

All participants in the open-label extension study will receive treatment with esketamine nasal spray, administered once weekly or every 2 weeks. The dosage of esketamine nasal spray will be determined based on the participant's dose and frequency at completion of the maintenance phase (Week 32) of Study TRD3013. Investigators will be allowed to change the dose and frequency during the open-label extension based on clinical judgment. All administrations of esketamine nasal spray will be performed at the study site.

The dosing recommendations for esketamine nasal spray for adults <65 years of age and for elderly participants ≥65 years of age and adults of Japanese ancestry are shown in Table 1.

**Table 1: Long-term Extension: Recommended Dosing for Esketamine Nasal Spray**

| **Adults <65 Years of Age** |
|---|
| From Day 1:<br>56 mg or 84 mg every 2 weeks or once weekly |
| **Elderly Participants ≥65 Years of Age and Adults of Japanese Ancestry** |
| From Day 1:<br>28 mg, 56 mg, or 84 mg every 2 weeks or once weekly, all dose changes should be in 28 mg increments. |

The need for continued treatment should be reexamined periodically.

Dosing may be increased at any visit, may remain the same, or may be reduced as determined by the investigator based on efficacy and tolerability. The highest dose that may be used in all participants is 84 mg.

The frequency of nasal treatment sessions for participants can be individualized on even week visits (Week 2, Week 4, etc) from once weekly to every 2 weeks based on the severity of depressive symptoms and at the discretion of the investigator. If participants show early signs of worsening of depressive symptoms after reduced frequency of the nasal treatment sessions, the frequency can be changed back to once weekly at any visit. Nasal treatment session frequency should be increased prior to increasing the esketamine nasal spray dose. Uneven week visits will only be performed for participants who are on a once-weekly dosing schedule.

Recommendations for dose adjustments of esketamine nasal spray based on efficacy and tolerability during the long-term extension are provided in Section 6.5 in Figure 2 for adults and Figure 3 for elderly participants and adults of Japanese ancestry.

### 6.1.4. Nasal Treatment Sessions

All participants will self-administer the esketamine nasal spray at nasal treatment sessions at the study site starting on Day 1 and continue treatment session once-weekly or every 2 weeks based on their dosing frequency.

Esketamine nasal spray dosing and related safety-monitoring procedures MUST be performed LAST at all visits. Esketamine nasal spray must NOT be administered before all other visit assessments are completed.

The esketamine nasal spray will be administered during nasal treatment sessions as described in Table 2.

**Table 2: Nasal Treatment (Esketamine) Sessions**

| Nasal Study Intervention | Time of Administration | | |
|---|---|---|---|
| | **0[a]** | **5 minutes** | **10 minutes** |
| Nasal Device [b] | First | Second | Third |
| Esketamine 28 mg | 1 spray of nasal spray to each nostril | No device required | No device required |
| Esketamine 56 mg | 1 spray of nasal spray to each nostril | 1 spray of nasal spray to each nostril | No device required |
| Esketamine 84 mg | 1 spray of nasal spray to each nostril | 1 spray of nasal spray to each nostril | 1 spray of nasal spray to each nostril |

[a] Time 0 is defined as the time of administration of the first esketamine nasal spray to 1 nostril from the first nasal device.

[b] One device will be used at each time point. Each nasal device contains 2 sprays. The esketamine nasal devices contain a total of 28 mg per individual device (ie, 2 sprays).

Recommendations for dose adjustments of esketamine nasal spray based on efficacy and tolerability during the long-term extension are provided in Section 6.5 in Figure 2 for adults and Figure 3 for elderly participants and adults of Japanese ancestry.

### 6.1.5. Background Medication - SSRI/SNRI

Participants will continue to take their current SSRI/SNRI as prescribed. The continuing SSRI/SNRI dose should have been optimized up to the maximum tolerated dose during Study TRD3013 as per the respective SmPC (or local equivalent, if applicable). During the long-term extension study, a stable dose should be maintained; however, dose modifications to the continuing SSRI/SNRI may be made, if necessary, at the investigator's discretion. Additionally, during the long-term extension study, the SSRI/SNRI may be switched for individual participants by the investigator for tolerability issues. The switch of a participant's SSRI/SNRI should occur at an "every 4 week visit" so that clinician-rated scales and PROs are captured prior to the switch; the reason for the switch must be documented in the eCRF.

If the SSRI/SNRI is discontinued at any time during the study, the esketamine nasal spray must also be discontinued.

The SSRI/SNRI tablets or capsules being taken by participants will not be provided by the sponsor.

The SSRI/SNRI being taken by a participant must be labeled for treatment of depression/MDD in their country of participation and the dosage being taken should be according to the respective SmPC (or local equivalent, if applicable). Off-label use of an SSRI/SNRI is not permitted.

## 6.2. Preparation/Handling/Storage/Accountability

**Preparation/Handling/Storage**

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

**Accountability**

The investigator is responsible for ensuring that study intervention (ie, esketamine nasal spray) received at the site is inventoried and accounted for throughout the study according to the sponsor's instructions and local controlled substance regulations. The study intervention administered to the participant must be documented on the intervention accountability form. All study intervention will be stored and disposed of according to the sponsor's instructions and local controlled substance regulations.

Study intervention 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 intervention 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 intervention, or used returned study intervention for destruction, will be documented on the intervention return form. When the study site is an authorized destruction unit and study intervention supplies are destroyed on-site, this must also be documented on the intervention return form.

Study intervention should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study intervention will be supplied only to participants participating in the study. Returned study intervention must not be dispensed again, even to the same participant. Study intervention may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study intervention from, nor store it at, any site other than the study sites agreed upon with the sponsor. Further guidance and information for the final disposition of unused study interventions are provided in the pharmacy manual/study-site investigational product and procedures manual.

## 6.3. Measures to Minimize Bias: Randomization and Blinding

Randomization and blinding procedures are not applicable in this study.

## 6.4. Study Intervention Compliance

All doses of esketamine nasal spray will be self-administered by the participants 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 esketamine nasal spray devices self-administered by participants. Study intervention supplies for each participant will be inventoried and accounted for throughout the study.

The SSRIs/SNRIs are not provided by the sponsor. Study-site personnel will provide medication compliance counseling regarding the SSRI/SNRI to all participants at the time points specified in the Schedule of Activities.

## 6.5. Dose Modification

Any dose/dosage adjustment should be overseen by medically-qualified study-site personnel (principal or subinvestigator unless an immediate safety risk appears to be present; for example, a rise in blood pressure noted by other study personnel following the first nasal spray in a dose).

The decision to change the dose or frequency of esketamine nasal spray (either an increase or a decrease) will be made by the investigator based on safety, tolerability, and efficacy assessed for each individual participant at their current dose level.

When the investigator wants to reduce nasal treatment in a stable episode, the dosing frequency should be reduced before considering reducing the dosage in line with the SmPC, ie, dosing should be individualized to the lowest frequency to maintain remission/response.

Recommendations for possible dose modification of esketamine nasal spray based on efficacy and tolerability during the long-term extension study are provided in Figure 2 for adults and Figure 3 for elderly participants and adults of Japanese ancestry.

**Figure 2: Adults: Recommendations for Possible Dose Modification of Esketamine Nasal Spray to Optimize Efficacy or Handle Decreased Tolerability During the Long-term Extension Phase**

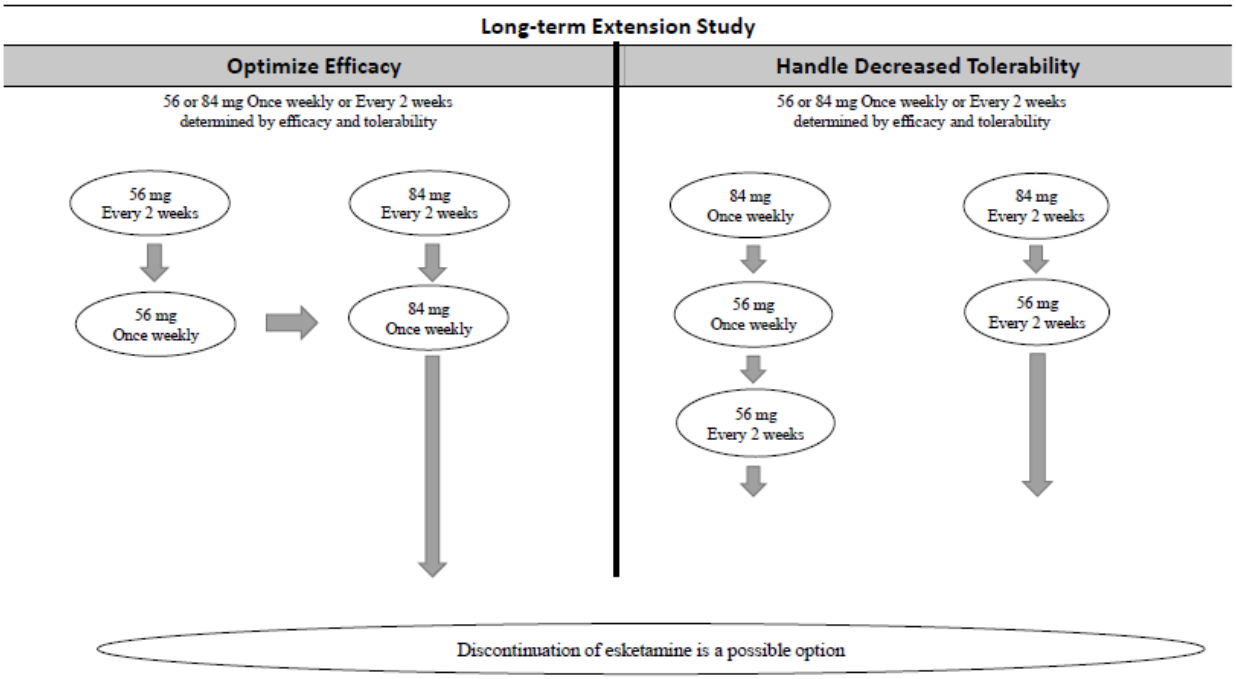
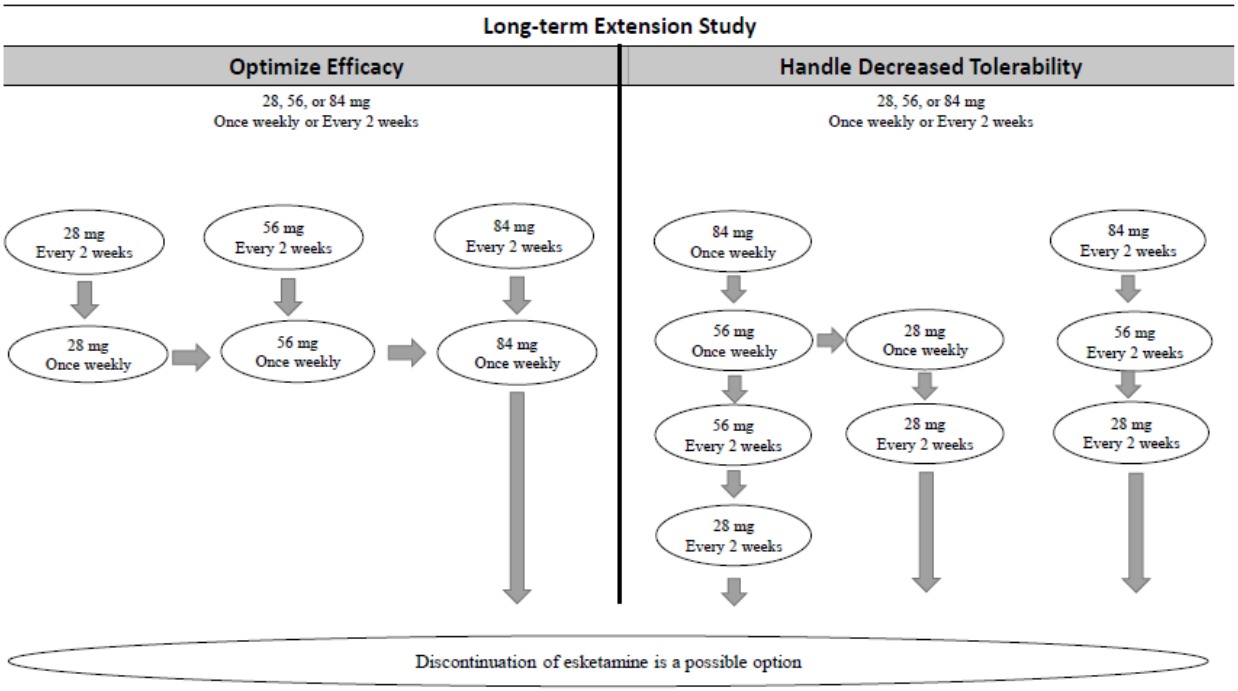


**Figure 3: Elderly and Adults of Japanese Descent: Recommendations for Possible Dose Modification of Esketamine Nasal Spray to Optimize Efficacy or Handle Decreased Tolerability During the Long-term Extension Phase**




## 6.6. Continued Access to Study Intervention After the End of the Study

Participants will be instructed that esketamine nasal spray will not be made available to them after they have completed the long-term extension study and that they should return to their primary physician to determine standard of care, if applicable.

Participants will have access to the medication for a maximum of 2 years during this study. If esketamine nasal spray becomes accessible locally before the 2-year endpoint, then participants will be considered as having completed the open-label extension study and will be switched to a commercially available supply if in the opinion of the treating physician, the participant continues to benefit from treatment and the participant wishes to continue the esketamine nasal spray treatment. The commercial esketamine nasal spray will not be provided to the participant by the sponsor, rather, the investigator/primary physician must prescribe the medication to the participant.

## 6.7. Treatment of Overdose

For this study, any dose of esketamine nasal spray greater than 84 mg within a 24-hour time period will be considered an overdose. There is no specific antidote for esketamine overdose.

In the event of an overdose, the investigator or treating physician should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for AEs/serious adverse events (SAEs) and laboratory abnormalities until esketamine nasal spray can no longer be detected systemically.
- If respiratory depression occurs, supportive ventilation should be employed.
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

For SSRIs/SNRIs, the investigator should refer to the respective SmPCs (or local equivalent, if applicable) for advice on overdose.

## 6.8. Concomitant Therapy

Except for the prohibited concomitant medications described in Appendix 6, Prohibited Concomitant Medications, any medications that are ongoing and stable at Day 1 may be allowed to continue thereafter into the open-label extension study. Ongoing psychotherapy and other psychosocial interventions are allowed to continue.

The list of prohibited concomitant medications is provided as general guidance for the investigator (but is not all inclusive). Investigators should refer to the applicable SmPCs (or local equivalent, if applicable) for prohibited concomitant medications for the SSRI/SNRI. Any prescribed medications will not be discontinued without the agreement of the participant's treating physician.

Drugs of abuse (including barbiturates, methadone, opiates, cocaine, cannabinoids, phencyclidine (PCP), and amphetamine/methamphetamine) are not permitted during the study

Participants prescribed psychostimulants for indications other than MDD (eg, attention deficit hyperactivity disorder) are permitted to continue taking this medication during the study. Use of psychostimulants for recreational use is not allowed during the study.

Electroconvulsive therapy is not allowed during the study while the participant is receiving study intervention.

Participants should continue to take their permitted concomitant medications (eg, antihypertensive medications) at their regular schedule; however, restrictions related to timing of certain medications on days of nasal treatment sessions as outlined in Appendix 6, Prohibited Concomitant Medications, should be considered.

Concomitant therapies (including psychotherapy) must be recorded throughout the study beginning with Day 1 and continuing up to the last visit. Concomitant therapies should also be recorded beyond the last study visit only in conjunction with new or worsening AEs until resolution of the event.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as psychotherapy, acupuncture, special diets, and exercise regimens) different from the study intervention must be recorded in the eCRF. Modification of an effective preexisting therapy should not be made for the explicit purpose of

entering a participant into the study, unless permitted by protocol (eg, adjustment of blood pressure medications).

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

### 6.8.1. Psychotherapy

Participants who are currently undergoing psychotherapy should be encouraged by the investigator to continue it during the study. In addition to psychotherapy, supportive therapies like psycho-education and/or counseling should be continued. Participants are allowed to start psychotherapy, psycho-education, and/or counseling during the long-term extension study.

All standardized psychotherapy, psycho-education, support, or counseling that participants were undergoing prior to inclusion or started during this long-term extension study should be categorized into the appropriate category: 1. Cognitive–behavioral therapy (CBT); 2. Nondirective supportive therapy (SUP); 3. Behavioral activation therapy (BA); 4. Psychodynamic therapy (DYN); 5. Systemic therapy; 6. Problem-solving therapy (PST); 7. Interpersonal psychotherapy (IPT); 8. Social skills training (SST); 9. Other (any standardized intervention that cannot be captured under 1 to 8). The category of psychotherapeutic intervention, start date, stop date, frequency, reason for starting, reason for stopping, reason for change to another psychotherapeutic intervention, and participant's adherence to the psychotherapeutic intervention must be documented accordingly in the source documents and on the concomitant therapy eCRF.

Participants will not be provided with psychotherapy by the study sponsor but will be allowed to receive it from external providers based on local standard-of-care and infrastructural availability. If available, participants may receive psychotherapy at the site. The study sponsor will not reimburse for psychotherapy.

## 7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

### 7.1. Discontinuation of Study Intervention

A participant's study intervention must be discontinued if:

- The participant withdraws consent to receive study intervention
- The participant discontinues SSRI/SNRI
- The participant has developed any of the following cardiovascular-related conditions where an increase in blood pressure or intracranial pressure poses a serious risk:
    - cerebrovascular disease following stroke or transient ischemic attack.
    - aneurysmal vascular disease (including intracranial, thoracic, or abdominal aorta, or peripheral arterial vessels).
    - intracerebral hemorrhage.

  - coronary artery disease following myocardial infarction, unstable angina, or revascularization procedure (eg, coronary angioplasty or bypass graft surgery).
  - uncontrolled brady or tachyarrhythmias that lead to hemodynamic instability.
  - hemodynamically significant valvular heart disease such as mitral regurgitation, aortic stenosis, or aortic regurgitation or heart failure (NYHA Class III-IV) of any etiology.
  - significant pulmonary insufficiency, including chronic obstructive pulmonary disease.
- The investigator believes that for safety reasons or tolerability reasons (eg, adverse event), not expected to be resolved by dose and/or frequency adjustment, it is in the best interest of the participant to discontinue study intervention
- The investigator's opinion is that further continuation of study intervention would not be clinically justified
- The participant becomes pregnant
- Noncompliance with study drug administration defined as missing 3 consecutive doses

If a participant discontinues study intervention for any reason before the end of the open-label extension study, then the early study withdrawal and 2-week safety follow-up assessments should be obtained. Study intervention assigned to the participant who discontinued study intervention may not be assigned to another participant.

## 7.2. Participant Discontinuation/Withdrawal From the Study

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

- The participant discontinues study intervention (see Section 7.1)
- Esketamine nasal spray becomes accessible in an individual's local country
- Lost to follow-up
- Withdrawal of consent
- Death

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document. If the reason for withdrawal from the study is withdrawal of consent then no additional assessments are allowed.

Refer to Section 4.4 for study completion definition for participants.

### Withdrawal of Consent

If a participant is unable to return for scheduled visits, it does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the participant agreed to when signing the consent form apply, as local regulations permit.

## 7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed

lost to follow-up until all reasonable efforts made by the study-site personnel to contact the participant are deemed futile. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study-site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, to ascertain whether the participant wishes to or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls, e-mails, fax, and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods. These contact attempts should be documented in the participant's medical records.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

Should a study site close, eg, for operational, financial, or other reasons, and the investigator cannot reach the participant to inform them, their contact information will be transferred to another study site.

# 8. STUDY ASSESSMENTS AND PROCEDURES

**Overview**

The Schedule of Activities (Section 1.2) summarizes the frequency and timing of efficacy and safety measurements applicable to this study.

Visit-specific PRO assessments should be conducted/completed before clinician-rated assessments, any tests, procedures, other consultations, or administration of esketamine nasal spray to prevent influencing participant perceptions. Refer to the PRO completion guidelines for instructions on the administration of PROs.

All clinician-rated scales must be completed prior to administration of esketamine nasal spray.

Actual dates of PRO and clinician-rated assessments will be recorded in the source documentation and eCRF.

Urine pregnancy tests (at site/local) will be performed in accordance with the Schedule of Activities (Section 1.2) and Section 8.2.4, Pregnancy Testing. Counseling on pregnancy prevention will be provided at all visits, when applicable.

The total blood volume to be collected from each participant will be approximately 30 mL (approximately 7-8 mL/visit), which may vary based on length of participation and local laboratory requirements. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

**Sample Collection and Handling**

The actual dates of sample collection must be recorded in the eCRF.

Refer to the Schedule of Activities (Section 1.2) for the timing and frequency of all sample collections.

**Study-Specific Materials**

The investigator will be provided with the following supplies:

- Investigator's Brochure for esketamine
- Investigational Product Binder, including the investigational product procedures manual
- Instructions for use documents (participant and healthcare provider versions) for esketamine nasal spray
- Instructions for product quality complaint (PQC) reporting requirements
- Paper versions of PRO questionnaires and PRO completion guidelines
- Paper versions of clinician-administered assessments (MADRS, C-SSRS)
- Rater qualifications/requirements for select clinician-administered assessments
- Electronic devices and associated materials, as applicable
- IWRS Manual
- Sample ICF
- Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approved participant materials

## 8.1. Efficacy Assessments

The sponsor will use the clinician-rated scales and PROs from Week 32 in Study TRD3013 in the database for Day 1 in this long-term extension study; these procedures do not need to be repeated for participants who return for esketamine nasal spray dosing within 14 days after the Week 32 visit in TRD3013.

### 8.1.1. Clinician-Rated

At all scheduled visits indicated in the Schedule of Activities, all clinician-rated scales must be completed prior to administration of esketamine nasal spray.

#### 8.1.1.1. Montgomery-Asberg Depression Rating Scale (MADRS)

The MADRS is a clinician-rated scale designed to measure depression severity and detect changes due to AD treatment (Montgomery 1979). The scale consists of 10 items, each of which is scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), for a total possible score of 60. Higher scores represent a more severe condition. The MADRS evaluates apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, inability to feel (interest level), pessimistic thoughts, and suicidal thoughts. The test exhibits high interrater reliability. The MADRS will be administered at the time points specified in the Schedule of Activities.

Rating of the MADRS will be conducted face-to-face with the participants by the rater. The rater should have sufficient qualifications as documented by experience or training prior to being assigned as rater. To avoid interrater variability, all efforts should be made to have the same independent rater rating the same study participants as much as possible. If possible, for individual participants, the independent rater from Study TRD3013 may continue performing the MADRS in this study. The MADRS takes about 30 minutes to complete.

In case of worsening of depressive symptoms and MADRS increase to ≥22, an additional assessment should be performed within the next 5 to 31 days to confirm the relapse criteria. The date of the second MADRS assessment will be used for the date of relapse.

The secondary efficacy endpoint, as described in Section 3, uses the MADRS (total score) as part of the criteria for relapse.

#### 8.1.1.2. Clinical Global Impression – Severity (CGI-S)

The CGI-S is an observer-rated scale that measures illness severity (Guy 1976). The CGI-S has proved to be a robust measure of efficacy in many clinical drug trials and is easy and quick to administer. The CGI-S is rated on a 7-point scale, with the severity of illness scale using a range of responses from 1 (normal) through to 7 (among the most severely ill participants). The CGI-S takes about 15 minutes to complete.

### 8.1.2. Patient-Reported Outcomes

Patient-reported outcomes will be completed by the participants at the timepoints indicated in the Schedule of Activities. As previously noted, all PRO assessments must be conducted/completed before clinician-rated assessments, any tests, procedures, other consultations, or administration of esketamine nasal spray.

The PRO assessments should be performed in the order as listed in the subsections below and in the Schedules of Activities in Section 1.3.

- The PRO instruments will be provided in the local language in accordance with local guidelines.
- The PRO instruments must be available for regulators and for IRB/IEC submissions, therefore the PRO instruments are attached to the protocol in Appendix 7.
- The PRO and AE data will not be reconciled with one another.

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

The PHQ-9 is a validated 9-item, PRO measure to assess depressive symptoms (Spitzer 1999). 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 participant'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 PHQ-9 takes about 5 minutes to complete.

#### 8.1.2.2. European Quality of Life (EuroQol) Group, 5-Dimension, 5-Level (EQ5D-5L)

The EQ-5D-5L is a validated standardized instrument for use as a measure of health outcome, primarily designed for self-completion by respondents (EuroQol Group n.d.; EuroQol Research Foundation 2009). It consists of the EQ-5D-5L descriptive system and a visual analogue scale (EQ-VAS). The EQ-5D-5L descriptive system comprises the following 5 dimensions: Mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each of the 5 dimensions is divided into 5 levels of perceived problems (Level 1 indicating no problem, Level 2 indicating slight problems, Level 3 indicating moderate problems, Level 4 indicating severe problems, and Level 5 indicating extreme problems).

The participant selects an answer for each of the 5 dimensions considering the response that best matches his or her health "today". The descriptive system can be represented as a health state. The EQ-VAS self-rating records the respondent's own assessment of his or her overall health status at the time of completion, on a scale of 0 ("The worst health you can imagine") to 100 ("The best health you can imagine"). The time taken to complete the questionnaire varies with age, health status, and setting but is likely to be around 5 minutes.

## 8.2. Safety Assessments

Adverse events will be reported and followed by the investigator as specified in Section 8.3, Adverse Events, Serious Adverse Events, and Other Safety Reporting, and Appendix 5, Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

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

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

The study will include the following evaluations of safety and tolerability according to the time points provided in the Schedule of Activities in Section 1.2.

The sponsor will use the safety assessments, including clinical laboratory tests, from Week 32 in Study TRD3013 in the database for Day 1 in this long-term extension study; these procedures do not need to be repeated for participants who return for esketamine nasal spray dosing within 14 days after the Week 32 visit in TRD3013.

### 8.2.1. Physical Examinations

**Body Weight**

Body weight will be measured as per the Schedule of Activities.

**Nasal Examinations**

Nasal examinations (including the upper respiratory tract/throat) will be conducted by a qualified healthcare practitioner authorized by local regulation to conduct a physical examination. The objective of the examination is to rule out any participants with medical conditions that may impede drug delivery or absorption. Abnormalities noted during the nasal examination will be reported as adverse events.

The nasal examination consists of a visual inspection of the nostrils, nasal mucosa, and throat for nasal erythema, rhinorrhea, rhinitis, capillary/blood vessel disruption, and epistaxis, and will be graded as follows: absent, mild, moderate, or severe.

### 8.2.2. Vital Signs

Pulse/heart rate, respiratory rate, and blood pressure will be assessed.

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).

### 8.2.3. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology and a random urine sample for urinalysis will be collected at the time points identified in the Schedule of Activities and as noted in Appendix 8, Clinical Laboratory Tests. Participants should fast for at least 8 hours prior to visits when blood samples 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 AE section of the eCRF. The laboratory reports must be filed with the source documents.

### 8.2.4. Pregnancy Testing

A negative urine pregnancy test must be obtained before the first dose of study intervention on Day 1. 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 participation in the study and

- every 4 weeks.
- at end of study intervention.
- at 2 weeks after the last dose of study intervention.

### 8.2.5. Suicidal Ideation and Behavior Risk Monitoring

Esketamine nasal spray is considered to be an antidepressant. There has been some concern that antidepressants may be associated with an increased risk of suicidal ideation or behavior when given to some participants with MDD. Although esketamine nasal spray or other similar treatments for MDD have not been shown to be associated with an increased risk of suicidal thinking or

behavior when given to this participant population, the sponsor considers it important to monitor for such events before or during this clinical study.

Participants being treated with esketamine nasal spray and an SSRI/SNRI should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. Consideration should be given to discontinuing esketamine nasal spray and/or the SSRI/SNRI in participants who experience signs of suicidal ideation or behavior.

If the participant agrees, the investigator can request that families and caregivers of participants being treated with study intervention monitor participants for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior, and to report such symptoms immediately to the study investigator.

Intervention-emergent suicidal ideation and behavior will be assessed during the study using the C-SSRS. If early signs of suicidal ideation are identified then the C-SSRS should be applied more frequently than the time points listed in the Schedule of Activities, at the discretion of the investigator.

The C-SSRS is a low-burden measure of the spectrum of suicidal ideation and behavior that was developed in the National Institute of Mental Health Treatment of Adolescent Suicide Attempters Study to assess severity and track suicidal events through any treatment (Posner 2011). It is a clinical interview which supports suicide risk assessment through a series of simple, plain-language questions. It identifies risk not only if someone has previously attempted suicide, but also if he or she has considered suicide, prepared for an attempt (for example, buying a gun, collecting pills, or writing a suicide note), or aborted plans for suicide because of a last-minute change of heart or a friend's intervention. Users of the C-SSRS tool ask people:

- Whether and when they have thought about suicide (ideation)
- What actions they have taken — and when — to prepare for suicide
- Whether and when they attempted suicide or began a suicide attempt that was either interrupted by another person or stopped of their own volition.

## 8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

Timely, accurate, and complete reporting and analysis of safety information, including adverse events, serious adverse events, and PQC, from clinical studies are crucial for the protection of participants, 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.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study.

For study intervention that meets the definition of a combination product, malfunctions or deficiencies of a device constituent will be reported as PQC.

Further details on adverse events, serious adverse events, and PQC can be found in Appendix 5, Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

### 8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

**All Adverse Events**

All adverse events and special reporting situations, whether serious or non-serious, will be reported from Day 1, starting after the first dose of esketamine nasal spray, until completion of the participant's 2-week safety follow-up visit. Prior to the first dose in this long-term extension, this information will be captured as part of Study TRD3013.

**Serious Adverse Events**

All serious adverse events, 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 intervention, must be reported. 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). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

### 8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events or serious adverse events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about adverse event occurrence.

### 8.3.3. Follow-up of Adverse Events and Serious Adverse Events

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated to elucidate the nature and causality of the adverse event, serious adverse event, or PQC as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Adverse events, including pregnancy, will be followed by the investigator as specified in Appendix 5, Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other

Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

### 8.3.4. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants 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 a serious adverse event reporting form. Any participant who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study intervention.

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

### 8.3.5. Disease-Related Events and Disease-Related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

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.

### 8.3.6. Adverse Events of Special Interest

Clinically relevant intervention-emergent AEs of special interest will be summarized separately grouped in the following MedDRA based categories:

- **Sedation:** sedation; somnolence; altered state of consciousness; depressed level of consciousness; hypersomnia; stupor
- **Dissociation:** depersonalisation/derealisation disorder; derealisation; dissociative disorder; flashback; hallucination; hallucination, auditory; hallucination, visual; illusion; somatic hallucination; hyperacusis; tinnitus; diplopia; vision blurred; ocular discomfort; photophobia; visual impairment; dysaesthesia; oral dysaesthesia; paraesthesia; paraesthesia oral; pharyngeal paraesthesia; time perception altered; daydreaming; delusional perception; feeling hot; feeling cold; feeling of body temperature change
- **Suicidality:** completed suicide; depression suicidal; intentional overdose; intentional self-injury; multiple drug overdose intentional; poisoning deliberate; self-injurious behavior; self-injurious ideation; suicidal behavior; suicidal ideation; suicide attempt; toxicity to various agents
- **Suggestive of abuse potential**: aggression; confusional state; decreased activity; dependence; disorientation; dissociation; dissociative disorder; dizziness; drug abuse; drug abuser; drug dependence; drug use disorder; drug detoxification; drug diversion; drug rehabilitation; drug tolerance; drug tolerance increased; drug withdrawal convulsions; drug withdrawal headache; drug withdrawal syndrome; euphoric mood; feeling abnormal; feeling drunk; feeling of relaxation; hallucination; hallucination, auditory; hallucination, gustatory; hallucination, olfactory; hallucination, synaesthetic; hallucination, tactile; hallucination, visual; hallucinations, mixed; inappropriate affect; mental impairment; product tampering; psychomotor hyperactivity; psychotic disorder; rebound effect; somatic hallucination;

somnolence; substance abuser; substance dependence; substance use; substance use disorder; substance-induced mood disorder; substance-induced psychotic disorder; thinking abnormal; withdrawal arrhythmia; withdrawal syndrome

- **Cystitis**: adenoviral hemorrhagic cystitis; allergic cystitis; bladder candidiasis; bladder diverticulitis; cystitis bacterial; cystitis erosive; cystitis escherichia; cystitis glandularis; cystitis gonococcal; cystitis helminthic; cystitis hemorrhagic; cystitis interstitial; cystitis klebsiella; cystitis noninfective; cystitis pseudomonal; cystitis radiation; cystitis ulcerative; cystitis viral; emphysematous cystitis; eosinophilic cystitis; fungal cystitis; lupus cystitis; malacoplakia vesicae; schistosomiasis bladder; trigonitis; tuberculosis bladder; urinary bladder abscess; viral hemorrhagic cystitis
- **Hepatic impairment**: acquired complement deficiency disease; bilirubin excretion disorder; crigler-najjar syndrome; HELLP (hemolysis, elevated liver enzymes, and a low platelet count) syndrome; hepatic function abnormal; hyperammonemic crisis; hyperammonemia; hypertransaminasemia; hypoalbuminemia; hypoproteinemia

### 8.4. Pharmacokinetics

Not applicable.

### 8.5. Genetics and Pharmacogenomics

Genetics or Pharmacogenomics are not evaluated in this study.

### 8.6. Biomarkers

Biomarkers are not evaluated in this study.

### 8.7. Immunogenicity Assessments

Immunogenicity is not evaluated in this study.

## 9. STATISTICAL CONSIDERATIONS

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.

### 9.1. Statistical Hypotheses

Due to the design of the study (single-arm, long-term extension) and the objective (exploratory nature) no hypothesis is described for this study.

### 9.2. Sample Size Determination

As no hypothesis is specified for this study, no sample size estimation is performed. Sample size will be driven by pragmatic considerations. It is expected that from 100 to 200 participants will be enrolled in this study.

## 9.3. Populations for Analysis Sets

For purposes of analysis, the following populations are defined:

| Population | Description |
|---|---|
| Enrolled | All participants who sign the ICF |
| Safety/Efficacy | All participants who take at least 1 dose of study intervention. |

## 9.4. Statistical Analyses

### 9.4.1. General Considerations

Descriptive analyses will be performed on the Safety/Efficacy analysis set.

All continuous variables will be summarized using descriptive statistics, which will include the number of participants, mean, standard deviation, median, minimum, maximum, and 95% confidence interval. All categorical variables will be summarized using frequencies and percentages. Distribution of time-to-event variables will be estimated using standard survival analysis methods, including Kaplan-Meier product-limit survival curves. The median time to event with 2-sided 95% confidence intervals will be estimated.

For continuous/ordinal parameters (eg, MADRS, CGI-S, PHQ-9, EQ-5D-5L) descriptive statistics of the observed values and change from Study TRD3013 baseline will be provided for each study visit. For categorical/dichotomous parameters descriptive statistics of the observed score will be provided for each study visit.

### 9.4.2. Primary Endpoints

For the analysis of adverse events, see Section 9.4.5.

The 10 items of the C-SSRS and the derived endpoints (Suicidal ideation, Suicidal behavior, Suicidal ideation or behavior, Suicidal ideation score) will be summarized as frequency distributions for each assessment during treatment.

### 9.4.3. Secondary Endpoints

For the MADRS (total and individual scores), CGI-S, and the PHQ-9 (total score), the scale score and changes from Study TRD3013 baseline will be analyzed by study visit.

Frequency of relapse and time to relapse will be described.

For the EQ5D-Health-Utility and the EQ5D-VAS, the score and changes from Study TRD3013 baseline will be analyzed by study visit.

### 9.4.4. Exploratory Analyses

In cases where the oral AD is switched to another compound from the SNRI/SSRI classes, the impact of switching will be explored. The reasons for the switches will be summarized, the impact on existing AEs will be described, and new AEs starting after the switches will be tabulated. Also, the impact on the efficacy parameters MADRS and CGI-S will be explored by summarizing the

observed values at the visit when the switch was made and changes from that visit at subsequent visits.

### 9.4.5. Safety Analyses

All safety analyses will be made on the Safety/Efficacy Population.

**Adverse Events**

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study intervention through the day of last dose plus 30 days is considered to be intervention-emergent. All reported intervention-emergent adverse events will be included in the analysis. For each adverse event, the percentage of participants who experience at least 1 occurrence of the given event will be summarized.

Intervention-emergent AEs of special interest will be summarized separately grouped in the categories as described in Section 8.3.6.

Summaries, listings, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue intervention due to an adverse event, or who experience a serious adverse event.

**Clinical Laboratory Tests**

Only clinically relevant changes in laboratory parameters that meet the definition of an AE during the study are reported by the investigator as AEs and these will be included in the all intervention-emergent AE analyses.

**Vital Signs**

Descriptive statistics of pulse/heart rate, respiratory rate, and supine blood pressure (SBP and DBP) values and changes from Study TRD3013 baseline will be summarized at each scheduled time point. The percentage of participants with values beyond clinically important limits will be summarized.

## 9.5. Interim Analysis

An interim analysis may be performed after approximately 50 participants have been enrolled in the study, when data have been accrued over a period of 9 to 12 months. The scope of the interim analysis will be developed and documented in a statistical analysis plan.

Other interim analyses may be planned based on specific questions from the medical field or from health authorities in certain countries.

# 10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## 10.1. Appendix 1: Abbreviations and Definitions

| | |
|---|---|
| AD | antidepressant |
| AE | adverse event |
| AUC | area under the plasma concentration-time curve |
| $AUC_{\infty}$ | area under the plasma concentration-time curve from time 0 to infinity |
| CADSS | Clinician-Administered Dissociative States Scale |
| CGI-C | Clinical Global Impression – Change |
| $C_{max}$ | maximum plasma concentration |
| COVID-19 | Coronavirus Disease 2019 |
| C-SSRS | Columbia-Suicide Severity Rating Scale |
| CYP | cytochrome P450, with any appended letters (2B6, 3A4, etc) indicating subtypes |
| DBP | diastolic blood pressure |
| DSM-5 | Diagnostic and Statistical Manual of Mental Disorders, fifth edition |
| eCRF | electronic case report form |
| eDC | electronic data capture |
| EQ-5D-5L | European Quality of Life (EuroQoL) Group, 5-Dimension, 5-Level (questionnaire) |
| EQ-VAS | EuroQoL Group: visual analogue scale |
| FDA | Food and Drug Administration |
| FOIA | Freedom of Information Act |
| GCP | Good Clinical Practice |
| HCl | hydrochloride |
| IB | Investigator's Brochure |
| ICF | informed consent form |
| ICMJE | International Committee of Medical Journal Editors |
| ICH | International Council on Harmonisation |
| IEC | Independent Ethics Committee |
| IRB | Institutional Review Board |
| IV | intravenous |
| IWRS | interactive web response system |
| MADRS | Montgomery-Asberg Depression Rating Scale |
| MDD | major depressive disorder |
| MDSI | patients with major depressive disorder who have active suicidal ideation with intent |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NMDAR | N-methyl-D-aspartate receptor |
| PHQ-9 | Patient Health Questionnaire, 9-item |
| PQC | product quality complaint |
| PRO | patient-reported outcome |
| QTc | corrected QT interval |
| SAE | serious adverse event |
| SBP | systolic blood pressure |
| SmPC | Summary of Product Characteristics |
| SNRI | serotonin-norepinephrine reuptake inhibitor |
| SSRI | selective serotonin reuptake inhibitor |
| SUSAR | suspected unexpected serious adverse reaction |
| TRD | treatment-resistant depression |

### Definitions of Terms

| | |
|---|---|
| Electronic source system | Contains data traditionally maintained in a hospital or clinic record to document medical care or data recorded in a case report form as determined by the protocol. Data in this system may be considered source documentation. |
| PRO | Reports directly from the participant without interpretation by clinician or anyone else |

## 10.2. Appendix 2: Contraceptive and Barrier Guidance

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.4, Pregnancy and Appendix 5 Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

**Definitions**

***Woman of Childbearing Potential (WOCBP)***

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

***Woman Not of Childbearing Potential***

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. If there is a question about menopausal status in women on HRT, the woman will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
- **permanently sterile (for the purpose of this study)**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) 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.

If reproductive status is questionable, additional evaluation should be considered.

Contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

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 participants in clinical studies.

## Examples of Contraceptives

| **EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:** |
|---|
| **USER INDEPENDENT** (**PREFERRED** METHOD FOR COMPOUNDS WITH POSSIBLE OR UNKNOWN TOXICITY AND **RECOMMENDED** METHOD FOR COMPOUNDS WITH SUSPECTED OR DEMONSTRATED TOXICITY)<br>**Highly Effective Methods That Are User Independent** *Failure rate of <1% per year when used consistently and correctly.* |
| • Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b] |
| • Intrauterine device (IUD) |
| • Intrauterine hormone-releasing system (IUS) |
| • Bilateral tubal occlusion |
| • Azoospermic partner *(vasectomized or due to medical cause)*<br>*(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*<br>**Note:** The spermatogenesis cycle is approximately 74 days; however it is prudent for purposes of a research study to estimate the cycle duration closer to 90 days to ensure adequate protection during a potentially vulnerable period with regard to exposure to the study intervention: informed consent should be obtained, as appropriate, from partners. |
| **USER DEPENDENT**<br>**Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.* |
| • Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b]<br>– oral<br>– intravaginal<br>– transdermal<br>– injectable |
| • Progestogen-only hormone contraception associated with inhibition of ovulation[b]<br>– oral<br>– injectable |
| • Sexual abstinence<br>*(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 intervention. 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 participant.)* |
| **NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of ≥1% per year)** |
| • Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action. |
| • Male or female condom with or without spermicide[c] |
| • Cap, diaphragm, or sponge with spermicide |
| • A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c] |
| • Periodic abstinence (calendar, symptothermal, post-ovulation methods) |
| • Withdrawal (coitus-interruptus) |
| • Spermicides alone |
| • Lactational amenorrhea method (LAM) |
| a) 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 participants in clinical studies.<br>b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention.<br>c) Male condom and female condom should not be used together (due to risk of failure with friction). |

## 10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

### 10.3.1. Regulatory and Ethical Considerations

**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 participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

**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 participants, 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) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

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

**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.

**Required Prestudy Documentation**

The following documents must be provided to the sponsor before shipment of study intervention 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, participant 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 participant:

- 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

**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 participants)
- IB (or equivalent information) and amendments/addenda
- Information on compensation for study-related injuries or payment to participants 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 participants
- 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 participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant 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 participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB 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 intervention
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants 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 participants, 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 (if applicable, the notification will be submitted through the head of investigational institution).

**Country Selection**

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.3.1, Study-Specific Ethical Design Considerations.

**Other Ethical Considerations**

For study-specific ethical design considerations, refer to Section 4.3.1.

### 10.3.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) and contracts for details on financial disclosure.

### 10.3.3. Informed Consent Process

Each participant 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 participant 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 participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants 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 participant will receive for the treatment of his or her disease. Participants 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 participant 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 participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant is authorizing such access. It also denotes that the participant

agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The participant 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 participant's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

### 10.3.4. Data Protection

**Privacy of Personal Data**

The collection and processing of personal data from participants 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 participants confidential.

The informed consent obtained from the participant 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 participant 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.

### 10.3.5. Publication Policy/Dissemination of Clinical Study Data

All information, including but not limited to information regarding esketamine nasal spray 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 exploratory 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 nasal spray, 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 for the study. Results of exploratory 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 participant 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 (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and sub-study approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, 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 ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**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. The disclosure of the final study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

### 10.3.6. Data Quality Assurance

**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, and periodic monitoring visits by the sponsor.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review eCRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

### 10.3.7. Case Report Form Completion

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

The study data will be transcribed by study-site personnel from the source documents onto an eCRF, 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 eCRF. Any such worksheets will become part of the participant's source documents. Data must be entered into eCRF in English. The eCRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

All participative measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the electronic data capture (eDC) tool. If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

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

### 10.3.8. Source Documents

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: participant 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; intervention receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable. Given that patient-reported outcomes (PROs) are reports of a patient's health condition that come directly from the patient, without interpretation by a clinician or anyone else, the responses to PRO measures entered by trial participants into source records cannot be overridden by site staff or investigators.

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

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

- Blood pressure and pulse/heart rate
- Body weight
- Investigator-completed scales and assessments, when applicable, and with the exception of MADRS

An 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 eSource is utilized, references made to the eCRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the eCRF.

### 10.3.9. Monitoring

The sponsor will use a combination of monitoring techniques central, remote, or on-site monitoring to monitor this study.

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. At these visits, the monitor will compare data entered into the eCRF with the source documents (eg, hospital/clinic/physician’s office medical records); a sample may be reviewed. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are

accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

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

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

### 10.3.10. 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. Participant 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.

### 10.3.11. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each participant, 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.

### 10.3.12. Study and Site Start and Closure

**First Act of Recruitment**

The first site open is considered the first act of recruitment and it becomes the study start date.

**Study/Site 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 participants by the investigator
- Discontinuation of further study intervention development

## 10.4. Appendix 4: Guidance on Study Conduct During a 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 participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study-related participant 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 participants and site staff. If, at any time, a participant's safety is considered to be at risk, study intervention will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up. Modifications to protocol-required assessments may be permitted via this COVID-19 Appendix after consultation with the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. If a participant 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. Discontinuations of study interventions and withdrawal from the study should be documented indicating "COVID-19-related" in the eCRF.

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

**GUIDANCE SPECIFIC TO THIS PROTOCOL:**

These emergency provisions are meant to ensure the safety of participants on study while site capabilities are compromised by any COVID-19-related restrictions. The situation should be continuously assessed throughout the evolution of the COVID-19 pandemic. Once any restrictions are lifted and the acute phase of a COVID-19 pandemic resolves, sites should revert to the original protocol conduct as soon as feasible.

Some medical or study procedures may make it impossible to practice physical distancing (eg, blood pressure or blood sampling will require a closer interaction between participant and study site staff), however such interactions should be limited to the absolute minimum required. During

close interactions, the participant and site staff should follow strict sanitizing/hygiene measures to minimize the risk for exposure to COVID-19.

**Remote Monitoring**

- Remote monitoring will be conducted (when possible) in-between on-site monitoring visits, to reduce the frequency of on-site monitoring visits to the lowest frequency possible. Risk-based-monitoring will be extensively used to monitor remotely the quality of data and optimize the frequency of onsite monitoring visits.

**Study Intervention**

- All efforts should be made to assure treatment continuation at the optimal individualized study dosing schedule for those that are on study intervention at the time when any restrictions are imposed.
- Administration of esketamine at an alternative location in the vicinity of the study site (under supervision of study staff), if permitted by local regulations, may be allowed after consultation with the sponsor. Reduction of visit frequency from weekly to every other week, is allowed based on clinical judgement, eg, the dosing schedule for participants receiving 56 mg once weekly is recommended to be modified to 84 mg every 2 weeks.
- Study intervention can be discontinued at any visit and the participant can be switched to an alternative standard of care treatment (both pharmacological and non-pharmacological) at the discretion of the treating investigator.
- In the event changes to the dosing schedule are introduced or doses are missed due to restrictive COVID-19 measures, then the required details should be captured in the participant's source notes as well as the eCRF. Missed study intervention doses due to COVID-19 does not result in automatic withdrawal from the study.

**Protocol Assessments**

- MADRS rating in this study should be conducted by an on-site MADRS rater. In circumstances where a study participant is not allowed (due to self-quarantine, lockdown, local restrictions, etc) to visit the study site, remote MADRS rating by videoconference application (eg, Skype, Zoom) will be acceptable in replacement of on-site MADRS rating. The process for MADRS rating should revert to the original on-site rating as soon as possible.
- Other clinician scales could be conducted by telephone interview in the event a participant is unable to visit the study site for a scheduled study visit.
- PROs in this study are paper based. PROs can be completed by the participant at home in those instances where the participant cannot visit the study site or wants to limit the time spent during a scheduled study visit. Completion should happen as close as possible to the date of the planned study visit and required PROs will be mailed to (and collected from) the participant's home by study staff.

**Participants with COVID-19 Infection**

- If a participant develops COVID-19 disease, then all the study physical interactions should be temporarily interrupted until the infection resolves. Study intervention may be temporarily interrupted at the discretion of the investigator and considering the severity of the viral

infection as well as safety and well-being of the participant. COVID-19 infection should be reported to the sponsor following the Adverse Event/Serious Adverse Event reporting requirements.

- When a participant recovers from COVID-19 infection, study intervention may be resumed when safe to do so as determined by the treating study investigator in consultation with the sponsor prior to resuming study intervention.

## 10.5. Appendix 5: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

### 10.5.1. Adverse Event Definitions and Classifications

**Adverse Event**

An adverse event is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the intervention. 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 All Adverse Events under Section 8.3.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last adverse event recording).

For combination products with a device constituent, adverse events include those resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the device. It includes any adverse event resulting from use error or from intentional misuse of the investigational device.

**Serious Adverse Event**

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

- Results in death
- Is life-threatening
  (The participant 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 participant 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 intervention 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).

For combination products with a device constituent, serious adverse events include adverse device effects that resulted in any of the consequences characteristic of a serious adverse event.

**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, the expectedness of an adverse event will be determined by whether or not it is listed in the IB. For the SSRI/SNRI with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the SmPC (or local equivalent, if applicable).

### 10.5.2. Attribution Definitions

**Assessment of Causality**

The causal relationship to study intervention is determined by the Investigator. The following selection should be used to assess all adverse events (AE).

**Related**

There is a reasonable causal relationship between study intervention administration and the AE.

**Not Related**

There is not a reasonable causal relationship between study intervention administration and the AE.

The term “reasonable causal relationship” means there is evidence to support a causal relationship.

### 10.5.3. 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 participant (eg, laboratory abnormalities).

### 10.5.4. Special Reporting Situations

Safety events of interest on a sponsor study intervention in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study intervention
- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention
- Any failure of expected pharmacologic action (ie, lack of effect) of a sponsor study intervention (to be reported as a PQC for marketed products)
- Unexpected therapeutic or clinical benefit from use of a sponsor study intervention
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without patient exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Exposure to a sponsor study intervention from breastfeeding

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

### 10.5.5. Procedures

**All Adverse Events**

All adverse events, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the participant 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 participant 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 personnel only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

**Serious Adverse Events**

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon the participant's discontinuation from 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 intervention or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during participation in the study must be reported as a serious adverse event, except hospitalizations for the following:

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

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

Information regarding serious adverse events will be transmitted to the sponsor using a serious adverse event reporting form, which must be completed and signed by a physician from the study site, and transmitted in a secure manner to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

### 10.5.6. 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.

This definition includes any PQC related to a device constituent in a combination product, including those used in the administration of the study intervention or the comparator. A device deficiency is an inadequacy of a device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.

**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.

**Esketamine-Specific Reporting Requirements for PQCs**

Additional PQC reporting requirements for esketamine nasal spray will be provided in a separate document.

### 10.5.7. Contacting Sponsor Regarding Safety, Including Product Quality

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

## 10.6. Appendix 6: Prohibited Concomitant Medications

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 participant's SSRI/SNRI for information regarding prohibited concomitant medications.

Except where specifically noted, the prohibited medications listed in the following table are prohibited until after the last dose of study intervention. Before prescribing any concomitant medications, an experienced clinician needs to evaluate the medical need and estimated risk for additional side effects. Additionally, the risk of cumulative increase in side effects (eg, sedation, QT-prolongation, weight gain) should be avoided.

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 |
|---|---|---|---|---|
| Attention deficit hyperactivity disorder (ADHD) medications (eg, atomoxetine, guanfacine) | N | Y | Can be continued but must not be taken within 12 hours prior to the esketamine nasal treatment session or for 2 hours after the nasal treatment session. | Safety |
| Amantadine | N | N | | PD interaction |
| Anorexiants (eg, phentermine, phendimetrazine) | N | N | | Safety |
| Anticholinesterase inhibitors | N | N | | Participant population is excluded |
| Anticonvulsants | N | N | Participants with seizures were excluded (per Study TRD3013). Use as adjunctive treatment for MDD is prohibited.<br>− Note: Anticonvulsants used for indications other than seizures may be allowed (eg, valproate for migraine; pregabalin). | Safety and PD interaction |
| Antidepressants (ADs) (*other than SSRI/SNRI as described in Section 6.1.5*) | Y | Y | − Monoamine oxidase inhibitors (MAOIs) use is prohibited. | Safety and PD interaction |
| Antipsychotics | N | N | | PD interaction |
| Benzodiazepines (at dosages equal to or less than the equivalent of 4 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 esketamine nasal treatment session.<br><br>The need for sleep medication should be evaluated critically and additional sedation should be taken in consideration. | Safety and PD interaction |
| Benztropine | Y | N | Prohibited if use is continuous. | Safety and PD interaction |

| Drug Class | Episodic Use (As Needed) | Continuous Use | Comments | Reason for Prohibition |
|---|---|---|---|---|
| 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, nasal, topical, and ophthalmic steroids are not prohibited. Nasally administered corticosteroids should not be used from 1 hour prior to each esketamine nasal spray administration.<br><br>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 | Nasally administered decongestants (vasoconstrictors) should not be used from 1 hour prior to each esketamine nasal spray administration.<br><br>Pseudoephedrine-containing oral products should not be used within 12 hours prior to a nasal treatment session. | Safety and PD interaction |
| CYP3A4 inducers - potent | N | N | Examples (not all-inclusive): amiodarone, 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 esketamine nasal treatment session.<br>The need for sleep medication should be evaluated critically, and additional sedation should be taken into consideration. | Safety |
| Ketanserin | N | N | | Safety |
| Lithium | N | N | | PD interaction |
| Memantine | N | N | | PD interaction |
| Methyldopa | N | N | | Safety and PD Interaction |
| Metyrosine | N | N | | Safety and PD interaction |
| Non-vitamin K antagonist oral anticoagulation agents (eg, dabigatran, rivaroxaban, apixaban) | N | N | | Safety |
| Opioids | N | N | Note: With sponsor approval, brief treatment with opiates may be allowed for treatment of acute injuries etc. | PD interaction |

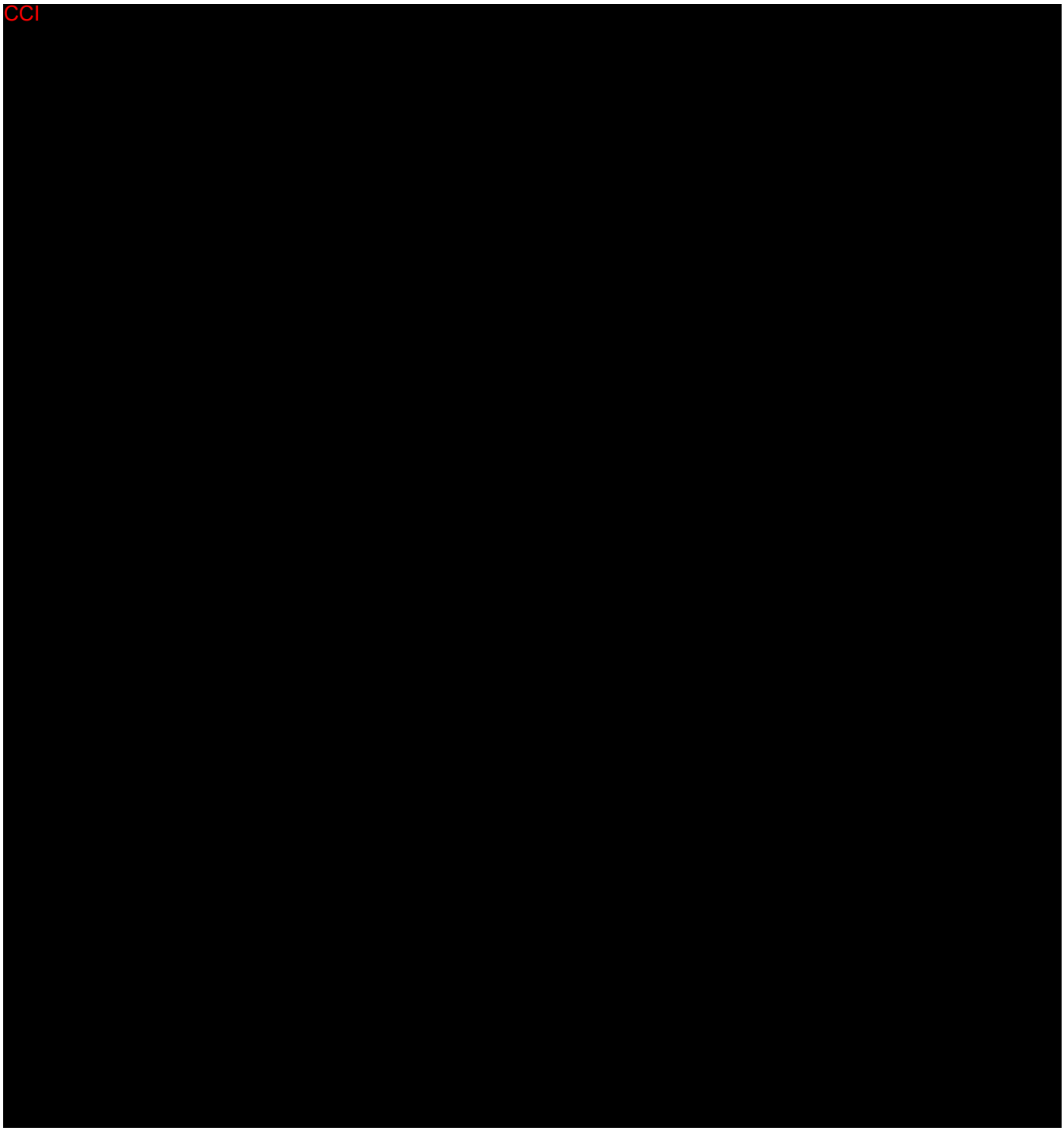
| Drug Class | Episodic Use (As Needed) | Continuous Use | Comments | Reason for Prohibition |
|---|---|---|---|---|
| Psychostimulants (eg, amphetamines, methylphenidate) | N | Y | Prescribed psychostimulants taken for indications other than MDD can be continued but must not be taken:<br>• Within 12 hours prior to the esketamine nasal treatment session or for 2 hours after the nasal treatment session. | Cardiovascular safety |
| Reserpine | N | N | | PD interaction |
| Scopolamine | N | N | | PD interaction |
| St. John's wort | N | N | | PD interaction and PK |
| Thyroid hormone supplement for treatment of thyroid condition only (not for depression) | N | Y | | Safety |
| Thyroxine/triiodothyronine (T3), thyroid hormone prescribed for depression | N | N | | PD interaction |
| Warfarin | N | N | | Primary condition where used is excluded |

Abbreviations: CYP=cytochrome P450; HIV= human immunodeficiency virus; IM=intramuscular; IV=intravenous; MDD=major depressive disorder; N=Prohibited; PD=pharmacodynamic; PK=pharmacokinetic; PO=oral; PRO=patient-reported outcomes; SSRI=selective serotonin reuptake inhibitor; SNRI=serotonin-norepinephrine reuptake inhibitor; Y=permitted, with restrictions (please refer to the column labeled "Comments" for additional guidance).

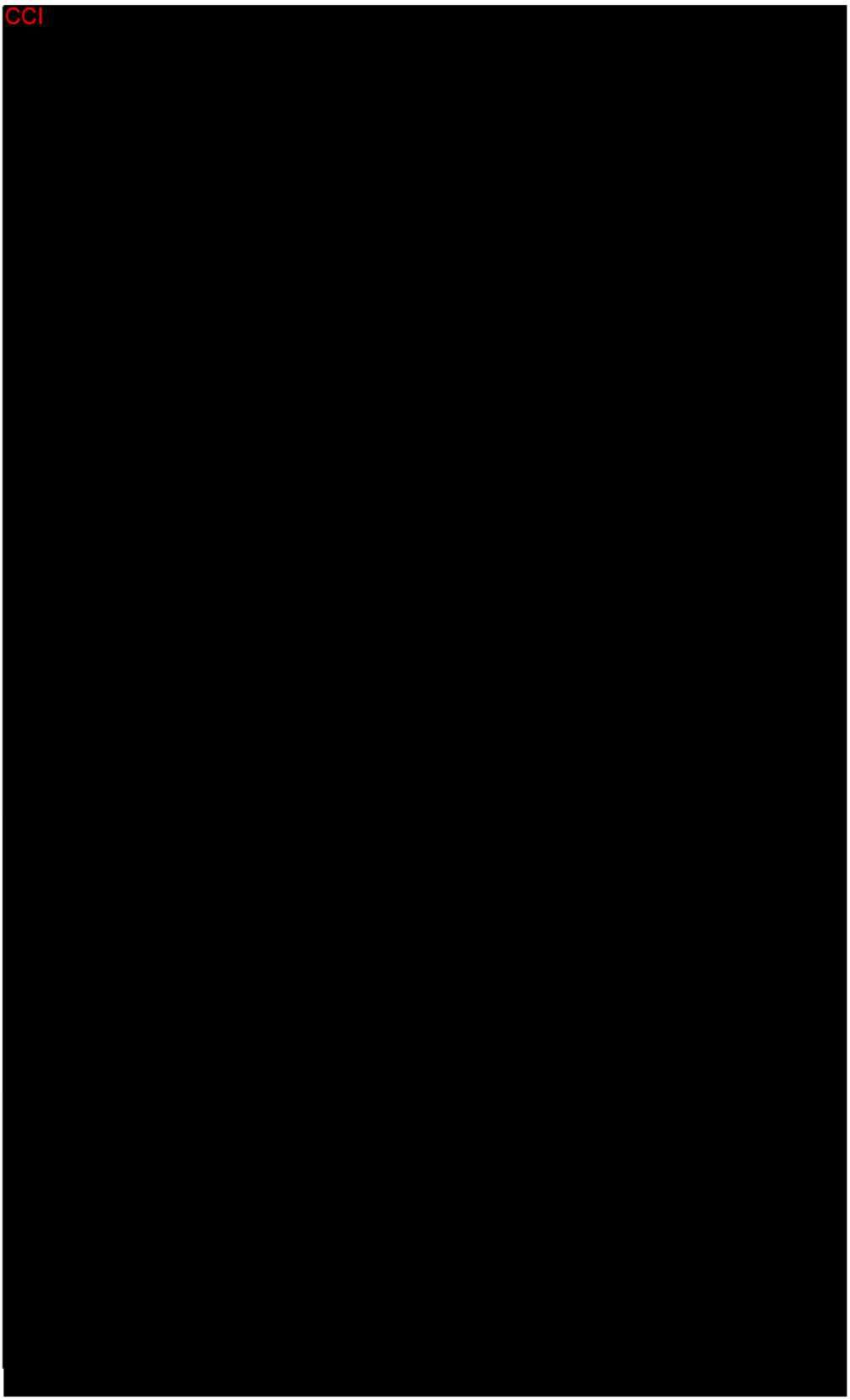
## 10.7. Appendix 7: Patient Reported Outcome Instruments

For the PHQ-9 and the EQ-5D-5L, validated translation copies will be provided to sites in local language as necessary.

### 10.7.1. Patient Health Questionnaire-9 (PHQ-9)



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



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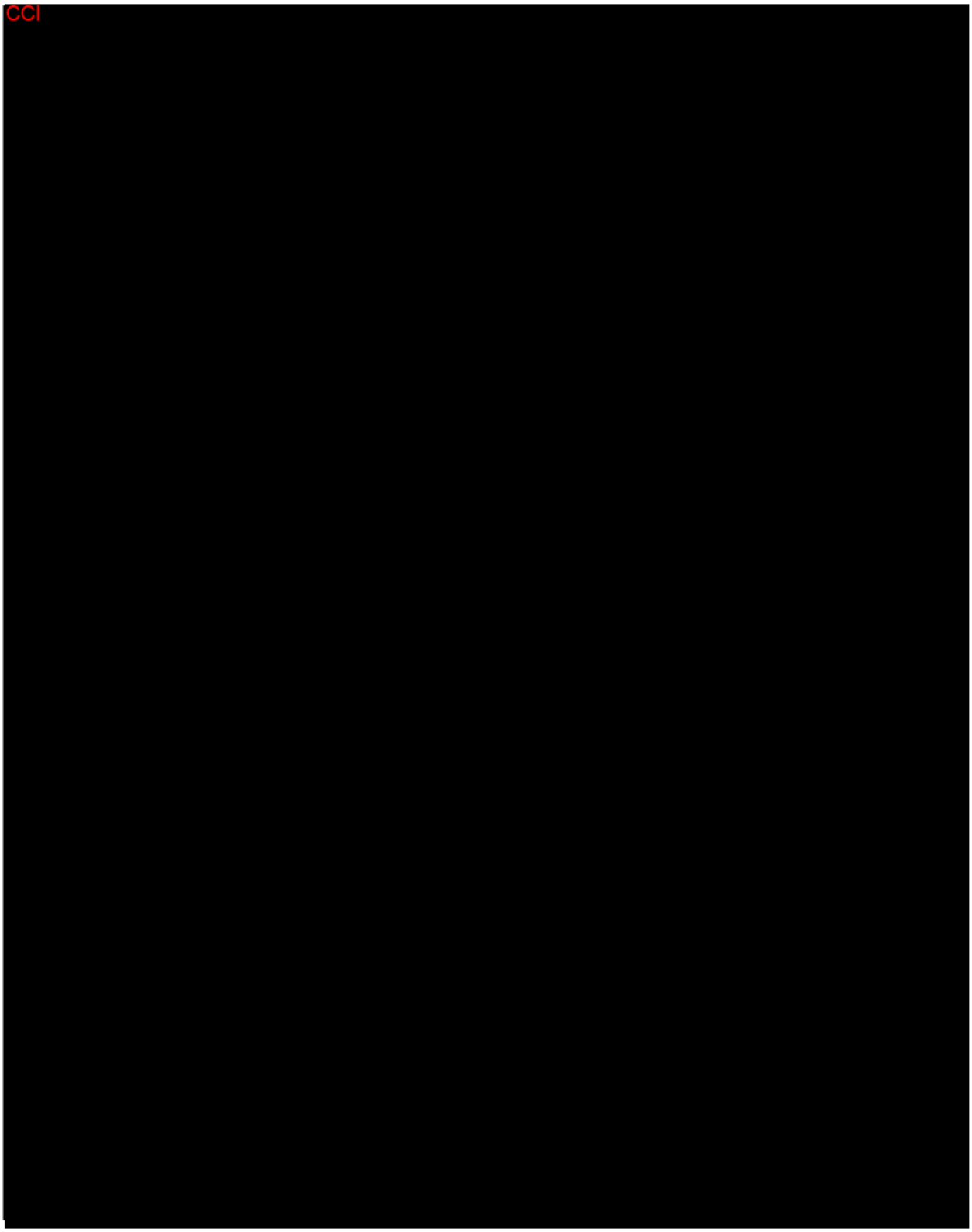
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## 10.8. Appendix 8: Clinical Laboratory Tests

The following tests will be performed according to the Schedule of Activities by the local laboratory:

**Protocol-Required Safety Laboratory Assessments**

| Laboratory Assessments | Parameters | |
|---|---|---|
| Hematology | -hemoglobin<br>-hematocrit<br>-red blood cell (RBC) count | -white blood cell (WBC) count with differential<br>-platelet count |
| Clinical Chemistry (fasting, at least 8 hours) | -sodium<br>-potassium<br>-chloride<br>-bicarbonate (optional) [a]<br>-blood urea nitrogen (BUN)<br>-creatinine<br>-glucose<br>-total cholesterol<br>-high-density lipoprotein cholesterol<br>-triglycerides<br>-low-density lipoprotein cholesterol | -aspartate aminotransferase (AST)<br>-alanine aminotransferase (ALT)<br>-gamma-glutamyltransferase (GGT)<br>-alkaline phosphatase<br>-creatine phosphokinase (CPK)<br>-calcium<br>-phosphate<br>-albumin<br>-total protein<br>-total bilirubin |
| Routine Urinalysis | Dipstick<br>-specific gravity<br>-pH<br>-glucose<br>-protein<br>-blood<br>-ketones<br>-bilirubin<br>-urobilinogen<br>-nitrite<br>-leukocyte esterase | Sediment (if dipstick result is abnormal)<br>-red blood cells<br>-white blood cells<br>-epithelial cells<br>-crystals<br>-casts<br>-bacteria |
| Pregnancy Tests | • Urine pregnancy testing for women of childbearing potential only; see Schedule of Activities and Section 8.2.4 | |

[a] Bicarbonate assay is optional, based on availability of the test at the local laboratory.

## 10.9. Appendix 9: Protocol Amendment History

This is the first protocol amendment; changes are detailed in the PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE at the start of the document.

# 11. REFERENCES

EuroQol Group (n.d.). About EQ-5D. https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/. Accessed July 21, 2019.

EuroQol Research Foundation (2009). EQ-5D-5L User Guide, 2019. Available from: https://euroqol.org/publications/user-guides. Accessed December 6, 2019.

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Posner K (2011), Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011;168:1266-1277.

Spitzer RL (1999), Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. JAMA. 1999;282:1737-1744.

## 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: J&J Bulgaria

Signature: electronic signature appended at the end of the protocol Date: _____

(Day Month Year)

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

# Signature

| User | Date | Reason |
| --- | --- | --- |
| PPD PPD | 08-Sep-2022 15:48:25 (GMT) | Document Approval |