Janssen EMEA *

Clinical Protocol

A Randomized, Open-label, Rater-Blinded, Active-Controlled, International, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Flexibly Dosed Esketamine Nasal Spray Compared With Quetiapine Extended-Release in Adult and Elderly Participants With Treatment-Resistant Major Depressive Disorder Who are Continuing a Selective Serotonin Reuptake Inhibitor/Serotonin-Norepinephrine Reuptake Inhibitor

ESCAPE-TRD

A Long-term Comparison of Esketamine Nasal Spray Versus Quetiapine Extended-Release, Both in Combination With a Selective Serotonin Reuptake Inhibitor/Serotonin-Norepinephrine Reuptake Inhibitor, in Participants With Treatment-Resistant Major Depressive Disorder

Protocol 54135419TRD3013; Phase 3b
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.

Confidentiality Statement

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	8 October 2020
Original Protocol	13 January 2020

Amendment 1 (8 October 2020)

Overall Rationale for the Amendment: To address the impact that the Coronavirus Disease 2019 (COVID-19) pandemic may have had on the conduct of this study and to address comments made by regional health authorities on the protocol.

Section Number and Name	Description of Change	Brief Rationale
10.8. Appendix 8, Guidance on Study Conduct During a COVID-19 Pandemic.	Added guidance on study conduct during a COVID-19 pandemic.	To provide guidance to investigators and participants on options for study assessments and procedures in the event of further restrictions/limitation to a COVID-19 pandemic.
1.3.1. Schedule of Activities (Weeks 1 to 8); 5.2. Exclusion Criteria; 10.2. Appendix 2: Clinical Laboratory Tests.	Added Exclusion criteria 30 to exclude patients with a pre-existing thyroid disease/disorder treated with thyroid hormones not on a stable dosage for 3 months prior to the start of the screening phase, and ensure patients with TSH value out of range are tested for free thyroxine (FT4) and, if out of range, are excluded.	To ensure pre-existing thyroid disease/disorder is sufficiently treated as esketamine should be used with caution in these patients, per SPRAVATO Summary of Product Characteristics (SmPC).
5.2. Exclusion Criteria.	Modified Exclusion criterion 6 to exclude current diagnosis of obsessive compulsive disorder; current or prior diagnosis of histrionic personality disorder or narcissistic personality disorder, and add DSM-5 diagnostic codes for intellectual disability.	For consistency with other clinical studies of esketamine.
5.2. Exclusion Criteria.	Modified Exclusion criterion 13 to exclude patients with confirmed or suspected cardiomyopathy or myocarditis.	Cardiomyopathy and myocarditis are advised for reassessment of quetiapine treatment in the Seroquel XR SmPC.[28]
5.2. Exclusion Criteria.	Added Exclusion criterion 31 to exclude patients with a white blood cell count $\leq 2.0 \times 10^3/\mu L$ at screening or history of drug induced neutropenia.	To address possible risk factors for neutropenia associated with quetiapine treatment in the Seroquel XR SmPC.[28]
1.3.1. Schedule of Activities (Weeks 1 to 8).	Added weekly assessments of C-SSRS during the first 4 weeks of the study and at the safety follow-up visit.	Sponsor's decision and health authority requests to monitor suicidality more intensively during the study.
1.3. Schedule of Activities.	Increased frequency of body weight monitoring throughout the study.	To address the metabolic risk associated with quetiapine (including body weight), per Seroquel XR SmPC.[28]
1.2. Schema; 1.3 Schedule of Activities;	Added treatment discontinuation of quetiapine by gradual dose reduction over 1 to 2 weeks.	Acute withdrawal symptoms have been described after sudden discontinuation of quetiapine.

Section Number and Name	Description of Change	Brief Rationale
6.1.2. Quetiapine Extended-release in Combination With a Continuing SSRI/SNRI.		
10.2 Appendix 2: Clinical Laboratory Tests.	Added magnesium to the clinical chemistry panel assessed during the study.	The Seroquel XR SmPC[28] indicates that caution should be exercised when quetiapine is prescribed in patients with hypomagnesaemia.
10.4. Appendix 4: Prohibited Concomitant Medications.	Updated concomitant medications table to include anti-cholinergic medications, medications that cause electrolyte imbalance or QT-prolongation, and revised use of antipsychotics.	To address health authority requests.
1.1. Synopsis; 8.3.7. Adverse Events of Special Interest.	Added events suggestive of abuse potential, cystitis, and hepatic impairment to AEs of special interest. Clarified that suicidality includes suicidal ideation and suicidal behavior.	To expand the list of AEs of special interest due to the evolving regulatory environment and company commitments.
8.2.3. Electrocardiograms.	Removed instructions for conducting triplicate ECGs.	To prevent confusion as no triplicate ECGs are required for the study.
1.1. Synopsis; 4.1. Overall Design; 4.2.1. Selection of Participant Population; 5.1. Inclusion Criteria.	Reworded inclusion criteria 4, 5 and 6.	To add clarification to existing wording.
7.1. Discontinuation of Study Intervention.	Added discontinuation of participants where the investigator believes there is no evidence of clinical improvement and further continuation of study intervention would not be in the best interest of the participant.	For consistency with existing wording in the protocol and to add it as a specific reason for discontinuation of study intervention.
10.7. Appendix 7: List of Acceptable Previous Antidepressive Treatments.	Added table of acceptable previous antidepressive treatments.	To specify which treatments are allowed including minimal doses and substance classes.
8.1.2.4. 36-Item Short-Form Health Survey (SF-36v2).	Clarified scoring and scales used in SF-36 questionnaire.	To add clarification to existing wording.
1.1. Synopsis; 9.4.3. Other Secondary/Exploratory Endpoints.	Stated that subgroup analyses will be performed for age (18 to 64 years [inclusive]; 65 to 74 years[inclusive]) and total number of treatment failures (2; 3 or more), as well as sex and severity of depression. Analysis by geographical region may also be provided.	To add clarification to existing wording and allow analysis by geographical region if required.
2. Introduction; 8.3. Adverse Events and Serious Adverse Events; 8.3.8. Medical Device Deficiencies; 10.5. Appendix 5: Adverse Events: Definitions and Procedures for	• Added text to state that for combination products with a device constituent, malfunctions or deficiencies will be reported as PQC. • Clarified procedures for reporting of adverse events and serious adverse events for combination products with a device constituent. • Removed Section 8.3.8. Medical Device Deficiencies.	To align with the most recent guidance and protocol procedures within Janssen regarding reporting of combination products with a device constituent. To clarify that combination products with a device constituent will have malfunctions or deficiencies reported as PQCs and not as adverse device effects.

Section Number and Name	Description of Change	Brief Rationale
Evaluating, Follow-up, and Reporting; 10.7. Appendix 7: Medical Device Adverse Events, Adverse Device Effects, Serious Adverse Events, and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting.	• Removed Appendix 7: Medical Device Adverse Events, Adverse Device Effects, Serious Adverse Events, and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting	
Throughout the protocol	• Changed source data so it may be recorded directly into the eCRF. • Added collection of height at Screening. • Updated Work Productivity and Activity Impairment Questionnaire from Specific Health Problem (WPAI:SHP) to Depression (WPAI:D). • Minor grammatical, formatting, spelling, editorial clarifications or consistency changes were made. • Revised confidentiality statement to comply with an update from the legal department.	To clarify scientific and operational aspects of the study design and correct or clarify minor errors that were noted.

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1. PROTOCOL SUMMARY

1.1. Synopsis

A Randomized, Open-label, Rater-Blinded, Active-Controlled, International, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Flexibly Dosed Esketamine Nasal Spray Compared With Quetiapine Extended-Release in Adult and Elderly Participants With Treatment-Resistant Major Depressive Disorder Who are Continuing a Selective Serotonin Reuptake Inhibitor/Serotonin-Norepinephrine Reuptake Inhibitor

A Long-term Comparison of Esketamine Nasal Spray Versus Quetiapine Extended-Release, Both in Combination With a Selective Serotonin Reuptake Inhibitor/Serotonin-Norepinephrine Reuptake Inhibitor, in Participants With Treatment-Resistant Major Depressive Disorder

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Depression is a major cause of morbidity and mortality, with global estimates of 300 million treated and untreated individuals worldwide. A depressive state with classical symptoms such as low (depressive/sad) mood, markedly diminished interest in activities, significant weight loss/gain, insomnia or hypersomnia, psychomotor agitation/retardation, excessive fatigue, inappropriate guilt, diminished concentration, and recurrent thoughts of death, persisting for more than 2 weeks is classified as major depressive disorder (MDD).

Ketamine affects fast excitatory glutamate transmission. Antidepressant (AD) effects may relate to increased brain-derived neurotrophic factor release and synaptogenesis. Esketamine, the S-enantiomer of ketamine, is approved and widely used for the induction and maintenance of anesthesia via intramuscular or intravenous (IV) administration. Because of the higher N-methyl-D-aspartate receptor affinity of esketamine over arketamine (R-enantiomer of ketamine), Janssen Research & Development is developing esketamine (not the racemate) for AD therapy. Moreover, intranasal administration was investigated instead of IV administration, since intranasal administration can offer better convenience for patients and fewer errors in dosing, and esketamine can be rapidly and well absorbed via the intranasal route.

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
The primary objective of this study is to evaluate the efficacy of flexibly dosed esketamine nasal spray compared with quetiapine extended-release (XR), both in combination with a continuing selective serotonin reuptake inhibitor (SSRI)/serotonin-norepinephrine reuptake inhibitor (SNRI), in achieving remission in participants who have treatment-resistant MDD with a current moderate to severe depressive episode.	Remission at the Week 8 visit, defined as a Montgomery-Asberg Depression Rating Scale (MADRS) total score of ≤10.
Key Secondary	
To assess the efficacy of esketamine nasal spray compared with quetiapine XR, both in combination with a continuing SSRI/SNRI, in the proportion of participants being relapse-free at Week 32 after remission at Week 8.	Remission at Week 8 visit (ie, MADRS total score of ≤10 at the end of Week 8) and no relapse within the consecutive 24 weeks until the end of the prospective observation period at Week 32 visit.

Objectives	Endpoints
	Note: A relapse is defined by any of the following: a) Worsening of depressive symptoms as indicated by MADRS total score ≥22 confirmed by 1 additional assessment of MADRS total score ≥22 within the next 5 to 15 days. The date of the second MADRS assessment will be used for the date of relapse. b) Any psychiatric hospitalization for – worsening of depression – suicide prevention or due to a suicide attempt for any of these events, the start date of hospitalization will be used for the date of relapse. c) 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. 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.
Other Secondary	
To assess the effect of esketamine nasal spray compared with quetiapine XR, both in combination with a continuing SSRI/SNRI, in: • Clinician-rated overall severity of depressive illness • Early onset of action • Clinician-rated depressive symptoms	Change from baseline at all visits for the following scale scores: • Clinician-rated MADRS: – Overall severity of depressive illness (total score) – Early onset of action (change in total score from baseline at Day 8 visit) – Depressive symptoms (individual items) • Clinician-rated overall severity of depressive illness: – Clinical Global Impression – Severity (CGI-S) – Clinical Global Impression – Change (CGI-C), is a measure of change,

Objectives	Endpoints
• Participant-reported depressive symptoms • Participant-reported functional impairment and associated disability • Participant-reported health-related quality of life and health status • Participant-reported work productivity	analyzed as a score not as change from baseline • Participant-reported depressive symptoms: Patient Health Questionnaire 9-item (PHQ-9) • Participant-reported functional impairment and associated disability: Sheehan Disability Scale (SDS) • Participant-reported health-related quality of life and health status: 36-item Short-Form Health Survey (SF-36) • Participant-reported Quality of Life in Depression Scale (QLDS) • Participant-reported European Quality of Life (EuroQoL) Group, 5-Dimension, 5-Level (EQ-5D-5L) questionnaire • Participant-reported work productivity: Work Productivity and Activity Impairment (WPAI): Depression (D) questionnaire
To assess the safety and tolerability of esketamine nasal spray compared with quetiapine XR, both in combination with a continuing SSRI/SNRI.	Intervention-emergent adverse events (AEs), including intervention-emergent AEs of special interest Suicidal ideation and behavior: Columbia-Suicide Severity Rating Scale (C-SSRS)
Exploratory	
To assess the potential relationship of biomarkers with response/nonresponse to study intervention in participants with treatment-resistant MDD.	-

Hypotheses

The primary hypothesis of this study is that among participants who have treatment-resistant MDD with a current moderate to severe depressive episode, the proportion of participants achieving remission at the Week 8 visit is greater in participants treated with flexibly dosed esketamine nasal spray than in participants treated with quetiapine XR, both administered in combination with a continuing SSRI/SNRI.

The major secondary hypothesis of this study is that among participants who have treatment-resistant MDD with a current moderate to severe depressive episode, the proportion of participants who achieved remission at the Week 8 visit and remain relapse-free through the Week 32 visit is greater in participants treated with esketamine nasal spray than in participants treated with quetiapine XR, both administered in combination with a continuing SSRI/SNRI.

OVERALL DESIGN

This is a randomized, open-label, rater-blinded, active-controlled, international, multicenter study to evaluate the efficacy, safety, and tolerability of flexibly dosed esketamine nasal spray compared with quetiapine XR, both in combination with a continuing SSRI/SNRI, in participants 18 to 74 years of age,

inclusive, with treatment-resistant MDD. A psychiatrist should determine eligibility of participants for inclusion in the study.

To be eligible for enrollment in the study:

- Participant must be on a *current* antidepressive treatment that includes an SSRI/SNRI at screening that resulted in nonresponse (less than 25% improvement of symptoms) after having been given at an adequate dosage (based on antidepressive dosages from Summary of Product Characteristics [SmPC; or local equivalent, if applicable]) for an adequate duration of at least 6 weeks and having been uptitrated to the maximum tolerated dose; however, at screening the participant must show signs of minimal clinical improvement to be eligible for the study.
- In addition the current antidepressive treatment must have been immediately preceded by nonresponse to at least 1 but not more than 5 different consecutive treatments (all within the current moderate to severe depressive episode) with ADs taken at an adequate dosage for an adequate duration of at least 6 weeks
  - "At least 1 but not more than 5" means that participants may be screened and enrolled while receiving treatment with their second to sixth consecutive treatment with oral ADs taken at adequate dosage for an adequate duration of at least 6 weeks to which they are having a nonresponse.
    - If a participant was receiving an oral AD at an adequate dosage for an adequate duration of at least 6 weeks and then had an augmentation therapy added or had combination AD therapy initiated, it would then be considered the next consecutive treatment with AD if taken at an adequate dosage for an adequate duration of at least 6 weeks.
  - For treatments with AD(s) to be counted as consecutive, there may have been interspersed insufficient treatments (ie, insufficient duration and/or at insufficient dosage). These insufficient treatments are allowed but will not be considered when documenting participant nonresponse.
- Participant must have been treated with at least 2 different antidepressive substance classes among the treatments taken at an adequate dosage for an adequate duration of at least 6 weeks resulting in nonresponse in the current moderate to severe depressive episode (including the current treatment with an SSRI/SNRI).
- Participant must be on a single oral SSRI/SNRI on Day 1 prior to randomization.
  - Participants who are taking combination ADs and/or augmentation (other than quetiapine XR which is exclusionary at doses >50 mg/day) for the current moderate to severe depressive episode at screening are eligible for the study. All AD treatments, including any augmenting substances, must be stopped prior to randomization on Day 1 according to applicable SmPCs (or local equivalents, if applicable), except the SSRI/SNRI to be continued.

The study has 4 phases: an up-to-14-day screening phase, an 8-week acute phase, a 24-week maintenance phase, and a 2-week safety follow-up phase. During the acute phase, participants in the esketamine arm will have twice-weekly visits from Week 1 to Week 4 and once weekly visits from Week 5 to Week 8; during the maintenance phase from Week 9 to Week 32, visits will be once weekly or every 2 weeks (even weeks) based on dosing. Participants in the comparator arm will have weekly visits from Week 1 to Week 4, and then every 2 weeks for the remainder of the acute phase (Week 6 and Week 8) and the maintenance phase (Week 10, Week 12, etc) through Week 32. All participants have a safety follow-up visit 2 weeks following the last dose of study intervention. Participants who discontinue the study intervention early (ie, discontinue either component of the randomized combination therapy) will remain in the study and continue to return for all follow-up visits through Week 32, according to the Schedule of Activities. The total duration of the study is approximately 36 weeks for all participants. The end of study is considered as the last visit for the last participant in the study.

For participants in the esketamine arm:

- At the Week 4 visit, evidence of therapeutic benefit of the study intervention (ie, esketamine nasal spray in combination with a continuing SSRI/SNRI) will be evaluated clinically by the investigator. In the evaluation of therapeutic benefit, the full scope of clinical improvement should be evaluated including any improvement in depressive symptoms, general functioning, social functioning, and self-care. If there is no evidence of therapeutic benefit, the investigator and the participant should discuss the treatment strategy and mutually agree on whether to continue or discontinue esketamine nasal spray.

Treatment Continuation Assessment of Study Intervention: Beginning at the Week 8 visit, *all participants* in both study intervention arms will undergo regular assessments of symptom changes from baseline (ie, treatment continuation assessment) to ensure that study intervention continuation is appropriate. This will be operationalized using the CGI-C clinician-rated scale (referring to study baseline [Day 1]) every 4 weeks, and treatment decisions will be made using cut-off values below.

Treatment Continuation Assessment of Study Intervention	
CGI-C ≥4 ("no change" or worse) at 2 consecutive visits	Recommendation to reconsider appropriateness of study intervention and to switch to an alternative standard-of-care treatment.
CGI-C <4 ("Minimally improved" or better) at any visit	Study intervention may be continued at the discretion of the investigator.

CGI-C= Clinical Global Impression – Change
Note: After early discontinuation of study intervention, the CGI-C will still be performed at follow-up visits according to the Schedule of Activities; however, treatment decisions will be at the discretion of the investigator and not based on the criteria for the treatment continuation assessment.

Participants who complete the study will have a safety follow-up visit performed 2 weeks after their last dose of study intervention.

Participants who discontinue the study intervention early (ie, discontinue either component of the randomized combination therapy) will remain in the study and continue to return for follow-up visits every 2 weeks through Week 32. For these participants, all safety follow-up visit assessments will be performed in addition to the assessments scheduled at their first 2-week follow-up visit, or if study intervention is discontinued after the Week 30 visit, the safety follow-up visit will be performed 2 weeks after their last dose. Refer to Safety Evaluations for details of AE reporting for participants who discontinue study intervention early.

If a participant withdraws from the study, an early study withdrawal visit should be conducted within 1 week of the date of withdrawal unless they withdraw consent, are lost to follow-up, or have died. Participants who are taking study intervention at the time of early withdrawal from the study should return for the safety follow-up visit 2 weeks after their last dose unless they withdraw consent, are lost to follow-up, or have died.

All procedures, assessments, follow-up visits for participants who discontinue study intervention before Week 32, early withdrawal visits, and safety follow-up visits will be performed according to the Schedule of Activities.

NUMBER OF PARTICIPANTS

A total of 622 participants will be randomly assigned on Day 1 (baseline) in a 1:1 ratio to 1 of 2 open-label study intervention arms (311 participants per arm). The randomization will be balanced by using randomly permuted blocks and will be stratified by age (18 to 64 years [inclusive]; 65 to 74 years [inclusive]) and total number of treatment failures (2; 3 or more [inclusive of current antidepressive treatment at screening used to determine eligibility]).

INTERVENTION GROUPS AND DURATION

- **Esketamine Arm:** Participants will continue to take their current SSRI/SNRI in combination with esketamine nasal spray.

  On Day 1, participants will have their first nasal treatment session. Adult participants aged 18 to 64 years will start with a dose of 56 mg. Elderly participants aged 65 to 74 years and adults of Japanese ancestry will start with a dose of 28 mg. As of Day 4, the dose may be increased from 56 mg to 84 mg in adult participants, from 28 mg to 56 mg in elderly participants and adults of Japanese ancestry, or participants may remain at the starting dose, as determined by the investigator based on efficacy and tolerability. Elderly participants and adults of Japanese ancestry may be uptitrated in 28 mg increments at subsequent visits. The highest dose that may be used in all participants is 84 mg. Nasal treatment sessions will occur twice weekly during Week 1 to Week 4, once weekly during Week 5 to Week 8, and once weekly or every 2 weeks, as determined by the investigator based on efficacy and tolerability, during the maintenance phase (Week 9 to Week 32). 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. Nasal treatment sessions should not take place on 2 consecutive days. 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. 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.

- **Comparator Arm:** Participants will continue to take their current SSRI/SNRI which will be augmented with quetiapine XR as per the SmPC (or local equivalent, if applicable) starting on Day 1 and will continue through Week 32. In adult participants aged 18 to 64 years, the initial dose of quetiapine XR is 50 mg/day on Days 1-2, 150 mg/day on Days 3-4 [lowest effective dose]; a further dose increase to 300 mg/day as of Day 5 will be based on individual participant evaluation. In elderly participants aged 65 to 74 years, the initial dose is 50 mg/day on Days 1-3, 100 mg/day on Days 4-7, and 150 mg/day on Day 8; a further dose increase to 300 mg/day will be based on individual participant evaluation no earlier than Day 22. If participants cannot tolerate at least 150 mg/day of quetiapine XR by the end of Week 2 (or at any subsequent time during the study), they must have quetiapine XR discontinued.

- **Continuing SSRI/SNRI:** The continuing 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.

  The investigator may optimize the dose of the continuing SSRI/SNRI, up to the maximum tolerated dose as per the respective SmPC (or local equivalent, if applicable). Once optimized, a stable dose should be maintained; however, dose modifications may be made, if necessary, at the investigator's discretion.

The study intervention will be considered discontinued if either component of the randomized combination therapy (ie, esketamine nasal spray, quetiapine XR, or continuing SSRI/SNRI) is stopped.

- If esketamine nasal spray or quetiapine XR is discontinued at any time during the acute or maintenance phase, the participant will be switched to an alternative standard of care treatment, which may or may not include the continuing SSRI/SNRI, at the discretion of the investigator and continue follow-up visits through Week 32. If determined by the investigator that the alternative standard of care will include esketamine nasal spray (when commercially available in country of participation) or quetiapine XR for a participant, it will not be provided to the participant, rather, the investigator must prescribe the medication to the participant.

- If the SSRI/SNRI is discontinued at any time during the acute or maintenance phase, the esketamine nasal spray or quetiapine XR must also be discontinued. The participant will be switched to an alternative standard of care treatment at the discretion of the investigator and continue follow-up visits through Week 32.

After participants have completed study intervention (Week 32), they should return to their primary physician to determine standard of care. In exceptional situations, where participants would not have access to commercially available esketamine nasal spray, those participants who, at the discretion of the investigator, could benefit from continuing treatment with esketamine nasal spray following their Week 32 visit, will be advised on how continuation of treatment can be assured. Country-specific details on accessibility will be evaluated by the sponsor on a case-by-case basis considering, among others, regulatory and operational requirements.

Standard of care treatment after completion of the study is at the discretion of the investigator or primary physician; there is no requirement to change a participant's standard of care treatment when they complete the study at Week 32.

EFFICACY EVALUATIONS

Efficacy will be assessed using clinician-rated scales (MADRS, CGI-S, and CGI-C) and patient-reported outcomes (PROs). As the MADRS is used to assess the primary and major secondary endpoints in the study, it must be performed by a qualified independent blinded rater.

All visit-specific PRO assessments (PHQ-9, QLDS, EQ-5D-5L, SF-36, SDS, and WPAI:D) should be conducted/completed before clinician-rated assessments, any tests (other than the urine drug screen at baseline visit [Day 1]; see Schedule of Activities), procedures, other consultations, or administration of esketamine nasal spray (in applicable participants) to prevent influencing participant perceptions.

BIOMARKERS AND PHARMACOGENOMIC (DNA AND RNA) EVALUATIONS

Blood samples will be collected for exploratory analysis of biomarkers (protein and metabolites) related to immune system activity, hypothalamic–pituitary–adrenal axis activation, neurotrophic and metabolic factors. Exploratory analyses may be performed for additional biomarkers as well. A pharmacogenomic blood sample will be collected to allow for pharmacogenomic (DNA and RNA) research (where local regulations permit). Biomarker and pharmacogenomic blood samples will only be collected at select study sites. Participation in the biomarker and pharmacogenomic research is optional for participants.

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

SAFETY EVALUATIONS

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

For participants who discontinue study intervention early: (1) if their alternative standard of care treatment includes commercial esketamine or another Janssen medicinal product for depression, AEs will continue to be collected after completion of the safety follow-up visit; (2) if their alternative standard of care treatment does not include commercial esketamine or another Janssen medication for depression, AEs will not be systemically collected after completion of the safety follow-up visit. For AEs that are not systematically collected (including AEs for Janssen medicinal products not indicated for depression) and where the participating physician considers there is at least a reasonable possibility of a causal relationship to a medicinal product (ie, spontaneous adverse drug reactions), the participating physician is requested to notify the manufacturer (ie, Janssen or other manufacturer) of the medicinal product or the appropriate regulatory/competent authority through the national spontaneous reporting system as soon as possible.

STATISTICAL METHODS

Sample Size Calculation

For the primary endpoint, the assumptions are that the rate of remission for completers at the Week 8 visit is 50% in the esketamine arm and 35% in the comparator arm, and that the rate for participants who discontinue study intervention between baseline and the Week 8 visit is 17.5% in both treatment arms (to be imputed as non-remitters). Combining these assumptions leads to an estimated remission rate at the Week 8 visit in non-responder imputation (NRI) analysis of 41.25% in the esketamine arm and 28.88% in the comparator arm. With a power of 90%, a 2-sided significance level of 0.05 and using chi-square test, a sample size of 311 participants per arm (622 participants in total) is needed to detect the difference between the study intervention arms.

For the key secondary endpoint, among participants who achieve remission at the Week 8 visit, a relapse rate of 30% is assumed for both study intervention arms and rates for participants who discontinue study intervention between the Week 8 and Week 32 visits (to be imputed as non-relapse-free after remission) is assumed to be 10% for the esketamine arm and 20% for the comparator arm. Combining these assumptions leads to an estimated rate of relapse-free after remission at the Week 32 visit in NRI analysis of 25.99% in the esketamine arm and 16.17% in the comparator arm. With a power of 80%, a 2-sided significance level of 0.05 and using a chi-square test, a sample size of 270 randomized participants per arm (540 participants in total) is needed to detect a difference between the study intervention arms.

When combining the 2 calculations above, a sample size of 311 participants per study intervention arm (622 participants in total) is needed to detect the difference between the study intervention arms with both a power of at least 90% on the primary endpoint and a power of 80% on the key secondary endpoint.

Efficacy Analyses

The efficacy analyses of data will be based on the full analysis set (ie, all participants who are randomized in the study). The rate of remission at the Week 8 visit (primary endpoint) and the rate of remission at the Week 8 visit without relapse up to the Week 32 visit (key secondary endpoint) will be tested between study intervention arms using a Cochran-Mantel-Haenszel (CMH) chi-square test adjusting for age (18 to 64 years [inclusive]; 65 to 74 years [inclusive]) and total number of treatment failures (2; 3 or more). Participants will be considered as having a positive outcome on relapse-free after remission if they are in remission at the Week 8 visit and do not experience any relapse between the Week 8 and Week 32 visits. All other cases (participants not achieving remission at the Week 8 visit, or participants achieving remission at the Week 8 visit but experiencing a relapse between the Week 8 and Week 32 visits) will be considered as having a negative outcome. Both the primary and key secondary endpoints will be analyzed using a NRI approach, meaning that participants discontinuing study intervention will be considered as having a negative outcome (non-remission for the primary endpoint, non-relapse-free-remission for the key secondary endpoint). In sensitivity analyses, for participants who stopped study intervention, but are still followed in the study, no imputation will be performed, and their observed status will be used for the analyses.

For continuous/ordinal parameters (eg, MADRS, CGI-S, PHQ-9, EQ-5D-5L, SF-36, SDS, WPAI:D) descriptive statistics of the score or values and change from baseline will be provided for each study visit during the study for the full analysis set. For CGI-C descriptive statistics of the score will be provided for each study visit during the study for the full analysis set. Summaries of both observed and last observation carried forward (LOCF) data will be presented. The change from baseline at each visit will be analyzed using a mixed model for repeated measurements based on observed cases. The model will include baseline score as a covariate, and study intervention, stratification factors (age [18 to 64 years (inclusive); 65 to 74 years (inclusive)] and total number of treatment failures [2; 3 or more]), visit, and visit-by-study-intervention interaction as fixed effects. The change from baseline at each visit will also be analyzed using an analysis of covariance model including LOCF data with factors for treatment, stratification factors (age [18 to 64 years (inclusive); 65 to 74 years (inclusive)] and total number of treatment failures [2; 3 or more])

and baseline score as a covariate. For all model approaches, least squares estimates of the treatment differences and 95% confidence intervals will be presented.

Additionally, for scales that have a minimum clinically important difference (MCID), the proportion of participants having improved by at least the MCID will be described at each visit and compared between study interventions using CMH chi-square test adjusting for age (18 to 64 years [inclusive]; 65 to 74 years [inclusive]) and total number of treatment failures (2; 3 or more). The same analysis will be conducted for the proportion of participants who deteriorate by at least the MCID. The MCIDs used in the analysis will be documented in the Statistical Analysis Plan.

Time to event parameters (eg, time to improvement by at least MCID) will be analyzed by the Kaplan-Meier method and study interventions will be compared using a 2-sided log-rank test for the full analysis set. Time to event will be summarized with median, 25^{th} and 75^{th} percentile (if estimable). Confidence intervals of 25^{th}, 50^{th}, and 75^{th} percentile of time to event will also be provided. Hazard ratios and their confidence intervals will be estimated using Cox proportional hazard models stratified by age (18 to 64 years [inclusive]; 65 to 74 years [inclusive]) and number of previous treatment failures (2; 3 or more).

Subgroup analyses will be performed for age (18 to 64 years [inclusive]; 65 to 74 years [inclusive]) and total number of treatment failures (2; 3 or more), as well as sex and severity of depression. Analysis by geographical region may also be provided.

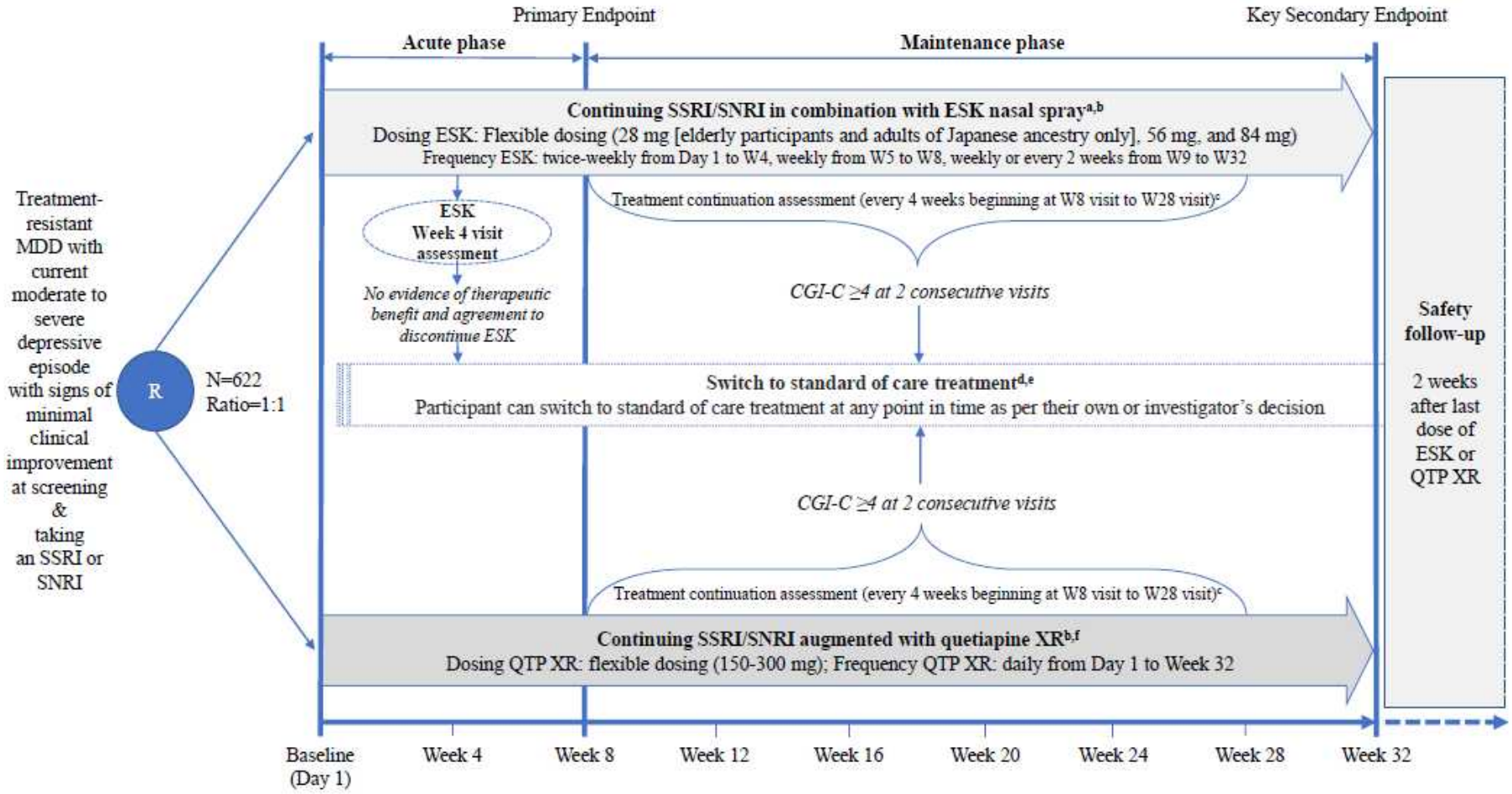
Safety Analyses

All safety analyses will be made on the Safety Population (ie, all randomized participants who take at least 1 dose of study intervention).

Intervention-emergent AEs are AEs occurring or worsening in severity after the start of study intervention. All reported intervention-emergent AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group. In addition, comparisons between intervention groups will be provided if appropriate.

Intervention-emergent AEs of special interest will be summarized separately grouped in the following Medical Dictionary for Regulatory Activities (MedDRA) based categories: sedation, dissociation, events suggestive of abuse potential, cystitis, hepatic impairment and suicidality (including suicidal ideation and behavior).

1.2. Schema



Abbreviations: CGI-C=Clinical Global Impression – Change; ESK=esketamine nasal spray; MDD=major depressive disorder; QTP XR=quetiapine extended-release; R=randomization; SmPC=Summary of Product Characteristics; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; W=week.

[a] On Day 1, adult participants aged 18 to 64 years will start with a dose of 56 mg; elderly participants aged 65 to 74 years and adults of Japanese ancestry will start with a dose of 28 mg. As of Day 4, the dose may be increased from 56 mg to 84 mg in adult participants, from 28 mg to 56 mg in elderly participants and adults of Japanese ancestry, or participants may remain at the starting dose, as determined by the investigator based on efficacy and tolerability. Elderly participants and adults of Japanese ancestry may be uptitrated in 28 mg increments at subsequent visits. 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. Based on the dosing frequency in the maintenance phase, the last nasal treatment session will occur at Week 30 (every 2 weeks frequency) or Week 31 (once-weekly frequency).

[b] The investigator may optimize the dose of the continuing SSRI/SNRI, up to the maximum tolerated dose as per the respective SmPC (or local equivalent, if applicable). Once optimized, a stable dose should be maintained; however, dose modifications may be made, if necessary, at the investigator's discretion.

[c] The treatment continuation assessment will be performed on all participants who are taking study intervention (ie, both components of the randomized combination therapy) and will be the basis for the decision to continue study intervention. If the study intervention is discontinued early, the CGI-C (ie, the basis of the treatment continuation assessment for the study interventions) will still be performed at time points noted in the Schedule of Activities; however, treatment decisions will be at the discretion of the investigator and not based on the criteria for the treatment continuation assessment.

[d] Participants who discontinue the study intervention early (ie, discontinue either component of the randomized combination therapy) will remain in the study and continue to return for follow-up visits (every 2 weeks) through Week 32 unless study intervention is discontinued after the Week 30 visit, in which case participants must have the safety follow-up visit 2 weeks after their last dose.

[e] If the SSRI/SNRI is discontinued at any time during the acute or maintenance phase, the esketamine nasal spray or quetiapine XR must also be discontinued. The participant will be switched to an alternative standard of care treatment at the discretion of the investigator. If esketamine nasal spray or quetiapine XR is discontinued at any time during the acute or maintenance phase, the participant will be switched to an alternative standard of care treatment, which may or may not include the continuing SSRI/SNRI, at the discretion of the investigator. If determined by the investigator that the alternative standard of care will include esketamine nasal spray (when commercially available in country of participation) or QTP XR, it will not be provided to the participant, rather, the investigator must prescribe the medication to the participant. Standard of care treatment after completion of the study is at the discretion of the investigator or treating physician; there is no requirement to change a participant's standard of care treatment when they complete the study at Week 32.

[f] Quetiapine XR will be uptitrated (starting at 50 mg/day) as per the SmPC (or local equivalent, if applicable); dosing may be adapted as determined by the investigator based on efficacy and tolerability. Participants should be uptitrated to at least 150 mg/day according to the recommended uptitration schedule and based on individual tolerability no later than the Week 2 visit (ie, end of Week 2). If participants cannot tolerate at least 150 mg/day of QTP XR by the end of Week 2 (or at any subsequent time during the study), they must have QTP XR discontinued. Treatment discontinuation by gradual dose reduction over 1 to 2 weeks is recommended.

1.3. Schedule of Activities

1.3.1. Schedule of Activities (Weeks 1 to 8)

Phase	Screening	Acute phase												
Week	W-2 to -1			W1		W2		W3		W4	W5	W6	W7	W8
Day – Esketamine arm	D-14 to 0[a]	D1[a]	D4	D8	D11	D15	D18	D22	D25	D29	D36	D43	D50	D57
Day – Comparator arm	D-14 to 0[a]	D1[a]	-	D8	-	D15	-	D22	-	D29	-	D43	-	D57
Visit Window (Days)			±1	±1	±1	±1	±1	±1	±1	±1	±2	±2	±2	±2
Administrative Procedures														
Informed consent	X													
Informed consent - optional biomarker, DNA/RNA		X												
Inclusion/exclusion criteria	X	X												
Document nonresponse to prior AD treatment	X													
Document nonresponse/minimal clinical improvement to current AD treatment	X	X[b]												
MINI	X													
IDS-C30	X	X												
Medical and psychiatric history, demographics, employment status	X													
Prestudy therapy and elective procedures	X													
Pregnancy testing[c]	X	X								X				X
12-lead ECG (local)	X	X[d]												X
Physical examination/nasal examination[e]	X													
Height	X													
Urine screen for drugs of abuse (local)		X[f]												
Document investigator discussion with the participant regarding psychotherapy		X[g]												
Randomization		X												
Patient-reported outcomes[h]														
PHQ-9		X				X				X		X		X
QLDS		X								X				X
EQ-5D-5L		X								X				X
SF-36		X								X				X
SDS		X								X				X
WPAI:D		X								X				X
Clinician-rated scales and questionnaires[i]														
C-SSRS (Baseline-Screening version)	X													
C-SSRS (Since Last Visit version)		X		X		X		X		X				X
MADRS: efficacy assessment/blinded rater		X		X		X				X		X		X
CGI-S	X	X		X		X		X		X				X
CGI-C				X		X		X		X				X

Phase	Screening	Acute phase												
Week	W-2 to -1			W1		W2		W3		W4	W5	W6	W7	W8
Day – Esketamine arm	D-14 to 0[a]	D1[a]	D4	D8	D11	D15	D18	D22	D25	D29	D36	D43	D50	D57
Day – Comparator arm	D-14 to 0[a]	D1[a]	-	D8	-	D15	-	D22	-	D29	-	D43	-	D57
Visit Window (Days)			±1	±1	±1	±1	±1	±1	±1	±1	±2	±2	±2	±2
Study intervention assessments														
Therapeutic benefit assessment (esketamine arm)[i]										X				
Treatment continuation assessment (participants taking study intervention)[i,j]														X
Safety assessments														
Hematology/chemistry (central), urinalysis (local)[k]	X	X[l]												X
TSH (FT4 if TSH is out of range)	X													X
Body weight	X									X				X
Vital signs[m]	X													
Vital signs (QTP XR arm)[m]		X		X		X		X		X		X		X
Additional safety assessments (esketamine arm)														
Vital signs predose[m]		X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs postdose[m,n]		X	X	X	X	X	X	X	X	X	X	X	X	X
Nasal examination predose[o]		X	X	X	X	X	X	X	X	X	X	X	X	X
Study intervention procedures														
Dispense QTP XR (comparator arm)[p]		X[q]		X[q]		X[q]		X[q]		X[q]		X[q]		X[q]
Training nasal spray device (esketamine arm)		X												
Nasal treatment sessions (esketamine arm)[r,s]		X	X	X	X	X	X	X	X	X	X	X	X	X[t]
Drug accountability: esketamine/QTP XR										X				X
Medication compliance counseling		X	X	X	X	X	X	X	X	X	X	X	X	X
Biomarker evaluations (optional)														
Blood sample[u]		X												X[v]
Menstrual cycle information		X												X[v]
Pharmacogenomic evaluations (optional)														
Blood sample: DNA		X												
Blood sample: RNA		X												
Ongoing														
Concomitant therapy/psychotherapy	X[w]	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X

NOTES: If the SSRI/SNRI is discontinued at any time during the acute phase, the esketamine nasal spray or quetiapine XR must also be discontinued. The participant will be switched to an alternative standard of care treatment at the discretion of the investigator and continue follow-up visits through Week 32; refer to the Maintenance Phase Schedule of Activities.
If esketamine nasal spray or quetiapine XR is discontinued at any time during the acute phase, the participant will be switched to an alternative standard of care treatment, which may or may not include the continuing SSRI/SNRI, at the discretion of the investigator and continue follow-up visits through Week 32; refer to the Maintenance Phase Schedule of Activities.
If determined by the investigator that the alternative standard of care will include esketamine nasal spray (when commercially available in country of participation) or QTP XR, it will not be provided to the participant, rather, the investigator must prescribe the medication to the participant.
Participants who withdraw early from the study must have the early study withdrawal visit performed within 1 week of the date of withdrawal and then return for the safety follow-up visit 2 weeks after their last dose of study intervention, unless they withdraw consent; refer to the Maintenance Phase Schedule of Activities. If the early study withdrawal visit is conducted on the same day as a scheduled visit, duplicate assessments are not required.

Abbreviations: AD=antidepressant; C-SSRS=Columbia-Suicide Severity Rating Scale; CGI-C=Clinical Global Impression – Change; CGI-S=Clinical Global Impression – Severity; D=day; ECG=electrocardiogram; EQ-5D-5L=European Quality of Life Group, 5 Dimension, 5-Level (questionnaire); FT4=free thyroxine; IDS-C30=Inventory of Depressive Symptomatology Clinician-rated, 30-item scale; NSAIDs=non-steroidal anti-inflammatory drugs; MADRS=Montgomery-Asberg Depression Rating Scale; MINI=Mini International Neuropsychiatric Interview; PHQ-9=Patient Health Questionnaire, 9-item; PRO=patient-reported outcome; QLDS=Quality of Life in Depression Scale; QTP XR=quetiapine extended-release; SDS=Sheehan Disability Scale; SF-36=36-item Short-Form Health Survey; SmPC=Summary of Product Characteristics; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; TSH=thyroid stimulating hormone; W=week; WPAI:D=Work Productivity and Activity Impairment: Depression.

[a] At the screening visit, all participants will be asked by the study staff to abstain from alcohol consumption for 24 hours before their baseline visit. All participants must restrict food and water intake from the time they arrive at the site for the baseline visit. Once eligibility is confirmed and participants are randomly assigned to a study intervention arm, only those participants randomly assigned to the esketamine arm will be required to continue to restrict food and water intake (until after dosing). If a participant is randomly assigned to the esketamine arm, the nasal treatment session must not be started until food has been restricted for at least 2 hours and water has been restricted for at least 30 minutes.

[b] The investigator will evaluate any changes in the participants signs/symptoms of depression since the screening assessment and confirm that the inclusion criteria for the current AD treatment are still met (ie, nonresponse and minimal clinical improvement).

[c] For women of childbearing potential, serum pregnancy test (central laboratory) only at screening; urine pregnancy test (at site/local) from baseline onwards. Counseling on pregnancy prevention will be provided at all visits, as 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.

[d] The ECG does not need to be repeated at baseline if the screening ECG was performed within 1 week before the Day 1 visit.

[e] Full nasal examination (including upper respiratory tract/throat) will be conducted at screening in all participants.

[f] This test will be performed **first on Day 1**. If the urine drug screen is positive, the participant may have their Day 1 visit rescheduled 1 time, if negative on retest then the participant will be allowed to continue.

[g] To minimize bias, psychotherapy has to be discussed with the participant prior to randomization.

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

[i] Must be performed prior to esketamine dosing in applicable participants (ie, randomly assigned to the esketamine arm).

[j] The treatment continuation assessment will be performed on all participants who are taking study intervention (ie, both components of the randomized combination therapy) (see Section 4.1) and will be the basis for the decision to continue study intervention. If the study intervention is discontinued early, the CGI-C (ie, the basis of the treatment continuation assessment for the study interventions) will still be performed at follow-up visits (refer to the Maintenance Phase Schedule of Activities); however, treatment decisions will be at the discretion of the investigator and not based on the criteria for the treatment continuation assessment.

[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.

[l] Hematology, chemistry, and urinalysis tests do not need to be repeated at baseline if screening tests were performed within 1 week before the Day 1 visit.

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

[n] 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.

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

[p] If participants cannot tolerate at least 150 mg/day of QTP XR by the end of Week 2 (or at any subsequent time during the study), they must have QTP XR discontinued. Treatment discontinuation by gradual dose reduction over 1 to 2 weeks is recommended.

[q] Quetiapine XR will be dispensed at the Day 1 visit and then as necessary at subsequent visits based on a participant's dose. If necessary, participants may need to return for an unscheduled visit to allow for dispensing of a new supply of quetiapine XR to accommodate changes in dosing.

[r] Nasal treatment sessions should not take place on 2 consecutive days. If the participant has nasal congestion on the dosing day, a nasal decongestant can be used (but not within 1 hour before esketamine dosing) to reduce congestion or the dosing day can be delayed (per the permitted visit window).

[s] 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.

[t] The frequency of nasal treatment sessions may be individualized from once weekly to every 2 weeks based on severity of depressive symptoms and at the discretion of the investigator. The next visit (ie, in the maintenance phase) will be at Week 9 if frequency remains once weekly or at Week 10 for participants who have their frequency changed to every 2 weeks at Week 8.

[u] If possible, blood samples should be collected under fasting conditions (minimum 8 hours prior to biomarker sample collection, water is permitted). Participants should refrain from exercise/strenuous physical activity and the use of NSAIDs for 24 hours prior to blood collection. Not following these recommendations will not constitute a protocol violation.
[v] If a participant is switched to an alternative standard of care treatment prior to Week 8, the blood sample for biomarker evaluation and menstrual cycle information should be collected at the visit when the switch is made.
[w] Prestudy non-AD therapies administered up to 30 days before screening must be recorded.

1.3.2. Schedule of Activities (Weeks 9 to 32)

Phase	Maintenance Phase																								Follow-up visits (study intervention discontinuation before Week 32)[a]		Early study with-drawal visit[b]	Safety follow-up visit[c,d]
	(Odd week visits are ONLY for participants in the esketamine arm with once weekly dosing frequency)																								Every			2 weeks after last dose
Week	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	2 weeks	4 weeks		
Visit Window (Days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		±2
Patient-reported outcomes[e]																												
PHQ-9		X		X		X		X		X		X		X		X		X		X		X		X	X		X	
QLDS				X				X				X				X				X				X		X	X	
EQ-5D-5L				X				X				X				X				X				X		X	X	
SF-36				X				X				X				X				X				X		X	X	
SDS				X				X				X				X				X				X		X	X	
WPAI:D				X				X				X				X				X				X		X	X	
Clinician-rated scales and questionnaires[f]																												
MADRS: efficacy assessment/blinded rater		X		X		X		X		X		X		X		X		X		X		X		X	X		X	
CGI-S				X				X				X				X				X				X		X	X	
CGI-C				X				X				X				X				X				X		X	X	
C-SSRS (Since Last Visit version)				X				X				X				X				X				X		X	X	X
Study intervention assessment[f,g]																												
Treatment continuation assessment (participants taking study intervention)				X				X				X				X				X								
Safety assessments																												
Hematology/chemistry (central), urinalysis (local)[h]												X												X			X	X
12-lead ECG (local)												X												X				
Pregnancy testing[i]				X				X				X				X				X				X			X	X
Body weight				X				X				X				X				X				X			X	X
Vital signs[j] (comparator arm)				X				X				X				X				X				X			X	X

Phase	Maintenance Phase																								Follow-up visits (study intervention discontinuation before Week 32)[a]		Early study withdrawal visit[b]	Safety follow-up visit[c,d]
	(Odd week visits are ONLY for participants in the esketamine arm with once weekly dosing frequency)																								Every			
Week	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	2 weeks	4 weeks		2 weeks after last dose
Visit Window (Days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		±2
Vital signs[j,k]/ nasal examination[k,l] (esketamine arm)																								X			X	X
Additional safety assessments (esketamine arm)																												
Vital signs predose[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Vital signs postdose[j,m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Nasal examination predose[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Study intervention procedures																												
Dispense QTP XR (comparator arm)[n]		X[o]		X[o]		X[o]		X[o]		X[o]		X[o]		X[o]		X[o]		X[o]		X[o]		X[o]						
Nasal treatment sessions[p,q] (esketamine arm)	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X					
Drug accountability: esketamine/QTP XR				X				X				X				X				X				X			X	
Medication compliance counseling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	
Biomarker evaluations (optional)																												
Blood sample[s]																											X[t]	
Menstrual cycle information																											X[t]	
Ongoing																												
Concomitant therapy/ psychotherapy		X		X		X		X		X		X		X		X		X		X		X		X	X	X	X	X
Adverse events		X		X		X		X		X		X		X		X		X		X		X		X	X[u]	X[u]	X	X

NOTES: If the SSRI/SNRI is discontinued at any time during the maintenance phase, the esketamine nasal spray or quetiapine XR must also be discontinued. The participant will be switched to an alternative standard of care treatment at the discretion of the investigator and continue follow-up visits through Week 32.
If esketamine nasal spray or quetiapine XR is discontinued at any time during the maintenance phase, the participant will be switched to an alternative standard of care treatment, which may or may not include the continuing SSRI/SNRI, at the discretion of the investigator and continue follow-up visits through Week 32. If determined by the investigator that the alternative standard of care will include esketamine nasal spray (when commercially available in country of participation) or QTP XR, it will not be provided to the participant, rather, the investigator must prescribe the medication to the participant.

Abbreviations: C-SSRS=Columbia-Suicide Severity Rating Scale; CGI-C=Clinical Global Impression – Change; CGI-S=Clinical Global Impression – Severity; ECG=electrocardiogram; EQ-5D-5L=European Quality of Life Group, 5 dimension, 5-level (questionnaire); MADRS=Montgomery-Asberg Depression Rating Scale; NSAIDs=non-steroidal anti-inflammatory drugs; PHQ-9=Patient Health Questionnaire – 9; PRO=patient-reported outcome; QLDS=Quality of Life in Depression Scale; QTP XR=quetiapine extended-release; SDS=Sheehan Disability Scale; SF-36=36-item Short-Form Health Survey; SmPC=Summary of Product Characteristics; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; WPAI:D=Work Productivity and Activity Impairment: Depression.

[a] Participants who discontinue the study intervention early (ie, discontinue either component of the randomized combination therapy) will remain in the study and continue to return for all follow-up visits after early study intervention discontinuation. For these participants, the first 2-week follow-up visit must include any additional assessments listed for the safety follow-up visit that are not included in this column. The last visit for these participants will be Week 32.

[b] Participants who withdraw early from the study must have the early study withdrawal visit performed within 1 week of the date of withdrawal and then return for the safety follow-up visit 2 weeks after their last dose of study intervention, unless they withdraw consent. If the early study withdrawal visit is conducted on the same day as a scheduled visit, duplicate assessments are not required.

[c] For participants in the esketamine arm, the safety follow-up visit will be performed 2 weeks after the last nasal treatment session. In participants with a dosing frequency of every 2 weeks, this visit will be at Week 32, and for participants with a dosing frequency of once weekly, this visit will be at Week 33.

[d] For participants in the comparator arm who complete the study through Week 32, the safety follow-up visit will be performed 2 weeks after the last dose of study intervention (ie, QTP XR in combination with a continuing SSRI/SNRI) was taken during the study.

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

[f] Must be performed prior to esketamine dosing in applicable participants (ie, randomly assigned to the esketamine arm).

[g] The treatment continuation assessment will be performed on all participants who are taking study intervention (ie, both components of the randomized combination therapy) (see Section 4.1) and will be the basis for the decision to continue study intervention. If the study intervention is discontinued early, the CGI-C (ie, the basis of the treatment continuation assessment for the study interventions) will still be performed at follow-up visits; however, treatment decisions will be at the discretion of the investigator and not based on the criteria for the treatment continuation assessment.

[h] 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.

[i] 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.

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

[k] At Week 32 and at the safety follow-up visit (no esketamine nasal spray dose), vital signs will be performed according to usual practice and nasal examination as described below will be performed.

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

[m] 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.

[n] If participants cannot tolerate at least 150 mg/day of QTP XR during the maintenance phase, they must have QTP XR discontinued. Treatment discontinuation by gradual dose reduction over 1 to 2 weeks is recommended.

[o] Quetiapine XR will be dispensed as necessary at visits based on a participant's dose. If necessary, participants may need to return for an unscheduled visit to allow for dispensing of a new supply of quetiapine XR to accommodate changes in dosing.

[p] 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).

[q] 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.

[r] 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.

[s] If possible, blood samples should be collected under fasting conditions (minimum 8 hours prior to biomarker sample collection, water is permitted). Participants should refrain from exercise/strenuous physical activity and the use of NSAIDs for 24 hours prior to blood collection. Not following these recommendations will not constitute a protocol violation.

[t] Only if a participant withdraws from the study at or prior to Week 8.

[u] For participants who discontinue study intervention early: (1) if their alternative standard of care treatment includes commercial esketamine or another Janssen medicinal product for depression, AEs will continue to be collected after completion of the safety follow-up visit; (2) if their alternative standard of care treatment does not include commercial esketamine or another Janssen medication for depression, AEs will not be systemically collected after completion of the safety follow-up visit. For AEs that are not systematically collected (including AEs for Janssen medicinal products not indicated for depression) and where the participating physician considers there is at least a reasonable possibility of a causal relationship to a medicinal product (ie, spontaneous adverse drug reactions), the participating physician is requested to notify the manufacturer (ie, Janssen or other manufacturer) of the medicinal product or the appropriate regulatory/competent authority through the national spontaneous reporting system as soon as possible.

2. INTRODUCTION

The mechanism of action of ketamine is distinct from conventional antidepressants (ADs), which target the monoamines (serotonin, norepinephrine, and/or dopamine). Ketamine affects fast excitatory glutamate transmission.[8] Antidepressant effects may relate to increased brain-derived neurotrophic factor release and synaptogenesis.

Esketamine, the S-enantiomer of ketamine, is approved and widely used for the induction and maintenance of anesthesia via intramuscular or intravenous (IV) administration.

Because of the higher N-methyl-D-aspartate (NMDA) receptor affinity of esketamine over arketamine (R-enantiomer of ketamine), Janssen Research & Development is developing esketamine (not the racemate) for AD therapy. Moreover, intranasal administration was investigated instead of IV administration, since intranasal administration can offer better convenience for patients and fewer errors in dosing, and esketamine can be rapidly and well absorbed via the intranasal route.[4,23] Esketamine nasal spray was approved by the United States Food and Drug Administration (FDA) on 5 March 2019 for use in conjunction with an oral AD to treat adults with treatment-resistant depression (TRD); and is under development in other countries for patients with TRD and with major depressive disorder (MDD) with current suicidal ideation with intent. A Marketing Authorisation Application was approved by European Medicines Agency in December 2019 for esketamine nasal spray in adults with treatment-resistant MDD (also referred to as TRD) who have not responded to at least 2 different treatments with ADs in the current moderate to severe depressive episode. It must be administered in combination with an oral AD from the selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) classes.

For the most comprehensive nonclinical and clinical information regarding esketamine (JNJ-54135419), refer to the latest edition of the Investigator's Brochure (IB).[15]

The term "sponsor" used throughout this document refers to the Janssen 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".

The term "study intervention" throughout the protocol refers to the combination product: esketamine nasal spray in combination with a continuing SSRI/SNRI or a continuing SSRI/SNRI augmented with quetiapine extended-release (XR), as defined in Section 6.1, Study Interventions Administered. The study intervention will be considered discontinued if either component of the randomized combination therapy is stopped.

In the text of this document, Studies ESKETINTRDxxxx (eg, ESKETINTRD3001) and 54135419TRDxxxx (eg, 54135419TRD3008) are abbreviated as TRDxxxx.

2.1. Study Rationale

Depression is a major cause of morbidity and mortality, with global estimates of 300 million treated and untreated individuals worldwide. In its severe forms, depression is the most common diagnosis associated with suicide, a leading cause of death among 15- to 29-year-olds, and is one of the top 10 causes of disability and years lost to disability in young and middle-aged adults.[1] A depressive state with classical symptoms such as low (depressive/sad) mood, markedly diminished interest in activities, significant weight loss/gain, insomnia or hypersomnia, psychomotor agitation/retardation, excessive fatigue, inappropriate guilt, diminished concentration, and recurrent thoughts of death, persisting for more than 2 weeks is classified as MDD.

Despite the years of research in depressive disorders, it remains a heterogenous disease with a host of genetic and physiological mechanisms warranting individualized treatment.[1] It is estimated that 10% to 15% of patients suffering from depression will have insufficient or no response to clinical intervention and retain a significant mortality risk by suicide. This is a part of a larger problem of partial or relative response to intervention in 50% to 70% of patients undergoing antidepressive treatment. Different definitions and staging exist for patients with TRD.[3,5,9]

There is a significant unmet need to develop novel AD treatments based on the relevant psychophysiological pathways underlying MDD. The goal of any novel treatment would be the rapid and long-lasting relief of depressive symptoms, especially in patients with TRD, who lack a sufficient response to the currently available treatment strategies. These patients are primarily treated by dose optimization, augmentation/combination therapies, and switching therapies.

Data from a Phase 3 study (TRD3004) of esketamine nasal spray in combination with a newly initiated SSRI/SNRI in participants with TRD showed improvements in depressive symptoms over the 4-week induction phase that appeared to be sustained in those participants who continued treatment for up to 1 year. The improvements with esketamine nasal spray in combination with a newly initiated SSRI/SNRI were in the range of the previous Phase 2 and Phase 3 short-term studies (TRD2003, TRD3001, and TRD3002). Additionally, in a relapse prevention study (TRD3003) that used a randomized withdrawal design in the context of continuing SSRI/SNRI treatment, a statistically significantly longer time to relapse was observed with continued esketamine treatment relative to discontinuation of esketamine in adult participants with TRD who had achieved stable remission (or stable response) of their depression symptoms during 16 weeks of treatment with esketamine in combination with an SSRI/SNRI.

The evaluation of esketamine in an elderly population (aged 65 to 74 years) is important as TRD in this population is more severe[5] and less responsive to treatment. Furthermore, treatment of depression in the elderly is challenging as patients not only commonly suffer from disability, functional decline, and diminished quality of life from TRD, but also as a consequence of comorbid medical conditions.[17] In a study in elderly patients (TRD3005), there was an estimated treatment difference in the Montgomery-Asberg Depression Rating Scale (MADRS) change from baseline of -3.6. Although this change was not statistically significant, it suggests a clinically meaningful benefit in this vulnerable and difficult-to-treat elderly population with TRD who were started at 28 mg and could be titrated to 56 or 84 mg as clinically appropriate. Additionally, results showed

a clinically meaningful treatment difference (a difference of -4.9 in the change from baseline in MADRS total score at Day 28) for participants aged 65 to 74 years favoring esketamine in combination with a newly initiated SSRI/SNRI. Treatment differences observed in the 65 to 74 years subgroup were comparable to MADRS results observed in the adult populations (18 to 64 years) in other Phase 3 studies of esketamine.

In the current study, participants will be included who are aged 18 to 74 years (inclusive). To complement the Phase 3 program and to generate clinical data for esketamine nasal spray taken by patients who are continuing their current SSRI/SNRI following the esketamine nasal spray label for the indication of TRD, this study will evaluate the efficacy, safety, and tolerability of flexibly dosed esketamine nasal spray compared with quetiapine XR, both in combination with a continuing SSRI/SNRI, in adult and elderly participants who have treatment-resistant MDD with a current moderate to severe depressive episode. This study has both a short-term (8-week primary efficacy endpoint) and long-term (24-week post primary efficacy endpoint) treatment period.

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.[15]

2.2.1. Pharmacologic Profile

Excitatory synaptic transmission in the central nervous system is primarily mediated by ionotropic glutamate receptors such as NMDA which require glutamate and D-serine and membrane depolarization for opening and allowing influx of calcium. Ketamine acts as a non-competitive, subtype nonselective, activity-dependent NMDA receptor antagonist functioning at the phencyclidine (PCP) binding site and enters the channel, blocking further calcium influx. Among ketamine enantiomers and their metabolites (including norketamine, hydroxynorketamine, and dehydronorketamine), esketamine is the most potent NMDA receptor antagonist.

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 (ECG) changes were observed. Minor, non-adverse histologic findings were noted 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. Repeated-dose neurotoxicity studies in juvenile rats and dogs did not cause brain lesions even at high exposures, consequently, the risk of neurotoxicity associated with nasal administration of esketamine to juvenile and adult patients is low. Intranasally administered ketamine or esketamine did not affect fertility, early embryonic development, and pre- and postnatal development in rats. When pregnant rabbits were treated with ketamine at maternally toxic dose levels, skeletal malformations were noted in the offspring. There

may be a relationship to ketamine treatment. Considering the published evidence on the developmental neurotoxicity potential of ketamine in animals during pregnancy and in early postnatal rodent pups, a similar risk with esketamine to humans cannot be excluded.

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.[15]

2.2.3. Clinical Studies

The clinical program for esketamine includes: a comprehensive clinical pharmacology program in healthy volunteers and special populations to fully characterize the product's pharmacokinetic and pharmacodynamic activity, including Phase 2 studies with IV esketamine and ketamine; a Phase 2 dose response study in adults with TRD; a Phase 2 proof-of-concept study in the related condition of MDD with imminent risk for suicide; and data from 5 completed Phase 3 studies establishing efficacy and safety in adults with TRD, including those 65 years and older. Results from 1 ongoing Phase 2 study and 2 ongoing Phase 3 studies in adults with TRD are not available at the time of finalization of this protocol.

2.2.3.1. Metabolism and Excretion

Esketamine undergoes extensive metabolism by human hepatic cytochrome P450 (CYP). Demethylation of esketamine to noresketamine (M10) is the initial, but not the primary metabolite, as multiple downstream metabolites are formed. Minor secondary pathways are produced by oxidation of the cyclohexanone moiety (M2, M4, and M5), oxidative deamination (M11), and keto-reduction of M10 (M12). In addition, traces of oxidation of the cyclohexanone moiety of esketamine (M6) has been observed. The major human hepatic cytochromes that catalyze esketamine N-demethylation in vitro were CYP2B6 and CYP3A4. The cytochrome enzymes responsible for the formation of norketamine metabolites include CYP2A6 and CYP2B6.

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

2.2.3.2. Pharmacokinetics

The mean absolute bioavailability of nasally administered esketamine is approximately 48%. Esketamine is rapidly absorbed through the nasal mucosa following administration as a nasal spray with measurable concentrations in plasma at 7 minutes after the first spray. The maximum plasma concentration (C_{max}) of esketamine is typically observed at approximately 20 to 40 minutes after the last nasal spray of a given dose. Mean C_{max} and area under the plasma concentration-time curve (AUC) values 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.

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 area under the plasma concentration-time curve from time 0 to infinity (AUC_∞) values produced by a 56-mg dose administered as a nasal spray were approximately 14% and 33% higher, respectively, in Chinese participants compared with white participants. Both parameters were approximately 40% higher in Japanese participants, compared with white participants. On average, esketamine C_{max} was 10% lower and AUC_∞ was 17% higher in Korean participants, relative to white participants. In Study TRD1002, the mean plasma esketamine C_{max} and AUC_∞ values produced by 28 mg, 56 mg, and 84 mg of intranasal esketamine were higher in Japanese participants as compared with white 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.
- **Elderly (≥65 years of age) 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_∞ were up to 21% and 18% higher, respectively, for the 28 mg dose and up to 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_∞ 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_∞ 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_∞ 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). The C_{max} of esketamine was on average 20% to 26% higher following administration of a 28-mg dose of esketamine in participants with mild (CL_{CR}, 58 to 77 mL/min), moderate (CL_{CR}, 30 to 47 mL/min), or severe (CL_{CR}, 5 to 28 mL/min, not on dialysis) renal impairment. The AUC_∞ was 13% to 36% higher in the participants with mild to severe renal impairment. The half-life of esketamine ranged between 11.0 and 16.3 hours and did not appear to be related to renal function.
- **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 are similar.

- **Participants with TRD:** At corresponding intranasal esketamine doses and timepoints, the mean plasma esketamine concentrations in samples collected in the Phase 2 and 3 studies were similar to the range of mean plasma esketamine concentrations in samples collected in the Phase 1 studies.
- **Effects of potent inducers and inhibitors of hepatic CYP:** On average, the C_{max} and AUC_{∞} 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). On average, the C_{max} and AUC_{∞} 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. Pretreatment with oral ticlopidine, an inhibitor of hepatic CYP2B6 activity, had no effect on the C_{max} of nasally administered esketamine, the AUC_{∞} of esketamine was increased by approximately 29%, and there was no effect on terminal half-life of esketamine.
- **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. 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

Efficacy of IV esketamine at 0.20 mg/kg and 0.40 mg/kg doses given over 40 minutes for TRD was established in the ESKETIVTRD2001 study. The proportion of responders (reduction in MADRS total score by ≥50% from baseline [Day 1] on Day 2, 3, or 4 [prior to dosing]) was 66.7% and 63.6% in the esketamine 0.20 mg/kg group and esketamine 0.40 mg/kg group, respectively, compared with no responders in the placebo group. The onset of a therapeutic effect was noted at 2 hours after the infusion for both 0.20 mg/kg and 0.40 mg/kg of esketamine, which was sustained with repeated dosing through to the end of the study.

Intranasal esketamine 56 and 84 mg achieved similar concentration as the 0.2 mg/kg IV dose and therefore could have similar efficacy. This was investigated in the double-blind phase of the TRD2003 study in non-Japanese participants with TRD. Intranasal esketamine had a rapid onset of effect within 24 hours, and repeated treatment sessions sustained the response throughout the study duration. A clear dose response was observed for the 28 mg, 56 mg, and 84 mg doses. While the change in MADRS total score for the 28 mg dose was statistically significant, the magnitude of effect was small. The AD effect for the 84 mg dose was sustained with twice-weekly dosing and the 56-mg dose effect was less well sustained. The AD effect for the 28 mg dose was the least well sustained with twice weekly dosing. Investigation of efficacy and safety of 14 mg dose group was completed in Japan.

Based on the efficacy and safety data from the TRD2003 study, the efficacy and safety of intranasal esketamine was further investigated in Phase 3 short-term studies in adults 18 to 64 years of age with TRD (TRD3001 [fixed doses of 56 mg or 84 mg] and TRD3002 [flexible doses of 56 mg or

84 mg]) and in elderly adults ≥65 years of age with TRD (TRD3005 [flexible doses of 28 mg, 56 mg, or 84 mg]). Esketamine, administered in combination with a newly initiated SSRI/SNRI, demonstrated robust and statistically significant relief of symptoms of depression in Study TRD3002 in participants with TRD who had not responded to 2 or more ADs for their current depression episode. Results in this Phase 3 study were consistent with those for the placebo-controlled Phase 2 adjunctive study (TRD2003) in showing a rapid onset of efficacy. Based on flexible dose Study TRD3002, clinical improvement with esketamine was observed as early as 24 hours and generally increased in subsequent weeks, with the full AD effect observed by the end of Week 4. Although not achieving statistical significance, results of similarly designed Phase 3 studies in adult (TRD3001) and elderly (TRD3005) participants with TRD numerically favored the esketamine administered in combination with a newly initiated SSRI/SNRI group. In addition, in Studies TRD3001 and TRD3002, results numerically favored esketamine administered in combination with a newly initiated SSRI/SNRI for the efficacy measure of onset of response by Day 2.

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 (flexible doses of 28 mg, 56 mg, or 84 mg of intranasal esketamine) were consistent with 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. The improvements in measures of depression were consistent across multiple assessments of depressive symptoms over the 4-week induction phase and appeared to be sustained in participants who continued treatment up to the 1-year exposure. The improvements observed with esketamine administered in combination with a newly initiated SSRI/SNRI were in the range of the previous Phase 2 and Phase 3 short-term studies, although caution is needed in interpreting the results of Study TRD3004, given the absence of a control arm and given that participants were unblinded.

In addition, results from Study ESKETINSUI2001 supported the hypothesis that 84 mg of intranasal esketamine is an efficacious treatment for the rapid reduction of the symptoms of MDD, including suicidal ideation, in participants assessed to be at imminent risk for suicide. The participants included in this study were severely depressed and suicidal as evidenced by their high

baseline MADRS and Clinical Global Judgment of Suicide Risk (a module of the clinician-rated Suicide Ideation and Behavior Assessment Tool) scores. All participants received comprehensive treatment with initial hospitalization and optimized standard of care AD medication. Despite some non-specific improvement in the placebo group, the beneficial effect of esketamine on the symptoms of MDD, as measured by the MADRS total score and the MADRS suicidality item, could be distinguished at early time points as well as at the double-blind endpoint (Day 25).

2.2.3.4. Safety Studies

As of 1 April 2019, the estimated cumulative number of participants exposed to esketamine in clinical trials (including healthy and special population [eg, renal and hepatic impairment but not with TRD or MDD] participants) was 2,955 (627 participants from Phase 1 program, 295 participants from Phase 2 program and approximately 2,033 participants from Phase 3 program). Key safety observations from this program are identified below.

- The safety profile of esketamine is well characterized and tolerable with manageable risks. Over the proposed therapeutic dose range for use in a TRD population (28 to 84 mg), most intervention-emergent adverse events (AEs) with esketamine occur shortly after dosing, when participants will be under the supervision of a health care professional, are transient, and resolve on the same day. Transient postdose symptoms were consistent with findings from the Phase 1 and 2a esketamine IV studies and were expected based on the pharmacologic profile. No new safety concerns associated with esketamine treatment were identified in Phase 2 and 3 studies.
- The most commonly observed adverse drug reactions in TRD patients treated with esketamine in combination with a newly initiated SSRI/SNRI in Phase 2 and Phase 3 studies (incidence ≥10% and greater than in the newly initiated SSRI/SNRI in combination with placebo group) were dissociation, dizziness, nausea, sedation, headache, vertigo, dysgeusia, hypoesthesia, anxiety, blood pressure increased, and vomiting.
- Several of the more common adverse effects of esketamine, including dissociative symptoms/perceptual changes, dizziness/vertigo, and anxiety, occurred on the day of dosing and resolved the same day. Dissociative symptoms/perceptual changes attenuated with continued treatment.
- The long-term safety profile of esketamine after continued treatment of up to 1 year was characterized in an uncontrolled, open-label study (TRD3004) of 802 participants (691 adults and 111 elderly [≥65 years of age]) with TRD. There were no new AEs reported with long-term repeated, intermittent weekly or every-other week dosing of esketamine (28, 56, or 84 mg) (following a 4-week induction phase of twice-weekly dosing) over a duration 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. In the ongoing esketamine studies, 4 additional deaths have been reported through 1 April 2019. In the ongoing long-term open-label safety extension Phase 3 study (TRD3008), 3 deaths (completed suicide, myocardial infarction, and death due to multiple injuries from car accident) were reported in esketamine-treated participants and 1 death (completed suicide) was reported in the ongoing MDD with imminent risk for suicide study (54135419SUI3001) in the posttreatment follow-up phase.

- 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 PTs) 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 majority of participants who were administered esketamine experienced dissociative symptoms as assessed by the Clinician-Administered Dissociative States Scale. The symptoms peaked at around 40 minutes from the time of esketamine nasal spray administration and typically resolved by 2 to 4 hours after dosing. Across completed Phase 2 and 3 studies, consistent with the observations captured in the Clinician-Administered Dissociative States Scale, median duration of the intervention-emergent AEs of dissociation, feeling abnormal, and feeling drunk across dosing sessions did not exceed 2 hours. Dissociation was reported as severe in intensity at an incidence of less than 4% across studies, was not considered serious for any participants in completed Phase 2 and 3 studies, and rarely led to discontinuation of study intervention. Transient dissociative/perceptual changes were more pronounced in participants receiving higher doses of esketamine.
- 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 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%.
- In the short-term Phase 3 studies, treatment with esketamine in combination with a newly initiated SSRI/SNRI did not influence any aspect of cognition studied in adult participants with TRD and was not associated with any systematic changes in cognition in the elderly participants. In the long-term open-label safety study, overall group mean performance on multiple cognitive domains including visual learning and memory, as well as spatial memory/executive function, either improved or remained stable postbaseline in adult participants. In the subset of elderly participants (≥65 years of age) from this study, a slowing of reaction time was observed starting at Week 20 and through the end of the study; however, this appeared to represent an isolated observation related to processing speed and not a broad

attentional impairment. Performance on all other cognitive tests remained stable in elderly participants in this study.

- Notably absent in the clinical studies with esketamine were respiratory depression, QT interval prolongation, development of psychotic-like symptoms or mania, interstitial or ulcerative cystitis, treatment-emergent hepatotoxicity, and clinically significant body weight gain.
- 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.

2.2.4. Comparator

Quetiapine Extended-Release[28]

Quetiapine is an atypical antipsychotic agent. Quetiapine and the active human plasma metabolite, norquetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and norquetiapine exhibit affinity for brain serotonin (5-hydroxytryptamine [5HT]$_2$) and dopamine D_1- and D_2-receptors. It is this combination of receptor antagonism with a higher selectivity for $5HT_2$ relative to D_2-receptors, which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal side effect liability of quetiapine compared to typical antipsychotics. Quetiapine and norquetiapine have no appreciable affinity at benzodiazepine receptors but high affinity at histaminergic and adrenergic alpha-1 receptors and moderate affinity at adrenergic alpha-2 receptors. Quetiapine also has low or no affinity for muscarinic receptors, while norquetiapine has moderate to high affinity at several muscarinic receptors, which may explain anti-cholinergic (muscarinic effects). Inhibition of the norepinephrine transporter and partial agonist action at 5HT1A sites by norquetiapine may contribute to the therapeutic efficacy of quetiapine XR as an AD.

Quetiapine XR is indicated as an add-on treatment of major depressive episodes in patients with MDD who have had suboptimal response to AD monotherapy.

Quetiapine XR should be administered prior to bedtime. The daily dose at the start of therapy is 50 mg on Day 1 and 2, and 150 mg on Day 3 and 4. Antidepressant effect was seen at 150 and 300 mg/day in short-term trials as add-on therapy. There is an increased risk of AEs at higher doses. Clinicians should therefore ensure that the lowest effective dose is used for treatment. The need to increase the dose from 150 to 300 mg/day should be based on individual patient evaluation.

Elderly

As with other antipsychotics and ADs, quetiapine XR should be used with caution in the elderly, especially during the initial dosing period. The rate of dose titration of quetiapine XR may need to

be slower, and the daily therapeutic dose lower, than that used in younger patients. The mean plasma clearance of quetiapine was reduced by 30% to 50% in elderly patients when compared to younger patients. Elderly patients should be started on 50 mg/day. The dose can be increased in increments of 50 mg/day to an effective dose, depending on the clinical response and tolerability of the individual patient.

In elderly patients with major depressive episodes in MDD, dosing should begin with 50 mg/day on Days 1-3, increasing to 100 mg/day on Day 4 and 150 mg/day on Day 8. Based on individual patient evaluation, if dose increase to 300 mg/day is required this should not be prior to Day 22 of treatment.

Clinical Efficacy in Major Depressive Episodes in MDD

Two short-term (6-week) studies enrolled patients who had shown an inadequate response to at least 1 AD. Quetiapine XR 150 and 300 mg/day, given as add-on treatment to ongoing AD therapy demonstrated superiority over AD therapy alone in reducing depressive symptoms as measured by improvement in MADRS total score (least squares [LS] mean change vs placebo of 2-3.3 points).

Long-term efficacy and safety in patients with MDD have not been evaluated as add-on therapy, however long-term efficacy and safety has been evaluated in adult patients as monotherapy (see below).

The following studies were conducted with quetiapine XR as monotherapy treatment, however quetiapine XR is only indicated for use as add-on therapy:

In 3 out of 4 short-term (up to 8 weeks) monotherapy studies, in patients with MDD, quetiapine XR 50, 150, and 300 mg/day demonstrated superior efficacy to placebo in reducing depressive symptoms as measured by improvement in the MADRS total score (LS mean change vs placebo of 2-4 points).

In a monotherapy relapse prevention study, patients with depressive episodes stabilized on open-label quetiapine XR treatment for at least 12 weeks were randomized to either quetiapine XR once daily or placebo for up to 52 weeks. The mean dose during the randomized phase was 177 mg/day. The incidence of relapse was 14.2% for quetiapine XR-treated patients and 34.4% for placebo-treated patients.

In a short-term (9 week) study, non-demented elderly patients (aged 66 to 89 years) with MDD, quetiapine XR dosed flexibly in the range of 50 to 300 mg/day demonstrated superior efficacy to placebo in reducing depressive symptoms as measured by improvement in MADRS total score (LS mean change vs placebo -7.54). In this study, patients randomized to quetiapine XR received 50 mg/day on Days 1-3, the dose could be increased to 100 mg/day on Day 4, 150 mg/day on Day 8, and up to 300 mg/day depending on clinical response and tolerability. The mean dose was 160 mg/day. Other than the incidence of extrapyramidal symptoms, the tolerability of quetiapine XR once daily in elderly patients was comparable to that seen in adults (aged 18 to 65 years). The proportion of randomized patients over 75 years of age was 19%.

Clinical Safety

Higher rates of extrapyramidal symptoms were seen in quetiapine treated patients compared to those treated with placebo in short-term, placebo-controlled clinical trials in MDD and bipolar depression. In short-term, placebo-controlled monotherapy clinical trials in MDD, the aggregated incidence of extrapyramidal symptoms was 5.4% for quetiapine XR and 3.2% for placebo. In a short-term placebo-controlled monotherapy trial in elderly patients with MDD, the aggregated incidence of extrapyramidal symptoms was 9.0% for quetiapine XR and 2.3% for placebo. In both bipolar depression and MDD, the incidence of the individual AEs (eg, akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, muscle contractions involuntary, psychomotor hyperactivity, and muscle rigidity) did not exceed 4% in any treatment group.

Suicide

Physicians should consider the potential risk of suicide-related events after abrupt cessation of quetiapine treatment, due to the known risk factors for the disease being treated.

Other psychiatric conditions for which quetiapine is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be comorbid with major depressive episodes.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of AD drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behavior with ADs compared to placebo in patients less than 25 years old.

Close supervision of patients, in particular those at high risk, should accompany drug therapy, especially in early treatment and following dose changes. Suicidal risk monitoring will be performed in this study as described in Section 8.2.5.

In clinical studies of patients with MDD the incidence of suicide-related events observed in young adult patients (younger than 25 years of age) was 2.1% (3/144) for quetiapine and 1.3% (1/75) for placebo. A population-based retrospective study of quetiapine for the treatment of patients with MDD showed an increased risk of self-harm and suicide in patients aged 25 to 64 years without a history of self-harm during use of quetiapine with other ADs.

Adverse Drug Reactions

The most commonly reported adverse drug reactions with quetiapine (≥10%) are somnolence, dizziness, headache, dry mouth, withdrawal (discontinuation) symptoms, elevations in serum triglyceride levels, elevations in total cholesterol (predominantly low-density lipoprotein cholesterol), decreases in high-density lipoprotein cholesterol, weight gain, decreased hemoglobin, and extrapyramidal symptoms.

Overdose

In general, reported signs and symptoms were those resulting from an exaggeration of the active substance's known pharmacological effects; ie, drowsiness and sedation, tachycardia, hypotension, and anti-cholinergic effects.

Overdose could lead to QT-prolongation, seizures, status epilepticus, rhabdomyolysis, respiratory depression, urinary retention, confusion, delirium and/or agitation, coma, and death. Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose.

For further information regarding the comparator refer to the Summary of Product Characteristics (SmPC)[28] (or local equivalent, if applicable).

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.[15]

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[6] 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	
The primary objective of this study is to evaluate the efficacy of flexibly dosed esketamine nasal spray compared with quetiapine extended-release (XR), both in combination with a continuing selective serotonin reuptake inhibitor (SSRI)/serotonin-norepinephrine reuptake inhibitor (SNRI), in achieving remission in participants who have treatment-resistant MDD with a current moderate to severe depressive episode.	Remission at the Week 8 visit, defined as a Montgomery-Asberg Depression Rating Scale (MADRS) total score of ≤10.
Key Secondary	
To assess the efficacy of esketamine nasal spray compared with quetiapine XR, both in combination with a continuing SSRI/SNRI, in the proportion of participants being relapse-free at Week 32 after remission at Week 8.	Remission at Week 8 visit (ie, MADRS total score of ≤10 at the end of Week 8) and no relapse within the consecutive 24 weeks until the end of the prospective observation period at Week 32 visit. **Note:** A relapse is defined by any of the following: d) Worsening of depressive symptoms as indicated by MADRS total score ≥22 confirmed by 1 additional assessment of MADRS total score ≥22 within the next 5 to 15 days. The date of the second MADRS assessment will be used for the date of relapse. e) Any psychiatric hospitalization for – worsening of depression – suicide prevention or due to a suicide attempt for any of these events, the start date of hospitalization will be used for the date of relapse. 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

Objectives	Endpoints
	hospitalized. The onset of the event will be used for the date of relapse. 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.
Other Secondary	
To assess the effect of esketamine nasal spray compared with quetiapine XR, both in combination with a continuing SSRI/SNRI, in: • Clinician-rated overall severity of depressive illness • Early onset of action • Clinician-rated depressive symptoms • Participant-reported depressive symptoms • Participant-reported functional impairment and associated disability • Participant-reported health-related quality of life and health status • Participant-reported work productivity	Change from baseline at all visits for the following scale scores: • Clinician-rated MADRS: – Overall severity of depressive illness (total score) – Early onset of action (change in total score from baseline at Day 8 visit) – Depressive symptoms (individual items) • Clinician-rated overall severity of depressive illness: – Clinical Global Impression – Severity (CGI-S) – Clinical Global Impression – Change (CGI-C), is a measure of change, analyzed as a score not as change from baseline • Participant-reported depressive symptoms: Patient Health Questionnaire 9-item (PHQ-9) • Participant-reported functional impairment and associated disability: Sheehan Disability Scale (SDS) • Participant-reported health-related quality of life and health status: 36-item Short-Form Health Survey (SF-36) • Participant-reported Quality of Life in Depression Scale (QLDS) • Participant-reported European Quality of Life (EuroQoL) Group, 5-Dimension, 5-Level (EQ-5D-5L) questionnaire • Participant-reported work productivity: Work Productivity and Activity Impairment (WPAI): Depression (D) questionnaire

Objectives	Endpoints
To assess the safety and tolerability of esketamine nasal spray compared with quetiapine XR, both in combination with a continuing SSRI/SNRI.	Intervention-emergent adverse events (AEs), including intervention-emergent AEs of special interest Suicidal ideation and behavior: Columbia-Suicide Severity Rating Scale (C-SSRS)
Exploratory	
To assess the potential relationship of biomarkers with response/nonresponse to study intervention in participants with treatment-resistant MDD.	-

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

HYPOTHESES

The primary and secondary hypotheses are provided in Section 9.1, Statistical Hypotheses.

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, open-label, rater-blinded, active-controlled, international, multicenter study to evaluate the efficacy, safety, and tolerability of flexibly dosed esketamine nasal spray compared with quetiapine XR, both in combination with a continuing SSRI/SNRI, in participants 18 to 74 years of age, inclusive, with treatment-resistant MDD. A psychiatrist should determine eligibility of participants for inclusion in the study.

To be eligible for enrollment in the study:

- Participant must be on a *current* antidepressive treatment that includes an SSRI/SNRI at screening that resulted in nonresponse (less than 25% improvement of symptoms) after having been given at an adequate dosage (based on antidepressive dosages from SmPC [or local equivalent, if applicable]) for an adequate duration of at least 6 weeks and having been uptitrated to the maximum tolerated dose; however, at screening the participant must show signs of minimal clinical improvement to be eligible for the study.
- In addition, the current antidepressive treatment must have been immediately preceded by nonresponse to at least 1 but not more than 5 different consecutive treatments (all within the current moderate to severe depressive episode) with ADs taken at an adequate dosage for an adequate duration of at least 6 weeks.
  - "At least 1 but not more than 5" means that participants may be screened and enrolled while receiving treatment with their second to sixth consecutive treatment with oral ADs taken at adequate dosage for an adequate duration of at least 6 weeks to which they are having a nonresponse.
    - If a participant was receiving an oral AD at an adequate dosage for an adequate duration of at least 6 weeks and then had an augmentation therapy added or had

combination AD therapy initiated, it would then be considered the next consecutive treatment with AD if taken at an adequate dosage for an adequate duration of at least 6 weeks.

  - For treatments with AD(s) to be counted as consecutive, there may have been interspersed insufficient treatments (ie, insufficient duration and/or at insufficient dosage). These insufficient treatments are allowed but will not be considered when documenting participant nonresponse.

- Participant must have been treated with at least 2 different antidepressive substance classes among the treatments taken at an adequate dosage for an adequate duration of at least 6 weeks resulting in nonresponse in the current moderate to severe depressive episode (including the current treatment with an SSRI/SNRI).
- Participant must be on a single oral SSRI/SNRI on Day 1 prior to randomization.
  - Participants who are taking combination ADs and/or augmentation (other than quetiapine XR which is exclusionary at doses >50 mg/day) for the current moderate to severe depressive episode at screening are eligible for the study. All AD treatments, including any augmenting substances, must be stopped prior to randomization on Day 1 according to applicable SmPCs (or local equivalents, if applicable), except the SSRI/SNRI to be continued.

The study has 4 phases: an up-to-14-day screening phase, an 8-week acute phase, a 24-week maintenance phase, and a 2-week safety follow-up phase. During the acute phase, participants in the esketamine arm will have twice-weekly visits from Week 1 to Week 4 and once weekly visits from Week 5 to Week 8; during the maintenance phase from Week 9 to Week 32, visits will be once weekly or every 2 weeks (even weeks) based on dosing. Participants in the comparator arm will have weekly visits from Week 1 to Week 4, and then every 2 weeks for the remainder of the acute phase (Week 6 and Week 8) and the maintenance phase (Week 10, Week 12, etc) through Week 32. All participants have a safety follow-up visit 2 weeks following the last dose of study intervention. The total duration of the study is approximately 36 weeks for all participants.

A total of 622 participants will be randomly assigned on Day 1 (baseline) in a 1:1 ratio to 1 of 2 open-label study intervention arms (311 participants per arm):

- **Esketamine Arm:** Participants will continue to take their current SSRI/SNRI in combination with esketamine nasal spray.
  - Study intervention (ie, esketamine nasal spray in combination with a continuing SSRI/SNRI) will be administered as described in Section 6.1.1.
- **Comparator Arm:** Participants will continue to take their current SSRI/SNRI which will be augmented with quetiapine XR as per its SmPC (or local equivalent, if applicable).
  - Study intervention (ie, quetiapine XR in combination with a continuing SSRI/SNRI) will be administered as described in Section 6.1.2.

The study intervention will be considered discontinued if either component of the randomized combination therapy (ie, esketamine nasal spray, quetiapine XR, or continuing SSRI/SNRI) is stopped.

- If the SSRI/SNRI is discontinued at any time during the acute or maintenance phase, the esketamine nasal spray or quetiapine XR must also be discontinued. The participant will be switched to an alternative standard of care treatment at the discretion of the investigator and continue follow-up visits through Week 32.
- If esketamine nasal spray or quetiapine XR is discontinued at any time during the acute or maintenance phase, the participant will be switched to an alternative standard of care treatment, which may or may not include the continuing SSRI/SNRI, at the discretion of the investigator and continue follow-up visits through Week 32. If determined by the investigator that the alternative standard of care will include esketamine nasal spray (when commercially available in country of participation) or quetiapine XR for a participant, it will not be provided to the participant, rather, the investigator must prescribe the medication to the participant.

A diagram of the study design is provided in Section 1.2, Schema.

All procedures and assessments will be performed according to the Schedule of Activities.

If necessary, the screening phase may be extended to allow additional time to obtain documentation for prior treatments with ADs (according to Appendix 3, Regulatory, Ethical, and Study Oversight Considerations: Source Documents) or to accommodate retesting. In all other cases, the screening phase may be extended only after approval by the Sponsor, as assessed on a case-by-case basis. Once all inclusion criteria are confirmed and none of the exclusion criteria are met, the baseline visit (which is also the date of randomization) can be scheduled with a participant immediately.

Baseline (Day 1) Visit and Acute (Weeks 1 to 8) and Maintenance (Weeks 9 to 32) Phases

All visit-specific patient-reported outcome (PRO) assessments (PHQ-9, QLDS, EQ-5D-5L, SF-36, SDS, and WPAI:D) should be conducted/completed before clinician-rated assessments, any tests (other than the urine drug screen at baseline visit [Day 1]; see Section 8.2.4, Clinical Safety Laboratory Assessments), procedures, other consultations, or esketamine nasal spray administration (in applicable participants) to prevent influencing participant perceptions.

Efficacy will be assessed using clinician-rated scales (MADRS, CGI-S, and CGI-C) and PROs. As the MADRS is used to assess the primary and major secondary endpoints in the study, it must be performed by a qualified independent blinded rater as described in Section 8.1.1.2.

Blood samples will be collected for exploratory analysis of biomarkers. Blood samples will also be collected to allow pharmacogenomic (DNA and RNA) research (where local regulations permit). Biomarker and pharmacogenomic blood samples will only be collected at select study sites. Participation in the biomarker and pharmacogenomic research is optional for participants.

For participants in the esketamine arm:

- All clinician-rated scales 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.

- At the Week 4 visit, evidence of therapeutic benefit will be evaluated clinically by the investigator as described in Section 6.1.1.4.

Beginning at the Week 8 visit, *all participants* in both study intervention arms will undergo regular assessments of symptom changes from baseline (ie, treatment continuation assessment) to ensure that study intervention continuation is appropriate. This will be operationalized using the CGI-C clinician-rated scale (referring to study baseline [Day 1]) every 4 weeks, and treatment decisions will be made using cut-off values in Table 1.

Table 1: Treatment Continuation Assessment of Study Intervention

CGI-C ≥4 ("no change" or worse) at 2 consecutive visits	Recommendation to reconsider appropriateness of study intervention and to switch to an alternative standard-of-care treatment.
CGI-C <4 ("Minimally improved" or better) at any visit	Study intervention may be continued at the discretion of the investigator.

CGI-C= Clinical Global Impression – Change

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

There is no requirement to change a participant's standard of care treatment when they complete the maintenance phase at the Week 32 visit. Refer to Section 6.7, for information regarding standard of care treatment following completion of the study.

Participants Who Discontinue the Study Intervention Early

Participants who discontinue the study intervention early (ie, discontinue either component of the randomized combination therapy) will remain in the study and continue to return for follow-up visits every 2 weeks through the Week 32 visit and have assessments performed according to the Schedule of Activities. Refer to Section 6.7 for information regarding standard of care treatment following early discontinuation of the study intervention. Refer to Section 8.3.1 for details of AE reporting for participants who discontinue study intervention early.

After early discontinuation of study intervention, the CGI-C will still be performed at follow-up visits according to the Schedule of Activities; however, treatment decisions will be at the discretion of the investigator and not based on the criteria for the treatment continuation assessment.

Early Study Withdrawal Visit

If a participant withdraws from the study, an early study withdrawal visit should be conducted within 1 week of the date of withdrawal unless they withdraw consent, are lost to follow-up, or have died.

Safety Follow-Up Visit

For participants in the esketamine arm who complete the study, the safety follow-up visit will be performed 2 weeks after the last nasal treatment session. In participants with a dosing frequency

of every 2 weeks, this visit will be at Week 32, and for participants with a dosing frequency of once weekly, this visit will be at Week 33.

For participants in the comparator arm who complete the study, a safety follow-up visit will be performed following the Week 32 visit. The safety follow-up visit will be performed 2 weeks after the last dose of study intervention (ie, quetiapine XR in combination with a continuing SSRI/SNRI) was taken during the study.

For participants who discontinue the study intervention early, all safety follow-up visit assessments as specified in the Schedule of Activities will be performed in addition to the assessments scheduled at their first 2-week follow-up visit, or if study intervention is discontinued after the Week 30 visit, the safety follow-up visit will be performed 2 weeks after their last dose.

Participants who are taking study intervention at the time of early withdrawal from the study should return for the safety follow-up visit 2 weeks after their last dose unless they withdraw consent, are lost to follow-up, or have died.

4.2. Scientific Rationale for Study Design

4.2.1. Selection of Participant Population

The study population will include adult men and women, 18 to 74 years of age (inclusive); this age range is considered appropriate based on the disorder being studied and the available dosing information for the study interventions.

Each participant must meet Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) diagnostic criteria for single-episode MDD or recurrent MDD, without psychotic features, based on clinical assessment and confirmed by the Mini International Neuropsychiatric Interview (MINI), and have an Inventory of Depressive Symptomatology Clinician-Rated 30 Items Scale (IDS-C30) total score of ≥34, which corresponds to moderate to severe depression.

Presentation, diagnosis, and treatment of late-onset MDD (first episode after 50 or 60 years of age) differs from earlier onset MDD due to confounding vascular risk factors, age-related cognitive deficits, and other comorbid medical conditions.[12,22] Decreased efficacy of AD treatments in adults and elderly with late-onset depression has been associated with diverse pathophysiological underpinnings (especially cerebrovascular disease), potentially related to increased neuromorphological changes and magnetic resonance imaging signal hyperintensities[16,17] and treatment resistance.[22] In this study, older adults and the elderly who had onset of their first episode of MDD at ≥55 years of age are excluded.

According to the European Medicines Agency's guideline on clinical investigation of medicinal products in the treatment of depression,[9] "In a clinical pragmatic view a patient has been considered suffering from TRD when consecutive treatment with 2 products of different pharmacological classes, used for a sufficient length of time at an adequate dose, fail to induce a clinically meaningful effect (inadequate response)." In line with the guideline and expanding to include patients who have had more than 2 consecutive treatment failures, participants in this study

must have had nonresponse (ie, lack of clinically meaningful improvement, defined as ≤25% improvement) to at least 1 but not more than 5 different, consecutive treatments with ADs taken at an adequate dosage for an adequate duration of at least 6 weeks in their current moderate to severe depressive episode and currently be receiving treatment with their second to sixth consecutive treatment to which they are having a nonresponse. Additionally, participants must show signs of minimal clinical improvement on their current treatment, which must include an SSRI/SNRI, to be eligible for the study. Participants must have been treated with at least 2 different antidepressive substance classes among the treatments taken at adequate dosage for an adequate duration of at least 6 weeks resulting in nonresponse in the current moderate to severe depressive episode (including the current treatment with an SSRI/SNRI).

Refer to Section 5.1 for the detailed inclusion criteria for participant entry into the study.

4.2.2. Selection of Active Comparator

Quetiapine XR was selected as the active comparator because it is labeled for an add-on treatment of major depressive episodes in patients with MDD who have had suboptimal response to AD therapy. It is widely used in patients with previous treatment failures, and its use is supported by various international guidelines for patients with previous treatment failures. Additional information on the efficacy of augmenting an ongoing AD with quetiapine XR is provided in Section 2.2.4.

Low-dose treatment with quetiapine, which in clinical practice is used for treatment of isolated symptoms (eg, insomnia or agitation), is not considered an appropriate antidepressive augmentation strategy (ie, 150 to 300 mg/day) according to the prescribing information. Therefore, participants who were taking ≤50 mg/day of quetiapine (XR or immediate-release) at screening are allowed to enter the study provided the quetiapine is washed-out by at least 7 days prior to randomization.

4.2.3. Selection of SSRI/SNRI as the Classes of Concomitant Oral Antidepressants

The SSRI and SNRI classes of ADs were selected because they are the most commonly prescribed AD classes in this population, they are generally well-tolerated, and they can be combined with quetiapine XR. In the Phase 3 studies of esketamine nasal spray in combination with SSRIs/SNRIs, it was shown that the combination was safe and well tolerated. The use of this combination also corresponds with the approved label for esketamine nasal spray. The continuing SSRI/SNRI being taken by a participant must be labeled for treatment of depression/MDD in their country of participation; off-label use of an SSRI/SNRI is not permitted. The continuing SSRI/SNRI must not be contraindicated in its SmPC (or local equivalent, if applicable) for augmentation with quetiapine XR.

4.2.4. Screening

The screening period of up to 2 weeks allows sufficient time for confirmation and documentation (according to Appendix 3, Regulatory, Ethical, and Study Oversight Considerations: Source

Documents) of nonresponse to prior treatment with ADs and nonresponse but signs of minimal clinical improvement to the current treatment with an SSRI/SNRI as described in Section 8.1.1.1.

4.2.5. Follow-up

At the start of follow-up after early discontinuation of study intervention, further clinical/standard of care for the treatment of depression will be arranged by the study investigator and/or the participant's treating physician.

4.2.6. Blinding, Control, Study Phase, Intervention Groups

This is an open-label study, study intervention blinding procedures are not applicable.

An active control will be used to determine the sensitivity of the clinical endpoints in this study. There is no placebo arm in this study. Randomization will be used to minimize bias in the assignment of participants to intervention groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across intervention groups, and to enhance the validity of statistical comparisons across intervention groups. The randomization will be balanced by using randomly permuted blocks and will be stratified by age (18 to 64 years [inclusive]; 65 to 74 years [inclusive]) and total number of treatment failures (2; 3 or more [inclusive of current antidepressive treatment at screening used to determine eligibility]).

To minimize bias on the MADRS score (total score is used for primary and key secondary endpoints), the MADRS will be assessed by a qualified independent on-site rater who is blinded to the participant's treatment and who is not involved in any other study assessments or treatment decisions for a given study participant.

4.2.7. Clinician and Participant-reported Efficacy Assessments

Medication guidelines for the treatment of MDD recommend changes in treatment tactics or strategies at critical decision points based on changes in baseline symptom severity. Self-reported or clinician ratings that provide simple measures of symptom severity may facilitate the implementation of such clinical procedures in representative practice and efficacy trials. The clinician and participant-reported scales in this study have been selected as they are validated, reliable, and acceptable to regulatory health authorities and health-technology assessment bodies to assess the efficacy of treatments in TRD.

Refer to Section 8 for details on the clinician and PRO scales used in this study.

4.2.8. Safety Evaluations

Evaluation of intervention-emergent AEs, concomitant therapies, clinical laboratory tests, pregnancy tests, vital signs (including blood pressure measurements), 12-lead ECGs, nasal examinations, and body weight will be performed throughout the study as per the Schedule of Activities to monitor participant safety.

4.2.9. Biomarker and Pharmacogenomic (DNA/RNA) Collection

Blood samples may be collected for the analysis of one or more candidate genes and/or the analysis of genetic and epigenetic markers as well as RNA expression markers. In addition, blood samples may be collected for the exploratory analysis of biomarkers (protein and metabolites) related to immune system activity, hypothalamic–pituitary–adrenal (HPA) axis activation, neurotrophic and metabolic factors.

It is recognized that genetic variation can be an important contributory factor to interindividual differences in intervention distribution and response and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain interindividual variability in clinical outcomes and may help to identify population subgroups that respond differently to an intervention. The goal of the pharmacogenomic component is to collect DNA to allow the identification of genetic and/or epigenetic factors that may influence the pharmacokinetics, pharmacodynamics, efficacy, safety, or tolerability of study intervention and to identify genetic factors associated with MDD. Specifically, genes and epigenetic changes in genes known to be in pathways relevant to depression (HPA axis, inflammation, growth factors, monoamine transporters, ion channels, circadian rhythm) will be evaluated. Expression analyses may include testing of known messenger RNA/microRNA transcripts or transcriptome-wide analysis in relationship to AD treatment response and MDD.

Increasingly, it is recognized that psychiatric disorders may be associated with altered immune/metabolic activation patterns. Blood samples will be used to explore biomarkers related to immune system activity, HPA axis activation, and neurotropic factors (including but not limited to growth factors, inflammation, or endocrine markers). Biomarker samples will be used to evaluate the mechanism of action of esketamine or help to explain interindividual variability in clinical outcomes or may help to identify population subgroups that respond differently to an intervention.

The DNA, RNA, protein, and metabolic biomarker samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

4.2.10. 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).

The comparator group will receive quetiapine XR, which is approved for augmentation therapy in MDD. A brief summary of the safety profile for quetiapine XR is provided in Section 2.2.4, Comparator; additional information can be found in its SmPC[28] (or local equivalent, if applicable).

Participants must be taking an SSRI/SNRI that is approved for use in depression in their country of participation. Potential participants who are taking an SSRI/SNRI off-label are not eligible for this study.

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 AEs of the study, and provide their consent voluntarily will be enrolled.

Participants at select study sites will be offered participation in optional biomarker and pharmacogenomic research components including collection of blood samples for biomarker and/or DNA and RNA analysis. Participants may decide to opt out of this optional research. The decision to opt out of either optional research component will not impact the eligibility to participate in the main study. Participants that take part in the optional research component(s) of the study will sign an additional informed consent form (ICF).

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

4.3. Justification for Dose

Esketamine Arm

All participants in the esketamine arm will receive flexible doses (either 28 [elderly participants and adults of Japanese ancestry only], 56, or 84 mg) of esketamine nasal spray, based on their tolerability and response to a first dose of 28 mg (elderly participants and adults of Japanese ancestry only) or 56 mg (adult participants) on Day 1.

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_{∞} values at studied doses, support the initial dose of 28 mg in these 2 populations. The Phase 3 short-term double-blind study (TRD3001) evaluated 2 fixed doses of esketamine (56 mg or 84 mg). Flexible dosing of esketamine was evaluated in the other Phase 3 short-term studies, TRD3002 (56 mg and 84 mg) and TRD3005 (28 mg, 56 mg, or 84 mg), as well as in the relapse prevention study (TRD3003) and long-term open-label study (TRD3004). A flexible dosing schedule was used 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. The fixed-dose design in Study TRD3001 was used to separately evaluate the superiority of esketamine doses of 56 mg and 84 mg in combination with a newly initiated SSRI/SNRI to the newly initiated SSRI/SNRI in combination with placebo comparator treatment. Based on the approved label for esketamine nasal spray, this study is being conducted with a flexible dosing scheme.

Dosing of nasal study treatments (esketamine or placebo) was twice weekly during the Phase 2 TRD2003 study and during the induction phases (ie, Week 1 to Week 4) of the Phase 3 studies. The initial twice-weekly administration schedule was selected based on results of Study KETIVTRD2002 in which similar efficacy was seen in participants with TRD receiving

ketamine, administered as 40-minute IV infusions either 2 or 3 times per week over a 15-day period. 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.

Comparator Arm

Quetiapine XR is labeled for add-on treatment of major depressive episodes in MDD and will be uptitrated according to its SmPC (or local equivalent, if applicable) at the discretion of the investigator to achieve a therapeutic dose (at least 150 mg/day).

Continuing SSRI/SNRI

All participants must be taking an SSRI/SNRI at screening 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).

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 assessment 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 through Week 32.

5. STUDY POPULATION

The study will be conducted internationally. Screening for eligible participants will be performed within 14 days before administration of the study intervention. Refer to Section 5.4, Screen Failures for conditions under which the repeat of any screening procedures are allowed.

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.

For a discussion of the statistical considerations of participant selection, refer to Section 9.2, Sample Size Determination.

5.1. Inclusion Criteria

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

1. male or female, 18 years (or older if the minimum legal age of consent in the country in which the study is taking place is >18 years) to 74 years of age, inclusive, at the time of signing the ICF.

2. at screening, each participant must meet DSM-5 diagnostic criteria for single-episode MDD or recurrent MDD, without psychotic features, based on clinical assessment and confirmed by the MINI (see Section 8.1.1.1).

3. at screening and baseline, each participant must have an IDS-C30 total score of ≥34 (see Section 8.1.1.1).

4. criterion changed per Amendment 1.

4.1 must be on a *current* antidepressive treatment that includes an SSRI/SNRI at screening that resulted in nonresponse (less than 25% improvement of symptoms) after having been given at an adequate dosage (based on antidepressive dosages from SmPC [or local equivalent, if applicable]) for an adequate duration of at least 6 weeks and having been uptitrated to the maximum tolerated dose; however, at screening the participant must show signs of minimal clinical improvement to be eligible for the study. (See also exclusion criterion 4.)

Clinical improvement of a participant on their current AD treatment will be retrospectively evaluated in a qualified psychiatric interview performed by an experienced clinician; additional guidance for this interview is provided in Section 8.1.1.1.

At baseline (Day 1) prior to randomization, the investigator will evaluate any changes in the participant's signs/symptoms of depression since the screening assessment and confirm that the inclusion criteria for the current AD treatment are still met (ie, nonresponse and minimal clinical improvement).

5. criterion changed per Amendment 1.

5.1 the current antidepressive treatment was immediately preceded by nonresponse to at least 1 but not more than 5 different consecutive treatments (all within the current moderate to severe antidepressive episode) with ADs taken at an adequate dosage for an adequate duration of at least 6 weeks and must be documented (as described in Appendix 3, Regulatory, Ethical, and Study Oversight Considerations: Source Documents) during screening.

6. criterion changed per Amendment 1.

6.1 must have been treated with at least 2 different antidepressive substance classes among the treatments taken at an adequate dosage for an adequate duration of at least 6 weeks

resulting in nonresponse in the current moderate to severe depressive episode (including the current treatment with an SSRI/SNRI).

7. must be on a single oral SSRI/SNRI on Day 1 prior to randomization.

   Participants who are taking combination ADs and/or augmentation[a] at screening are eligible for the study. All AD treatments, including any augmenting substances, must be stopped prior to randomization on Day 1 according to applicable SmPCs (or local equivalents, if applicable), except the SSRI/SNRI to be continued; investigator guidance for discontinuing other AD treatment(s) is provided in Section 6.5, Concomitant Therapy.

   [a] Other than quetiapine XR which is exclusionary at doses >50 mg/day for the current moderate to severe depressive episode; see exclusion criterion 2.

8. must be medically stable based on physical examination, medical history, vital signs (including blood pressure) at screening. If there are any abnormalities that are not specified in the inclusion and exclusion criteria, their clinical significance must be determined by the investigator and recorded in the participant's source documents.

9. must be comfortable with self-administration of nasal medication and be able to follow the nasal administration instructions provided.

10. 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.

11. must sign a separate ICF at baseline (Day 1) visit if he or she agrees to provide optional biomarker and/or genomic (DNA and RNA) samples for research (where local regulations permit). Refusal to give consent for the optional biomarker and/or genomic DNA and RNA research samples does not exclude a participant from participation in the main study.

12. a woman of childbearing potential must have a negative highly sensitive serum pregnancy test (β-human chorionic gonadotropin [β-hCG]) at screening and a negative urine pregnancy test prior to the first dose of study intervention on Day 1.

13. a woman must be (as defined in Appendix 6, Contraceptive and Barrier Guidance and Collection of Pregnancy Information)

    - Not of childbearing potential
    - 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.

    Examples of highly effective methods of contraception are located in Appendix 6, Contraceptive and Barrier Guidance and Collection of Pregnancy Information.

14. a man who is sexually active with a woman of childbearing potential during the study (ie, from Day 1 prior to first dosing) and for a minimum of 1 spermatogenesis cycle (defined as approximately 90 days) after receiving the last dose of study intervention (ie, esketamine nasal spray or quetiapine XR, both in combination with continuing SSRI/SNRI), 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.

15. willing and able to adhere to the lifestyle restrictions specified in this protocol (Section 5.3).

5.2. Exclusion Criteria

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

1. received treatment with esketamine or ketamine in the current moderate to severe depressive episode.

2. received treatment with quetiapine extended- or immediate-release in the current moderate to severe depressive episode of a dose higher than 50 mg/day.

    Note: If participants are receiving quetiapine (extended- or immediate-release) of ≤50 mg in the current episode, it needs to be stopped (wash-out period) at least 7 days prior to randomization.

3. had depressive symptoms in the current moderate to severe depressive episode that previously did not respond to an adequate course of treatment with electroconvulsive therapy (ECT), defined as at least 7 treatments with unilateral/bilateral ECT.

4. has no signs of clinical improvement *at all* or with a significant improvement on their *current* AD treatment that includes an SSRI/SNRI as determined at screening by an experienced clinician during the qualified psychiatric interview (Section 8.1.1.1, Screening Evaluations).

    Note: If a participant does not show signs of minimal clinical improvement at screening on their current treatment with AD that includes an SSRI/SNRI, they may be rescreened (1 time) on the next consecutive line of treatment with AD (if it includes an SSRI/SNRI)

after they have taken it at an adequate dosage for an adequate duration of at least 6 weeks (see Section 5.4, Screen Failures).

5. received vagal nerve stimulation or has received deep brain stimulation in the current episode of depression.

6. criterion changed per Amendment 1.

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

7. age at onset of first episode of MDD was ≥55 years.

8. 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 screening, per the investigator's clinical judgment; or based on the C-SSRS, corresponding to a response of "Yes" on Item 4 (active suicidal ideation with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent) for suicidal ideation, or a history of suicidal behavior within the past year prior to screening. Participants reporting suicidal ideation with intent to act or suicidal behavior prior to the start of the acute phase should also be excluded.

9. history of moderate or severe substance use disorder or severe alcohol use disorder according to DSM-5 criteria, except nicotine or caffeine, within 6 months before the start of the screening or current clinical signs.

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

11. has a neurodegenerative disorder (eg, Alzheimer's disease, vascular dementia, Parkinson's disease with clinical evidence of cognitive impairment) or evidence of mild cognitive impairment.

12. is currently suffering from seizures, has a history of epilepsy, Neuroleptic Malignant Syndrome, or Tardive Dyskinesia.

13. criterion changed per Amendment 1.

13.1 has one of the following cardiovascular-related conditions:

- cerebrovascular disease with a history of stroke or transient ischemic attack.
- aneurysmal vascular disease (including intracranial, thoracic, or abdominal aorta, or peripheral arterial vessels).

- history of intracerebral hemorrhage.
- coronary artery disease with myocardial infarction, unstable angina, or revascularization procedure (eg, coronary angioplasty or bypass graft surgery) within 12 months before baseline (Day 1). Participants who have had a revascularization performed >12 months prior to screening and are clinically stable and symptom-free, per investigator's clinical judgment, can be included.
- uncontrolled brady- or tachyarrhythmias that lead to hemodynamic instability.
- hemodynamically significant valvular heart disease such as mitral regurgitation, aortic stenosis, or aortic regurgitation.
- confirmed or suspected cardiomyopathy or myocarditis.
- New York Heart Association Class III-IV heart failure of any etiology.

14. has clinically significant or unstable respiratory conditions, including, but not limited to:
    - significant pulmonary insufficiency, including chronic obstructive pulmonary disease.
    - sleep apnea with morbid obesity (body mass index ≥35).
15. uncontrolled hypertension despite diet, exercise, or antihypertensive therapy on Day 1 or any history of hypertensive crisis or ongoing evidence of uncontrolled hypertension defined as a supine SBP >140 mmHg or DBP >90 mmHg.

    Note: On Day 1 (prior to initiation of study intervention) a supine SBP >140 mmHg or DBP >90 mmHg is exclusionary.

    Potential participants may have their current antihypertensive medication(s) adjusted during the screening phase and be re-evaluated to assess their blood pressure control prior to randomization.

16. history of additional risk factors for torsade des pointes (eg, heart failure, hypokalemia, or family history of long QT syndrome).

17. history of, or symptoms and signs suggestive of, liver cirrhosis (eg, esophageal varices, ascites, and increased prothrombin time) or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values ≥3 × the upper limit of normal in routine laboratory test or medical record or at screening.

18. has a fasting triglyceride concentration ≥500 mg/dL at screening.

19. has positive urine test result(s) for drugs of abuse (including barbiturates, cannabinoids, methadone, opiates, cocaine, PCP, and amphetamine/ methamphetamine) on Day 1 prior to randomization,

    OR

if prescribed psychostimulants (eg, amphetamine, methylphenidate) for MDD, the medication must be discontinued at screening and participants must agree not to take during the study. Participants are excluded if they have a positive urine test result for a prescribed psychostimulant for MDD on Day 1 prior to randomization. However, 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 exclusionary.

Note: intermittent use of cannabinoids prior to the start of the screening phase is not exclusionary as long as the participant does not meet the criteria for substance use disorder or have a positive urine test result for cannabinoids on Day 1 prior to randomization.

See Section 8.2.4, Clinical Safety Laboratory Assessments for additional information on the timing of the urine drug screen at baseline (Day 1) visit.

20. has uncontrolled diabetes mellitus, as evidenced by HbA1c >9% in the medical records, routine laboratory test, or history in the 3 months prior to baseline; or diabetic ketoacidosis, hyperglycemic coma, or severe hypoglycemia with loss of consciousness evaluated from medical history.

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

22. has any anatomical or medical condition that, per the investigator's clinical judgment based on assessment, may impede delivery or absorption of esketamine nasal spray.

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

24. has known allergies, hypersensitivity, intolerance, or contraindications to esketamine/ketamine, quetiapine XR, and/or any excipients.[15,28]

25. has taken any prohibited therapies that would not permit dosing on Day 1 as defined in protocol (Section 6.5, Concomitant Therapy and Appendix 4, Prohibited Concomitant Medications).

26. is taking a total daily dose of benzodiazepines greater than the equivalent of 4 mg/day of lorazepam on Day 1.

27. has been included in any esketamine or ketamine clinical study, or has received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 60 days before the start of the screening phase, or

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

28. 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.

29. is a woman who is pregnant, breastfeeding, or planning to become pregnant or a man that plans to father a child while enrolled in this study or within 90 days after the last dose of study intervention.

30. criterion added per Amendment 1.
has thyroid disease/disorder that has not been sufficiently treated:

    - pre-existing thyroid disease/disorder treated with thyroid hormones not on a stable dosage for 3 months prior to the start of the screening phase.
    - regardless of thyroid history, if the thyroid-stimulating hormone (TSH) value is out of range, a free thyroxine (FT4) will be conducted. If the FT4 value is abnormal and considered to be clinically significant (after discussion with the medical monitor), the participant is not eligible.

31. criterion added per Amendment 1.
has a white blood cell count (WBC) $\leq 2.0 \times 10^3/\mu L$ at screening or history of drug induced neutropenia.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but 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. Section 5.4, Screen Failures, describes options for rescreening and retesting. The required source documentation to support meeting the enrollment criteria are noted in Appendix 3, Regulatory, Ethical, and Study Oversight Considerations: Source Documents.

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; following randomization, items 9 through 12 will only apply to participants in the esketamine arm:

1. refer to Section 6.5, 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 at each visit until study procedures have been completed.

4. agree to fast (water is permitted) for 8 hours before visits when clinical laboratory (screening, Day 1, Week 8, Week 20, Week 32, 2-week safety follow-up visit) or optional biomarker (Day 1, Week 8) blood samples will be collected.

5. agree to refrain from exercise/strenuous physical activity and the use of non-steroidal anti-inflammatory drugs (NSAIDs) for 24 hours before visits (Day 1, Week 8) when optional biomarker blood samples are collected, for applicable participants

6. acknowledge that use of alcohol with study interventions in this study may cause sedation; therefore, alcohol consumption should be limited during the study.

7. agree to restrict food and water intake from the time they arrive at the site for the baseline (Day 1) visit (once eligibility is confirmed and participants are randomly assigned to a study intervention arm, only those participants randomly assigned to the esketamine arm will be required to continue to restrict food and water intake [until after dosing]).

8. agree to abstain from alcohol consumption for 24 hours before their baseline (Day 1) visit.

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

10. 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.

11. 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.

12. 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.

5.4. 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. In cases where the participant is not randomized into the study, the date seen and age at initial informed consent will be used.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened, except where the reason for screen failure was that they did not meet the signs of minimal clinical improvement criteria (Section 8.1.1.1) on their current treatment with AD that includes an SSRI/SNRI. If a participant does not show signs of minimal clinical improvement at screening on their current treatment with AD, they may be rescreened (1 time) on the next consecutive line of treatment with AD (if it includes an SSRI/SNRI) after they have taken it at an adequate dosage for an adequate duration of at least 6 weeks. Participants who are rescreened will be assigned a new participant number, undergo the informed consent process, and then restart a new screening phase.

If clinical safety laboratory tests (serum chemistry, hematology, and urinalysis) or ECG results are abnormal at screening then retesting is allowed and screening may continue if a normal result is achieved. If the urine drug screen is positive on Day 1, the participant may have their Day 1 (baseline) visit rescheduled 1 time, if negative on retest then the participant will be allowed to continue.

6. STUDY INTERVENTION

6.1. Study Interventions Administered

6.1.1. Esketamine Nasal Spray in Combination With a Continuing SSRI/SNRI

Study intervention (ie, esketamine nasal spray and continuing SSRI/SNRI) administration must be captured in the source documents and the electronic case report form (eCRF). Refer to Section 6.1.3, for information on the continuing SSRI/SNRI component of the study intervention.

During the acute and maintenance phases, if esketamine nasal spray is discontinued at any visit, the participant will be switched to an alternative standard of care treatment, which may or may not include the continuing SSRI/SNRI, at the discretion of the investigator. If the continuing SSRI/SNRI is discontinued at any visit, esketamine nasal spray must also be discontinued and the participant will be switched to an alternative standard of care treatment at the discretion of the investigator. If determined by the investigator that the alternative standard of care will include esketamine nasal spray (when commercially available in country of participation) or quetiapine XR for a participant, it will not be provided to the participant, rather, the investigator must prescribe the medication to the participant.

Participants who discontinue the study intervention early (ie, discontinue either component of the randomized combination therapy) will remain in the study and continue to return for all follow-up visits (every 2 weeks) according to the Schedule of Activities.

Refer to Section 6.7 for information regarding standard of care treatment following completion of the study or early discontinuation of the study intervention.

6.1.1.1. 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.

Instructions for use documents for esketamine nasal spray administration will be provided for participants and healthcare providers.

Prior to the first nasal dose on Day 1, participants in the esketamine arm will practice spraying (into the air, not nasally) a demonstration nasal spray device that is filled with a placebo solution.

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). 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.

Post-dosing, 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 8.4, Treatment of Overdose.

6.1.1.2. Esketamine Nasal Spray Dosing Recommendations

On Day 1, participants randomly assigned to the esketamine arm will have their first nasal treatment session as described in Section 6.1.1.3. Adult participants aged 18 to 64 years will start with a dose of 56 mg. Elderly participants aged 65 to 74 years and adults of Japanese ancestry will start with a dose of 28 mg. As of Day 4, the dose may be increased from 56 mg to 84 mg in adult participants, from 28 mg to 56 mg in elderly participants and adults of Japanese ancestry, or participants may remain at the starting dose, as determined by the investigator based on efficacy and tolerability. Elderly participants and adults of Japanese ancestry may be uptitrated in 28 mg increments at subsequent visits. 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 (see Section 6.6.1, Figure 1 and Figure 2, respectively for adults Figure 3 and Figure 4, respectively for elderly participants and adults of Japanese ancestry). The highest dose that may be used in all participants is 84 mg.

The dosing recommendations for esketamine nasal spray for adults <65 years of age are shown in Table 2 and for elderly participants 65 to 74 years of age, inclusive, and adults of Japanese ancestry in Table 3.

Table 2: Recommended Dosing for Esketamine Nasal Spray in Adults <65 Years of Age

Weeks 1-4: Starting Day 1 dose: 56 mg Subsequent doses: 56 mg or 84 mg twice a week	Weeks 5-8: 56 mg or 84 mg once weekly	From Week 9: 56 mg or 84 mg every 2 weeks or once weekly
Evidence of therapeutic benefit should be evaluated at the end of Week 4 to determine need for continued treatment.	The need for continued treatment should be reexamined periodically. Beginning at the Week 8 visit and every 4 weeks thereafter, the treatment continuation assessment of study intervention (see Table 1) will be performed.	

Table 3: Recommended Dosing for Esketamine Nasal Spray in Elderly Participants 65 to 74 Years of Age, Inclusive, and Adults of Japanese Ancestry

Weeks 1-4: Starting Day 1 dose: 28 mg Subsequent doses: 28 mg, 56 mg, or 84 mg twice a week, all dose changes should be in 28 mg increments.	Weeks 5-8: 28 mg, 56 mg, or 84 mg once weekly, all dose changes should be in 28 mg increments.	From Week 9: 28 mg, 56 mg, or 84 mg every 2 weeks or once weekly, all dose changes should be in 28 mg increments.
Evidence of therapeutic benefit should be evaluated at the end of Week 4 to determine need for continued treatment.	The need for continued treatment should be reexamined periodically. Beginning at the Week 8 visit and every 4 weeks thereafter, the treatment continuation assessment of study intervention (see Table 1) will be performed.	

6.1.1.3. Nasal Treatment Sessions

All participants in the esketamine arm will self-administer the esketamine nasal spray at nasal treatment sessions at the study site starting on Day 1.

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.

Based on the dosing frequency in the maintenance phase, the last nasal treatment session will occur at Week 30 (every 2 weeks frequency) or Week 31 (once weekly frequency).

The esketamine nasal spray will be administered during nasal treatment sessions as described in Table 4.

Table 4: 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 acute and maintenance phases are provided in Section 6.6.1 in Figure 1 and Figure 2, respectively for adults and Figure 3 and Figure 4, respectively for elderly participants and adults of Japanese ancestry.

6.1.1.4. Acute (Weeks 1 to 8) and Maintenance (Weeks 9 to 32) Phases

Acute Phase: Week 1 to Week 8

The frequency of nasal treatment sessions will be twice weekly in Week 1 to Week 4 and will be reduced to once weekly in Week 5 to Week 8.

At the Week 4 visit, evidence of therapeutic benefit of the study intervention (ie, esketamine nasal spray in combination with continuing SSRI/SNRI) will be evaluated clinically by the investigator. In the evaluation of therapeutic benefit, the full scope of clinical improvement should be evaluated including any improvement in depressive symptoms, general functioning, social functioning, and self-care. If there is no evidence of therapeutic benefit, the investigator and the participant should discuss the treatment strategy and mutually agree on whether to continue or discontinue esketamine nasal spray. At this visit, if esketamine nasal spray is discontinued, the participant will be switched to an alternative standard of care treatment, which may or may not include the continuing SSRI/SNRI, at the discretion of the investigator.

Beginning at the Week 8 visit, the treatment continuation assessment of study intervention (see Section 4.1, Table 1) should be the basis for the decision to continue study intervention.

At the Week 8 visit the investigator will determine if a participant's frequency of nasal treatment sessions during the maintenance phase should remain once weekly or be changed to every 2 weeks based on the severity of depressive symptoms and their discretion.

Maintenance Phase: Week 9 to Week 32

The frequency of nasal treatment sessions for participants in the esketamine arm can be further individualized during this phase on even week visits (Week 10, Week 12, 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 during this phase. 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 acute and maintenance phases are provided in Section 6.6.1 in Figure 1 and Figure 2, respectively for adults and Figure 3 and Figure 4, respectively for elderly participants and adults of Japanese ancestry.

During this phase, the treatment continuation assessment of study intervention (Week 12, Week 16, etc) (see Section 4.1, Table 1) should be the basis for the decision to continue study intervention.

6.1.2. Quetiapine Extended-Release in Combination With a Continuing SSRI/SNRI

Study intervention (ie, quetiapine XR in combination with a continuing SSRI/SNRI) administration must be captured in the source documents and the eCRF. Study-site personnel will instruct participants on how to store quetiapine XR for at home use as indicated for this protocol.

Refer to Section 6.1.3, for information on the continuing SSRI/SNRI component of the study intervention.

Participants in this arm will have weekly visits from Week 1 to Week 4, and then every 2 weeks for the remainder of the acute phase (Week 6 and Week 8) and the maintenance phase (Week 10, Week 12, etc) through Week 32.If quetiapine XR is discontinued, the participant will be switched to an alternative standard of care treatment, which may or may not include the continuing SSRI/SNRI, at the discretion of the investigator. If the continuing SSRI/SNRI is discontinued at any visit, quetiapine XR must also be discontinued and the participant will be switched to an alternative standard of care treatment at the discretion of the investigator. If determined by the investigator that the alternative standard of care will include quetiapine XR or esketamine nasal spray (when commercially available in country of participation) for a participant, it will not be provided to the participant, rather, the investigator must prescribe the medication to the participant.

Participants who discontinue the study intervention early (ie, discontinue either component of the randomized combination therapy) will remain in the study and continue to return for all follow-up visits according to the Schedule of Activities.

Acute withdrawal symptoms such as insomnia, nausea, headache, diarrhea, vomiting, dizziness and irritability have been described after the sudden discontinuation of quetiapine. Treatment discontinuation by gradual dose reduction over 1 to 2 weeks is recommended.

Refer to Section 6.7 for information regarding standard of care treatment following completion of the study or early discontinuation of the study intervention.

6.1.2.1. Quetiapine Extended-Release

Quetiapine XR tablets will be obtained from commercial stock and will be re-packed (whenever required) into a child-resistant packaging to constitute a participant kit. These will be labeled according to applicable regulatory requirements, will be identified with a unique medication kit number, and provided under the responsibility of the sponsor. Storage should occur in accordance with the label. Please refer to the SmPCs (or local equivalents, if applicable) for the physical description and a list of excipients.

It is recommended that quetiapine XR be administered prior to bedtime, or as directed by the investigator based on individual participant circumstances.

Week 1 to Week 32

Participants will continue to take their current SSRI/SNRI which will be augmented with quetiapine XR as per the SmPC (or local equivalent, if applicable) starting on Day 1 and will continue through Week 32.

The recommended uptitration schedule for quetiapine XR for adults (aged 18 to 64 years) and elderly (aged 65 to 74 years) participants is provided in Table 5. Dosing may be adapted as determined by the investigator based on efficacy and tolerability.

Quetiapine XR will be dispensed at the Day 1 visit and then as necessary at subsequent visits based on a participant's dose. If necessary, participants may need to return for an unscheduled visit to allow for dispensing of a new supply of quetiapine XR to accommodate changes in dosing.

According to the SmPC (or local equivalent, as applicable) for quetiapine XR, the minimum therapeutic dose for add-on treatment of major depressive episodes in MDD is 150 mg/day. Participants should be uptitrated to at least 150 mg/day according to the recommended uptitration schedule and based on individual tolerability no later than the Week 2 visit (ie, end of Week 2). If participants cannot tolerate at least 150 mg/day of quetiapine XR by the end of Week 2 (or at any subsequent time during the study), they must have quetiapine XR discontinued.

The need to increase the dose from 150 up to 300 mg/day should be based on individual patient evaluation.

Table 5: Recommended Uptitration Schedule for Quetiapine Extended-Release

Age Group	Day	Dosage
Adults (18-64 years)	1-2	50 mg/day
	3-4	150 mg/day
	5 or after	300 mg/day (based on individual participant evaluation)
Elderly (65-74 years)	1-3	50 mg/day
	4-7	100 mg/day
	8	150 mg/day
	22 (no earlier than)	300 mg/day (based on individual participant evaluation)

Beginning at the Week 8 visit, the treatment continuation assessments of study intervention (see Section 4.1, Table 1) should be the basis for the decision to continue study intervention.

6.1.3. Continuing SSRI/SNRI

Participants will continue to take their current SSRI/SNRI as prescribed. For participants who are taking combination ADs and/or augmentation at screening, refer to Section 6.5 for guidance on discontinuing other AD treatment(s). The current SSRI/SNRI tablets or capsules being taken by participants will not be provided by the sponsor.

The continuing 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.

The investigator may optimize the dose of the continuing SSRI/SNRI, up to the maximum tolerated dose as per the respective SmPC (or local equivalent, if applicable). Once optimized, a stable dose should be maintained; however, dose modifications may be made, if necessary, at the investigator's discretion.

6.1.4. Medical Devices

- The sponsor-manufactured medical devices (or devices manufactured for the sponsor by a third party) provided for use in this study are disposable single-use nasal spray devices.

- Instructions for medical device use documents for esketamine nasal spray administration will be provided for participants and healthcare providers.
- All device deficiencies (including malfunction, use error, and inadequate labeling) shall be documented and reported by the investigator throughout the clinical investigation, see Section **Error! Reference source not found.**, Medical Device Deficiencies, and appropriately managed by the sponsor.

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

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

Accountability

The investigator is responsible for ensuring that all study intervention components (ie, esketamine nasal spray and quetiapine XR) received at the site are inventoried and accounted for throughout the study.

The esketamine nasal spray administered to the participant must be documented on the intervention accountability form. All esketamine nasal spray will be stored and disposed of according to the sponsor's instructions.

The dispensing of quetiapine XR, and the return of quetiapine XR from the participant (if applicable), must be documented on the intervention accountability form. Participants must be instructed to return all original containers, whether empty or containing quetiapine XR. Study-site personnel must not combine contents of the quetiapine XR containers.

Study intervention components 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 and used esketamine nasal spray, and quetiapine XR returned by the participant, 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 components, or used returned study intervention components for destruction, will be documented on the intervention return form. When the study site is an authorized destruction unit and study intervention component supplies are destroyed on-site, this must also be documented on the intervention return form.

Study intervention components 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 components will be supplied only to participants participating in the study. Returned study intervention components must not be dispensed again, even to the same participant. Whenever a participant brings his or her quetiapine XR to the study site for pill count, this is not seen as a return of supplies. Study intervention may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study intervention components from, nor store them at, any site other than the study sites agreed upon with the sponsor. Further guidance

and information for the final disposal of unused study intervention components are provided in the pharmacy manual/study-site investigational product and procedures manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 2 study intervention groups in a 1:1 ratio based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by age (18 to 64 years [inclusive]; 65 to 74 years [inclusive]) and total number of treatment failures (2; 3 or more [inclusive of current antidepressive treatment at screening used to determine eligibility]).

The interactive web response system (IWRS) will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit (esketamine nasal spray or quetiapine XR) 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.

Blinding

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

To minimize bias, the MADRS (total score is used for primary and key secondary endpoints) will be assessed by a qualified independent rater-blinded to the participant's treatment and who is not involved in any other study assessments or treatment decisions for a given study participant (see Section 8.1.1.2).

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.

Participants will receive instructions on compliance with quetiapine XR dosing. During the study, the investigator or designated study-site personnel will be responsible for providing additional instruction to re-educate (ie, medication compliance counseling) any participant to ensure compliance with taking quetiapine XR.

The investigator or designated study-site personnel will maintain a log of all esketamine nasal spray devices self-administered by participants and of the oral study intervention component (ie, quetiapine XR) dispensed and returned. Study intervention component supplies for each participant will be inventoried and accounted for throughout the study.

Quetiapine XR compliance will be assessed by performing pill counts (ie, compliance check) and drug accountability at the time points specified in the Schedule of Activities.

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

6.5. Concomitant Therapy

Prestudy non-AD therapies administered up to 30 days before screening must be recorded.

All consecutive treatment(s) with AD taken at an adequate dosage (based on antidepressive dosages from label) for adequate duration of at least 6 weeks, including adjunctive treatment for MDD, during the current moderate to severe depressive episode (ie, including those taken more than 30 days prior to screening) will be documented at screening (see Appendix 3, Regulatory, Ethical, and Study Oversight Considerations: Source Documents).

Participants who were taking ≤50 mg/day of quetiapine (XR or immediate-release) at screening (eg, for insomnia or agitation) are allowed to enter the study provided it is washed-out by at least 7 days prior to randomization.

Participants who are taking combination ADs and/or augmentation (other than quetiapine XR, which is exclusionary at doses >50 mg/day for the current moderate to severe depressive episode) at screening must stop all AD treatment, including any augmenting substances, prior to randomization on Day 1, except the SSRI/SNRI to be continued.

- For participants taking combination therapy with an SSRI/SNRI and an antipsychotic medication or any other augmenting substances, the antipsychotic medication and other augmenting substances need to be down-titrated and stopped prior to randomization. The investigator should follow the SmPCs (or local equivalents, if applicable) for all treatments that need to be discontinued. Although not standard practice, should a participant be taking more than 1 SSRI/SNRI at screening, the investigator should choose the one most likely to have a beneficial effect on depressive symptoms when combined with intranasal esketamine or augmented with quetiapine XR, based on individual participant characteristics. The choice of the SSRI/SNRI to continue should take into account potential side-effects when given in combination with quetiapine XR, should the patient be randomized to that arm.

A list of prohibited concomitant medications is provided in Appendix 4 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 continuing 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, PCP, and amphetamine/methamphetamine) are not permitted during the study. If a participant has a positive urine test result(s) for drugs of abuse on Day 1 prior to randomization, the participant may have their Day 1 visit rescheduled 1 time. If negative on retest then the participant will be eligible if remaining inclusion and exclusion criteria are confirmed. See Section 8.2.4, Clinical Safety Laboratory Assessments, for additional information on the timing of the urine drug screen at baseline (Day 1) visit.

If a participant is prescribed psychostimulants (eg, amphetamine, methylphenidate) for MDD, the medication must be discontinued at screening and participants must agree not to take during the study. The investigator should allow adequate time between the screening and randomization visit for wash-out of these medications. Participants will be excluded if they have a positive urine test result for a prescribed psychostimulant for MDD prior to randomization on Day 1 (as above, 1 retest will be allowed). However, 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. If study intervention is discontinued early, ECT is allowed as a standard of care treatment and it must be recorded in the eCRF.

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 in the esketamine arm as outlined in Appendix 4, Prohibited Concomitant Medications, should be considered.

Concomitant therapies (including psychotherapy) must be recorded throughout the study beginning with signing of the informed consent 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 pre-existing 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.

6.5.1. Psychotherapy

The investigator needs to ensure that participants have all necessary information for psychotherapeutic options available. To minimize bias, psychotherapy has to be discussed with the participant prior to randomization.

During this discussion, 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.

For participants not currently undergoing psychotherapeutic intervention, investigators should discuss available options in line with routine clinical practice; this discussion must be documented

by the investigator. If considered as beneficial and in line with national (eg, German Society for Psychiatry, Psychotherapy and Neurology S3 Guidelines, 2015; National Institute for Health and Care Excellence [NICE] Guidelines, 2010) and international guidelines (eg, World Federation of Societies of Biological Psychiatry Guidelines, 2013), the investigator should recommend to participants that they should seek psychotherapy. The selection of the psychotherapeutic intervention is at the discretion of the investigator and should be individually selected according to local availability (internal or external) and should reflect the needs and preference of a participant. Participants must choose if they will start psychotherapy and what type of psychotherapy prior to randomization. Due to waiting time in settings with limited availability, participants are allowed to start their first psychotherapeutic session after randomization according to their choice prior to randomization.

All standardized psychotherapy, psycho-education, support, or counseling that participants were undergoing prior to the study or individually prescribed and started based on the choice before randomization 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.

6.6. 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) and should be documented in the participant's source document as well as in the eCRF.

6.6.1. Esketamine Nasal Spray

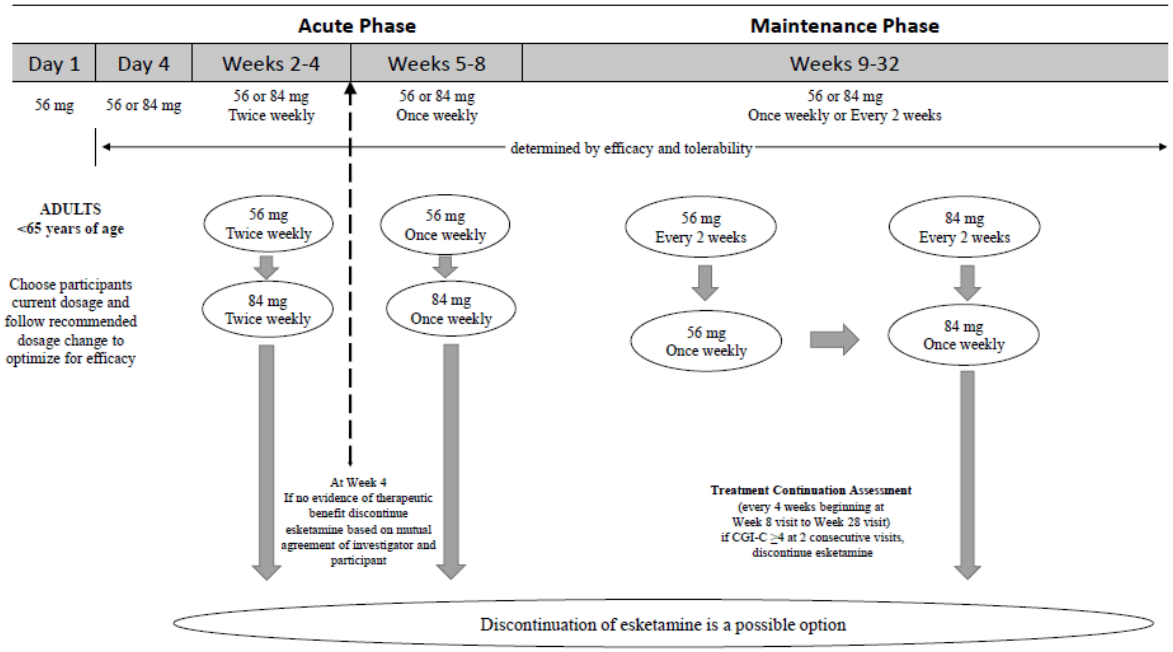
The decision to proceed to the next dose level of esketamine nasal spray (either an increase or a decrease) will be made by the investigator based on safety, tolerability, and efficacy assessed for each individual participant at their current dose level.

When the investigator wants to reduce nasal treatment in a stable episode, the dosing frequency should be reduced before considering reducing the dosage.

Recommendations for dose modification of esketamine nasal spray based on efficacy and tolerability during the acute and maintenance phases are provided in Figure 1 and Figure 2,

respectively for adults and Figure 3 and Figure 4, respectively for elderly participants and adults of Japanese ancestry.

Figure 1: Adults: Recommendations for Dose Modification of Esketamine Nasal Spray to Optimize Efficacy During the Acute and Maintenance Phases



Notes: During the maintenance phase, the frequency of treatment with esketamine nasal spray 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.

Figure 2: Adults: Recommendations for Dose Modification of Esketamine Nasal Spray to Handle Decreased Tolerability During the Acute and Maintenance Phases

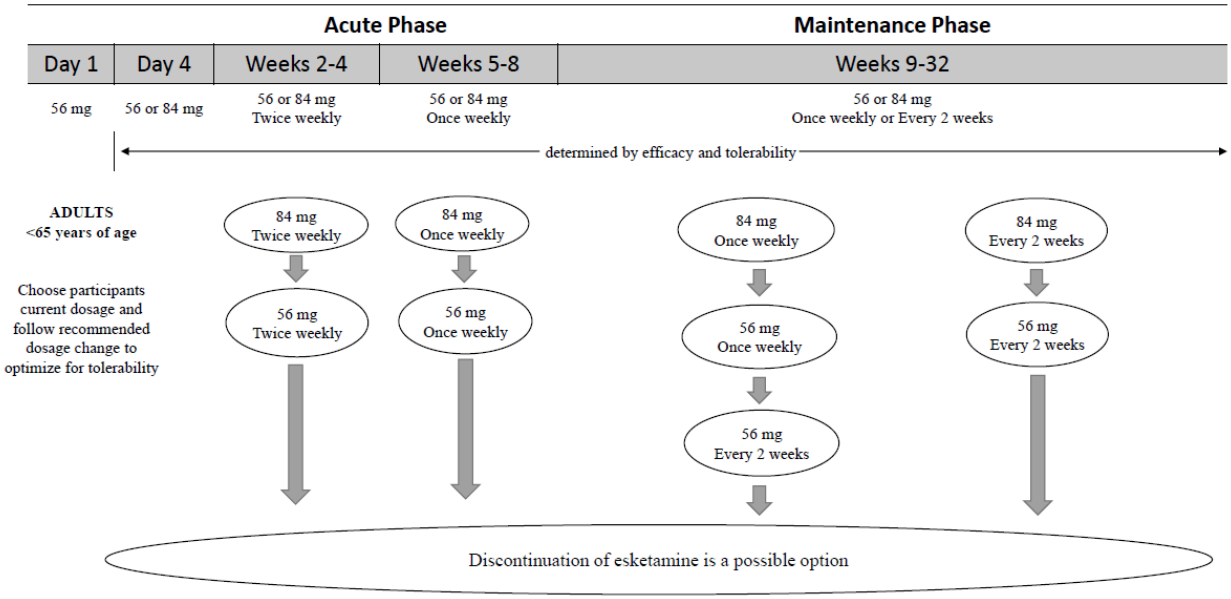
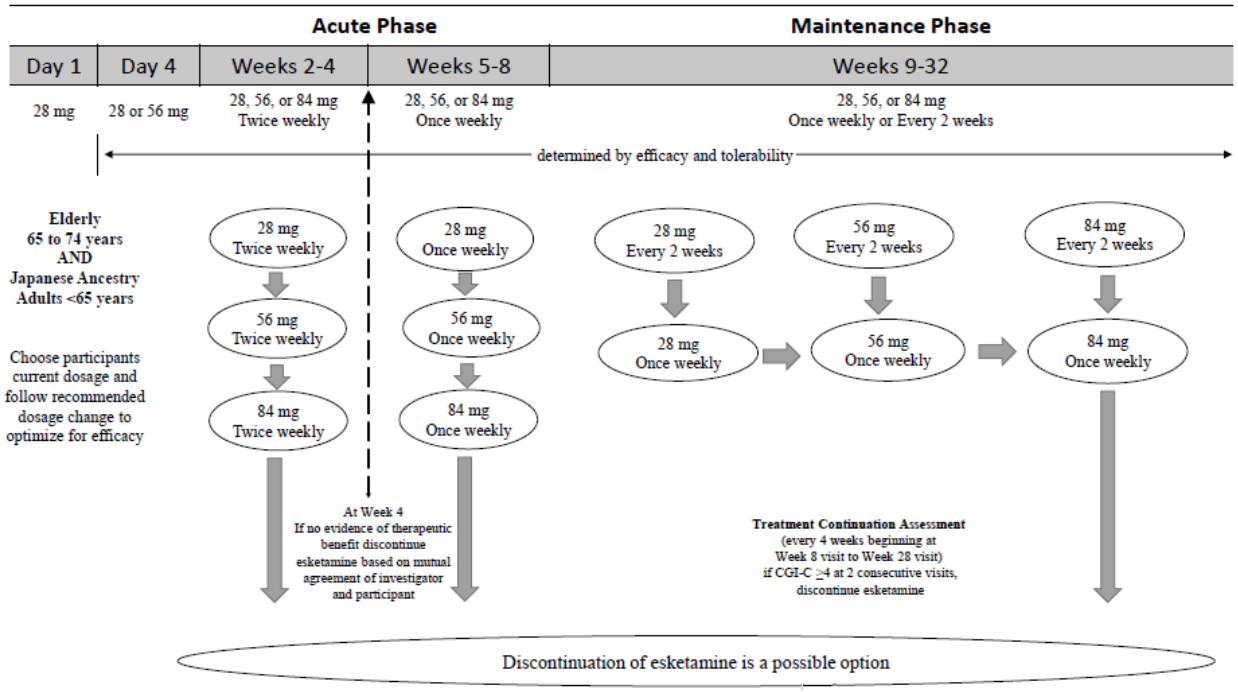
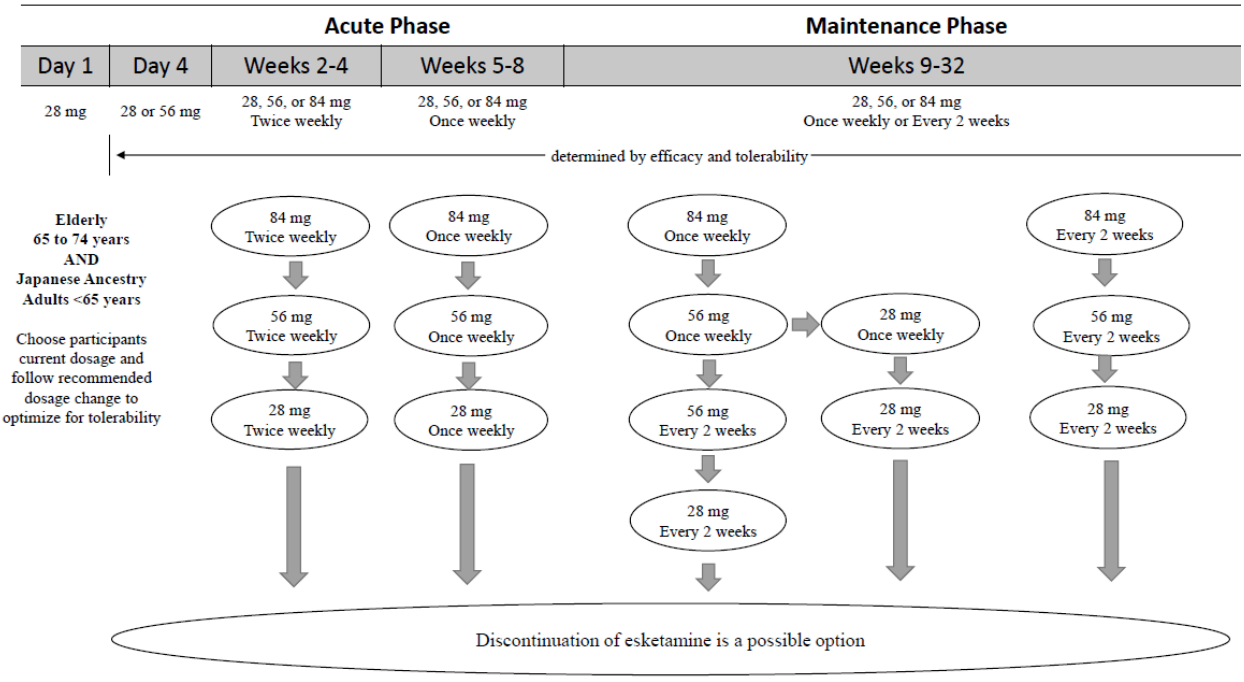


Figure 3: Elderly and Adults of Japanese Descent: Recommendations for Dose Modification of Esketamine Nasal Spray to Optimize Efficacy During the Acute and Maintenance Phases



Notes: During the maintenance phase, the frequency of treatment with esketamine nasal spray 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.

Figure 4: Elderly and Adults of Japanese Descent: Recommendations for Dose Modification of Esketamine Nasal Spray to Handle Decreased Tolerability During the Acute and Maintenance Phases



6.6.2. Quetiapine Extended-Release

The decision to proceed to the next dose level of quetiapine XR (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 and according to the SmPC (or local equivalent, if applicable). Additional information regarding dose adjustments is provided in Section 6.1.2.1.

6.6.3. Continuing SSRI/SNRI

For the continuing SSRI/SNRI, the decision to proceed to the next dose level (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 and according to the respective SmPC (or local equivalent, if applicable).

Additional information regarding dose adjustments is provided in Section 6.1.3, Continuing SSRI/SNRI.

6.7. Intervention After the End of the Study

After participants have completed study intervention (Week 32), they should return to their primary physician to determine standard of care. In exceptional situations, where participants would not have access to commercially available esketamine nasal spray, those participants who, at the discretion of the investigator, could benefit from continuing treatment with esketamine nasal spray following their Week 32 visit, will be advised on how continuation of treatment can be assured. Country-specific details on accessibility will be evaluated by the sponsor on a case-by-case basis considering, among others, regulatory and operational requirements.

Participants who discontinue esketamine nasal spray or quetiapine XR early (ie, before Week 32), continue in the study and will be switched to an alternative standard of care treatment, which may or may not include the continuing SSRI/SNRI, at the discretion of the investigator. If determined by the investigator that the alternative standard of care will include esketamine nasal spray (when commercially available in country of participation) or quetiapine XR for a participant, it will not be provided to the participant, rather, the investigator must prescribe the medication to the participant.

Standard of care treatment after completion of the study is at the discretion of the investigator or primary physician; there is no requirement to change a participant's standard of care treatment when they complete the study at Week 32.

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 investigator believes that for safety reasons or tolerability reasons (eg, AE), 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 believes there is no evidence of clinical improvement and further continuation of study intervention would not be in the best interest of the participant.
- A participant in the comparator arm cannot tolerate at least 150 mg/day of quetiapine XR by the end of Week 2, or at any subsequent time during the study.
- The participant becomes pregnant. Refer to Appendix 6, Contraceptive and Barrier Guidance and Collection of Pregnancy Information.

Participants who discontinue study intervention early (ie, discontinue either component of the randomized combination therapy) for any reason (except withdrawal of consent, lost to follow-up, or death) before the end of the study will remain in the study and continue to return for all follow-up visits according to the Schedule of Activities through Week 32 (safety follow-up visit is performed as part of first 2-week follow-up visit).

Study intervention assigned to the participant who discontinued study intervention may not be assigned to another participant. Additional participants will not be entered.

7.2. Participant Discontinuation/Withdrawal From the Study

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

- Lost to follow-up
- Withdrawal of consent
- Death

When a participant withdraws before study completion for any reason, 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.

Participants who withdraw early from the study must return for the safety follow-up visit 2 weeks after their last dose of study intervention (ie, day when either component of the randomized combination therapy is stopped), unless they withdraw consent, are lost to follow-up, or have died.

7.2.1. Withdrawal From the Use of Research Samples

A participant who withdraws from the study will have the following options regarding the optional research samples (ie, biomarker and/or DNA/RNA samples):

- The collected sample(s) will be retained and used in accordance with the participant's original separate informed consent for optional research samples.
- The participant may withdraw consent for optional research sample(s), in which case the sample(s) will be destroyed and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor study site contact of withdrawal of consent for the optional research sample(s) and to request sample destruction. The sponsor

study site contact will, in turn, contact the appropriate sponsor representative to execute sample(s) destruction. If requested, the investigator will receive written confirmation from the sponsor that the sample(s) have been destroyed.

Withdrawal From the Optional Research Samples While Remaining in the Main Study

The participant may withdraw consent for optional research sample(s) while remaining in the study. In such a case, the optional research sample(s) will be destroyed. The sample destruction process will proceed as described above.

Withdrawal From the Use of Samples in Future Research

The participant may withdraw consent for use of sample(s) for research (refer to Long-Term Retention of Samples for Additional Future Research in Appendix 3, Regulatory, Ethical, and Study Oversight Considerations). In such a case, sample(s) will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the separate ICF for optional research samples.

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.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities (Section 1.3) summarizes the frequency and timing of efficacy, biomarker, pharmacogenomic, and safety measurements applicable to this study.

The MINI used to confirm the diagnosis of single-episode MDD or recurrent MDD, without psychotic features, and the IDS-C30 used to determine symptom severity at screening are described in Section 8.1.1.1, Screening Evaluations.

Visit-specific PRO assessments should be conducted/completed before clinician-rated assessments, any tests (other than the urine drug screen at baseline visit [Day 1]), procedures, other consultations, or administration of esketamine nasal spray (in applicable participants) to prevent influencing participant perceptions.

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

A serum pregnancy test (central laboratory) will be performed during screening. Urine pregnancy tests (at site/local) will be performed on Day 1 and throughout the study in accordance with the Schedule of Activities (Section 1.3). 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. Counseling on pregnancy prevention will be provided at all visits, when applicable.

For each participant, the total blood drawn in this study will be approximately 30 mL. When optional biomarker and/or DNA/RNA samples are collected, approximately 48.5 mL (biomarker: two 10 mL samples per visit [40 mL total]; DNA: one 6 mL sample; RNA: one 2.5 mL sample) will be collected from each participant.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Sample Collection and Handling

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

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

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

Study-Specific Materials

The investigator will be provided with the following supplies:

- Practice nasal devices
- Investigator's Brochure for esketamine
- SmPC (or local equivalent, if applicable) and local prescribing information for quetiapine XR provided in English
- Investigational Product Binder, including the investigational product procedures manual
- Instructions for product quality complaint (PQC) reporting requirements
- Clinician-administered and participant-completed outcomes assessments

- Rater qualifications/requirements for select clinician-administered assessments
- Electronic devices and associated materials, as applicable
- IWRS Manual
- Instructions for use documents for esketamine nasal spray for participants and healthcare providers
- Procedural documents for Site-Independent Qualification Assessment
- Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approved participant materials
- Central laboratory manual and materials

8.1. Efficacy Assessments

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 (in applicable participants).

8.1.1.1. Screening Evaluations

Mini International Neuropsychiatric Interview (MINI)

Participants will undergo the MINI[30] (a brief, structured diagnostic interview) to confirm the diagnosis of MDD and to determine if there are other psychiatric conditions present. It has an administration time of approximately 60 to 80 minutes.

Inventory of Depressive Symptomatology Clinician-Rated 30 Items Scale (IDS-C30)

Participants will undergo the 30-item IDS-C30 at screening and baseline to assess the severity of depressive symptoms. The IDS-C30 was designed to assess all the criterion symptom domains designated by Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), to diagnose a major depressive episode.[27] These assessments can be used to screen for depression, although they have been used predominantly as measures of symptom severity. The 7-day period prior to assessment is the usual time frame for assessing symptom severity. The psychometric properties of the IDS-C30 have been established in various study samples.[32] It has an administration time of approximately 30 minutes.

Guidance for Screening Interview to Determine Clinical Improvement

As part of screening, a retrospective evaluation of how much the participant has clinically improved on their *current* treatment with AD, which must include an SSRI/SNRI, will be performed. Even though a participant's current treatment with AD must have resulted in nonresponse (less than 25% improvement of symptoms), the participant must show signs of minimal clinical improvement to be eligible for the study.

The qualified psychiatric interview is the core element of psychiatric examination. At screening, all sources available should be used to gather the necessary information to evaluate symptom improvement under a current antidepressive treatment.

Clinical improvement will be assessed retrospectively starting on the date of initiation of the current antidepressive treatment through the date of the screening interview, *which must not be performed until the potential participant has been on their current antidepressive treatment at an adequate dosage for an adequate duration of at least 6 weeks*. During this retrospective assessment of clinical improvement, the following should be considered:

1. All available patient files, referral letters, communication from treating physicians and the information the potential participant gives to evaluate the severity of the depressive syndrome at the timepoint of the initiation of the current treatment.
2. During the psychiatric interview the following sources of information have to be taken in consideration to evaluate the validity of verbal information given by the potential participant: appearance, voice, facial expression, gesture, psychomotor activities, personal hygiene, general behavior.
3. If medical records and or referral letters, etc. are available, the interviewer should verify and check the congruence with the potential participant's statements.
4. The potential participant should be given the opportunity to describe in detail and in their own words how they feel and let them give examples of what has changed since treatment initiation.

In the clinical psychiatric interview, the following dimensions of depression must be evaluated, and the interviewer needs to determine if there has been any improvement *(after an adequate dosage for an adequate duration of at least 6 weeks)* compared to the time point of the initiation of the current antidepressive treatment:

- **Depressive symptoms:** reported sadness, inner tension, reduced sleep/hypersomnia, reduced/increased appetite, concentration difficulties, lassitude, exhaustibility, inability to feel, pessimistic thought, feeling of guilt, suicidal thoughts, somatic symptoms (body pain, headache, changes in digestions, etc)
- **Social functioning:** Social interaction in the family, social interaction outside of family, pleasure in social interaction
- **General functioning:** Ability to work/go to school, ability to take care of home responsibilities
- **Self-care:** Body hygiene, clean and tidy clothes, general healthy behavior

In the evaluation of signs of clinical improvement, the full scope of potential clinical improvement should be evaluated. To be considered as showing signs of minimal clinical improvement, the participant must have "minimal improvement" *in at least 1* domain and not "significant improvement" in *any* domain. If there is "no improvement at all" in *all* domains, the participant is not eligible for the study.

Based on the evaluation by an experienced clinician, does the potential participant show any clinical improvement since the current treatment was initiated?

	No improvement at all, or deterioration	Minimal improvement	Significant improvement
Depressive symptoms			
Social functioning			
General functioning			
Self-care			

If a participant does not show signs of minimal clinical improvement at screening on their current treatment with AD, which must include an SSRI/SNRI, they may be rescreened (1 time) on the next consecutive line of treatment with AD (if it includes an SSRI/SNRI) after they have taken it at an adequate dosage for an adequate duration of at least 6 weeks. Participants who are rescreened will be assigned a new participant number, undergo the informed consent process, and then restart a new screening phase.

8.1.1.2. 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.[21] 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 blinded (ie, to study intervention assignment) and will be conducted face-to-face with the participants by an independent rater. The independent rater should have sufficient qualifications as documented by experience or training prior to being assigned as rater. To minimize bias, the independent rater should not be involved in any study assessments, other than performing the MADRS rating, or treatment decisions for a given study participant. To avoid interrater variability, all efforts should be made to have the same independent rater rating the same study participants as much as possible. The MADRS takes about 30 minutes to complete.

The primary and secondary endpoints, as described in Section 3, use the rater-blinded MADRS (total score) to determine remission at Week 8 and as part of the criteria for relapse after Week 8.

8.1.1.3. Clinical Global Impression – Severity (CGI-S) and Change (CGI-C)

The CGI-S and CGI-C are observer-rated scales that measure illness severity (CGI-S) and global improvement or change (CGI-C).[13] The CGI 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). CGI-C scores range from 1 (very much improved) through to 7 (very much worse) as compared to baseline. The CGI-S and CGI-C each take about 15 minutes to complete.

Beginning at the Week 8 visit, the CGI-C scores (referring to study baseline [Day 1]) will be used in the treatment continuation assessment (Section 4.1, Table 1) that is performed every 4 weeks in participants who are taking study intervention. For participants who discontinue study intervention early, the CGI-C will still be performed at follow-up visits according to the Schedule of Activities; however, treatment decisions will be at the discretion of the investigator and not based on the criteria for the treatment continuation assessment.

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 (other than the urine drug screen at baseline visit [Day 1]), procedures, other consultations, or administration of esketamine nasal spray (in applicable participants).

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.

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.[31] 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. Quality of Life in Depression Scale (QLDS)

The QLDS is a disease-specific validated PRO measure which assesses the impact that depression has on a participant's quality of life.[14,20,33] It is a 34-item self-rated questionnaire which consists of dichotomous response questions, with the response being either True/Not True. It is scored binomially (0-1) and high scores on the QLDS indicate a lower quality of life. The scale has good reliability and internal consistency and has wide applicability. It has been shown to be user-friendly, both for respondents and investigators. The QLDS takes about 10 minutes to complete.

8.1.2.3. European Quality of Life (EuroQol) Group, 5-Dimension, 5-Level (EQ-5D-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.[10,11] 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 to 100. The time taken to complete the questionnaire varies with age, health status, and setting but is likely to be around 5 minutes.

8.1.2.4. 36-Item Short-Form Health Survey (SF-36v2)

The SF-36 is a validated 36-item questionnaire which measures quality of life across 8 domains, which are both physically and emotionally based.[19,34] The 8 domains that the SF-36 measures are as follows: physical functioning; role limitations due to physical health; role limitations due to emotional problems; energy/fatigue; emotional wellbeing; social functioning; pain; general health. A single item is also included that identifies perceived change in health, making the SF-36 a useful indicator for change in quality of life over time and treatment. In addition to the 8 scales, 2 summary scales are calculated: the physical component summary scale (PCS) and the mental component summary scale (MCS). For each of the 8 domains and the 2 summary scales that the SF-36 measures, a norm-based score is produced. Higher scores indicate better functioning or quality of life. Version 2 of this questionnaire, with a 4-week recall (standard version) will be used for this study. The SF-36 takes about 15 minutes to complete.

8.1.2.5. Sheehan Disability Scale (SDS)

The SDS will be used to assess the secondary objective of functional impairment and associated disability. The SDS is a validated PRO measure consisting of a 5-item questionnaire that has been widely used and accepted for assessment of functional impairment and associated disability.[18,29] The first 3 items cover (1) work/school, (2) social life, and (3) family life/home responsibilities using a rating scale from 0 to 10. The SDS also has 1 item assessing days lost from school or work and 1 item assessing days of underproductivity. The scores for the first 3 items are summed to create a total score of 0 to 30, where higher score indicates greater impairment. The SDS takes about 5 minutes to complete.

8.1.2.6. Work Productivity and Activity Impairment (WPAI): Depression (D)

The WPAI:D questionnaire is a validated short instrument that assesses impairment in work and other regular activities over the past 7 days.[26] The WPAI questionnaire assesses 4 separate measures: absenteeism (ie, the proportion of work time missed due to MDD), presenteeism (ie, the degree of impairment while working due to MDD), work productivity loss (ie, overall work impairment due to MDD/absenteeism plus presenteeism), and activity impairment (ie, the degree of impairment of regular, nonwork activity due to MDD). WPAI scores are expressed as percent impairment, with higher values indicating greater impairment. The WPAI:D takes about 5 minutes to complete.

8.2. Safety Assessments

In the esketamine arm, on all nasal treatment session days, participants must remain at the site until study procedures have been completed and the participant is 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.

A list of prohibited concomitant medications is provided in Appendix 4 as general guidance for the investigator (but is not all-inclusive).

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

Any clinically relevant changes occurring during the study (from the time the informed consent is signed) must be recorded on the Adverse Event section of the eCRF.

Any clinically significant abnormalities persisting at the end of the study/early study 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.

8.2.1. Physical Examinations

Physical Examination

A physical examination will be performed at screening.

Body Weight and Height

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

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 at screening is to rule out any participants with anatomical or medical conditions that may impede drug delivery or absorption.

Subsequent examinations will only be performed in participants randomly assigned to the esketamine arm and will consist of a visual inspection of the nostrils, nasal mucosa, and throat for nasal erythema, rhinorrhea, rhinitis, capillary/blood vessel disruption, and epistaxis, and will be graded as follows: absent, mild, moderate, or severe.

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. Electrocardiograms

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

Participants ECGs will be collected at screening, baseline (Day 1), and at additional time points identified in the Schedule of Activities. If ECG results are abnormal at screening, then retesting is allowed and screening may continue if a normal result is achieved. The ECG does not need to be repeated at baseline if the screening ECG was performed within 1 week before the Day 1 visit.

Electrocardiograms may be performed at the investigator's site or at an external facility. The ECGs should be interpreted by a qualified reader, with sufficient clinical experience in ECG interpretation, at screening and with all subsequent ECGs compared to the screening ECG and post-screening ECGs to determine clinically relevant changes. If performed at an external facility, a report for each ECG, along with clinically relevant changes from the screening or post-screening ECGs will be provided to the investigator prior to a participant's scheduled visit. Electrocardiograms may be performed up to 1 week before a visit to allow time for the report to be sent to the investigator. The investigator is required to review the ECG report (internal or external) at the participant's visit to assess for any potential safety concerns related to study intervention, as per respective SmPCs (or local equivalent, if applicable). Based on the review of the ECG report, the investigator should determine if it is appropriate to continue study intervention. The investigator must document this review and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The ECG reports (internal or external) must be filed with the source documents.

If participants ECGs result in abnormalities, retesting may be conducted at the discretion of the investigator at screening or at any time during the study for individual participants based on potential safety concerns (eg, QT interval prolongation) that may be associated with study intervention (as per SmPCs [or local equivalents, where applicable]). For participants with clinically significant ECG abnormalities, the investigator should refer the participant to a cardiologist for follow-up.

If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

8.2.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology and a random urine sample for urinalysis will be collected at screening, baseline (Day 1), and at additional time points identified in the Schedule of Activities and as noted in Appendix 2, 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.

If clinical safety laboratory tests (serum chemistry, hematology, and urinalysis) results are abnormal at screening then retesting is allowed and screening may continue if a normal result is achieved. Hematology, chemistry, and urinalysis tests do not need to be repeated at baseline if screening tests were performed within 1 week before the Day 1 visit.

To alleviate unnecessary completion of clinician-rated scales and PRO questionnaires and other baseline assessments by ineligible participants, the urine drug screen should be performed first at the baseline visit (Day 1). If the urine drug screen is positive, the participant may have their Day 1 visit rescheduled 1 time, if negative on retest then the participant will be allowed to continue with all assessments to have inclusion and exclusion criteria confirmed.

8.2.5. Suicidal Risk Monitoring

There has been some concern that ADs 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 in its class 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 and during this clinical study.

Quetiapine XR is an atypical antipsychotic agent and suicidal risk is discussed in Section 2.2.4.

Participants being treated with study intervention, which includes an SSRI/SNRI as a component in each arm, 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 study intervention 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.

Baseline assessment of suicidal ideation and behavior and 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.[25] 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 and Serious Adverse Events

Timely, accurate, and complete reporting and analysis of safety information, including adverse events, serious adverse events, and PQCs, 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 (a) PQC(s).

For further details on AEs and serious adverse events (SAEs) (Definitions and Classifications; Attribution Definitions; Severity Criteria; Special Reporting Situations; Procedures) as well as product quality complaints, refer to Appendix 5, Adverse Events: 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 AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the participant's 2-week safety follow-up visit. Serious AEs, including those spontaneously reported to the investigator within 30 days after the last dose of study intervention, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Serious Adverse Events

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

Information regarding SAEs 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 SAE should be made by facsimile (fax).

Adverse Event Reporting Following Early Discontinuation of Study Intervention

For participants who discontinue study intervention early, the safety follow-up visit will be performed 2 weeks after their last dose of study intervention. These participants will remain in the study and continue to return for follow-up visits every 2 weeks through Week 32.

For participants who discontinue study intervention early but agree to continue the bi-weekly follow-up assessments until Week 32 of the study:

1. If their alternative standard of care treatment includes commercial esketamine or another Janssen medicinal product for depression, AEs will continue to be collected after completion of the safety follow-up visit until Week 32 of the study.
2. If their alternative standard of care treatment does not include commercial esketamine or another Janssen medication for depression, AEs will not be systemically collected after completion of the safety follow-up visit. For AEs that are not systematically collected (including AEs for Janssen medicinal products not indicated for depression) and where the participating physician considers there is at least a reasonable possibility of a causal relationship to a medicinal product (ie, spontaneous adverse drug reactions), the participating physician is requested to notify the manufacturer (ie, Janssen or other manufacturer) of the medicinal product or the appropriate regulatory/competent authority through the national spontaneous reporting system as soon as possible.
   As described above, all SAEs spontaneously reported within 30 days after the last dose of study intervention must be reported using the Serious Adverse Event Form.)

   Where available, reports of spontaneous adverse drug reactions will be summarized in the clinical study report.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

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

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

Adverse events, including pregnancy, will be followed by the investigator as specified in Appendix 5, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

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

An anticipated event is an adverse event that commonly occurs in the study population independent of exposure to the drug under investigation. For the purposes of this study the following SAEs will be considered anticipated events:

For esketamine and major depressive disorder (MDD) (including TRD; based on DSM-5):

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

These anticipated events will be periodically analyzed in aggregate by the sponsor during study conduct. The sponsor will prepare a safety report in narrative format if the aggregate analysis indicates that the anticipated event occurs more frequently in the treatment group than in the control group and the sponsor concludes there is a reasonable possibility that the drug under investigation caused the anticipated event.

The plan for monitoring and analyzing the anticipated events is specified in a separate Anticipated Events Safety Monitoring Plan. The assessment of causality will be made by the sponsor's unblinded safety assessment committee.

The sponsor assumes responsibility for appropriate reporting of the listed anticipated events according to the requirements of the countries in which the studies are conducted.

8.3.5. 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 SAEs and must be reported using the Serious Adverse Event Form.

Any participant who becomes pregnant during the study must discontinue further study intervention and continue follow-up visits through Week 32 (see Section 7.1); alternative standard of care treatment will be at the discretion of the investigator.

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

8.3.6. Disease-Related Events and Disease-Related Outcomes not Qualifying as Adverse Events or Serious Adverse Events

All events that meet the definition of a SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments.

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 SAE.

8.3.7. 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; hallucination, illusion; somatic hallucination; hyperacusis; tinnitus; diplopia; vision blurred; ocular discomfort; photophobia; visual impairment; dysesthesia; oral dysesthesia; 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, synesthetic; 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**: allergic cystitis; chemical cystitis; cystitis; cystitis erosive; cystitis hemorrhagic; cystitis interstitial; cystitis noninfective; cystitis ulcer active; cystitis-like symptom; pollakiuria; dysuria; micturition urgency; nocturia
- **Hepatic impairment**: cholestasis and jaundice of hepatic origin; hepatic failure; fibrosis and cirrhosis; other liver damage-related conditions

8.4. 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.

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

- Contact the Medical Monitor immediately.
- Closely monitor the participant for AEs/SAEs and laboratory abnormalities until esketamine 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.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

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

8.5. Pharmacokinetics

Pharmacokinetic evaluations are not performed in this study.

8.6. Pharmacodynamics

Pharmacodynamic evaluations are not performed in this study.

8.7. Biomarker and Pharmacogenomic (DNA and RNA) Evaluations

Biomarker and pharmacogenomic blood samples will only be collected at select study sites.

Participation in the biomarker and pharmacogenomic research is optional for participants and blood samples will only be collected from participants who provide consent.

Biomarker Evaluations

Blood samples will be collected as indicated in the Schedule of Activities for exploratory analysis of biomarkers (protein and metabolites) related to immune system activity, HPA axis activation, neurotrophic and metabolic factors. Exploratory analyses may be performed for additional biomarkers as well. Results may be presented in a separate biomarkers report.

If possible, blood samples should be collected under fasting conditions (minimum 8 hours prior to biomarker sample collection, water is permitted). Participants should refrain from exercise/strenuous physical activity and the use of NSAIDs for 24 hours prior to blood collection. Not following these recommendations will not constitute a protocol violation.

Biomarkers may be added or deleted based on scientific information or technical innovations under the condition that the total volume of blood collected will not be increased.

All biomarker data obtained during this study may be included in ongoing cross-study analyses to investigate the relationship between depression severity and phenotypes and biomarkers.

Information on menstrual cycle (date of first day of last period, average length of cycle) will be recorded on days when blood samples for biomarker analysis are collected.

Pharmacogenomic Evaluations

Whole blood samples for DNA and RNA analyses will be collected at the time points indicated in the Schedule of Activities.

DNA samples will be analyzed for the assessment of genetic and epigenetic variation in genes in pathways relevant to MDD. Additional analyses may be conducted if it is hypothesized that this may help resolve issues with the clinical data. RNA expression analyses may include testing of known messenger RNA/microRNA transcripts or transcriptome-wide analysis in relationship to AD treatment response and MDD.

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

8.8. Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are 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

The primary hypothesis of this study is that among participants who have treatment-resistant MDD with a current moderate to severe depressive episode, the proportion of participants achieving remission at the Week 8 visit is greater in participants treated with flexibly dosed esketamine nasal spray than in participants treated with quetiapine XR, both administered in combination with a continuing SSRI/SNRI.

The major secondary hypothesis of this study is that among participants who have treatment-resistant MDD with a current moderate to severe depressive episode, the proportion of participants who achieved remission at the Week 8 visit and remain relapse-free through the Week 32 visit is greater in participants treated with esketamine nasal spray than in participants treated with quetiapine XR, both administered in combination with a continuing SSRI/SNRI.

Both the primary and major secondary endpoint will be analyzed using a non-responder imputation (NRI) approach, meaning that participants discontinuing study intervention will be considered as

having a negative outcome (non-remission for the primary endpoint, non-relapse-free-remission for the key secondary endpoint).

9.2. Sample Size Determination

For the primary endpoint, the assumptions are that the rate of remission for completers at the Week 8 visit is 50% in the esketamine arm and 35% in the comparator arm, and that the rate for participants who discontinue study intervention between baseline and the Week 8 visit is 17.5% in both treatment arms (to be imputed as non-remitters). Combining these assumptions leads to an estimated remission rate at the Week 8 visit in NRI analysis of 41.25% in the esketamine arm and 28.88% in the comparator arm. With a power of 90%, a 2-sided significance level of 0.05 and using chi-square test, a sample size of 311 participants per arm (622 participants in total) is needed to detect the difference between the study intervention arms.

For the key secondary endpoint, among participants who achieve remission at the Week 8 visit, a relapse rate of 30% is assumed for both study intervention arms and rates for participants who discontinue study intervention between the Week 8 and Week 32 visits (to be imputed as non-relapse-free after remission) is assumed to be 10% for the esketamine arm and 20% for the comparator arm.[2,7,24] Combining these assumptions leads to an estimated rate of relapse-free after remission at the Week 32 visit in NRI analysis of 25.99% in the esketamine arm and 16.17% in the comparator arm. With a power of 80%, a 2-sided significance level of 0.05 and using a chi-square test, a sample size of 270 randomized participants per arm (540 participants in total) is needed to detect a difference between the study intervention arms.

When combining the 2 calculations above, a sample size of 311 participants per study intervention arm (622 participants in total) is needed to detect the difference between the study intervention arms with both a power of at least 90% on the primary endpoint and a power of 80% on the key secondary endpoint.

Randomization will be stratified by age (18 to 64 years [inclusive]; 65 to 74 years [inclusive]) and total number of treatment failures (2; 3 or more [inclusive of current antidepressive treatment at screening used to determine eligibility]).

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF
Full analysis set	All participants who are randomized in the study
Safety	All randomized participants who take at least 1 dose of study intervention

9.4. Statistical Analyses

The statistical analysis plan will be developed prior to enrollment of the first participant in the study and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

Demographic and baseline characteristics and psychiatric history at baseline will be summarized by study intervention arm for the full and safety analysis sets. Continuous variables will be summarized using descriptive statistics (N, mean, standard deviation, median, minimum, and maximum). Categorical variables will be summarized using a frequency distribution with the number and percentage of participants in each category.

9.4.2. Efficacy Endpoints

The efficacy analyses of data will be based on the full analysis set defined in Section 9.3.

The rate of remission at the Week 8 visit (primary endpoint) and the rate of remission at the Week 8 visit without relapse up to the Week 32 visit (key secondary endpoint) will be tested between study intervention arms using a Cochran-Mantel-Haenszel (CMH) chi-square test adjusting for age (18 to 64 years [inclusive]; 65 to 74 years [inclusive]) and total number of treatment failures (2; 3 or more). Participants will be considered as having a positive outcome on relapse-free after remission if they are in remission at the Week 8 visit and do not experience any relapse between the Week 8 and Week 32 visits. All other cases (participants not achieving remission at the Week 8 visit, or participants achieving remission at the Week 8 visit but experiencing a relapse between the Week 8 and Week 32 visits) will be considered as having a negative outcome. Both the primary and key secondary endpoints will be analyzed using a NRI approach as defined in Section 9.1. In sensitivity analyses, for participants who stopped study intervention, but are still followed in the study, no imputation will be performed, and their observed status will be used for the analyses.

For continuous/ordinal parameters (eg, MADRS, CGI-S, PHQ-9, EQ-5D-5L, SF-36, SDS, WPAI:D) descriptive statistics of the score or values and change from baseline will be provided for each study visit during the study for the full analysis set. For CGI-C descriptive statistics of the score will be provided for each study visit during the study for the full analysis set. Summaries of both observed and last observation carried forward (LOCF) data will be presented. The change from baseline at each visit will be analyzed using a mixed model for repeated measurements based on observed cases. The model will include baseline score as a covariate, and study intervention, stratification factors (age [18 to 64 years (inclusive); 65 to 74 years (inclusive)] and total number of treatment failures [2; 3 or more]), visit, and visit-by-study-intervention interaction as fixed effects. The change from baseline at each visit will also be analyzed using an analysis of covariance model including LOCF data with factors for treatment, stratification factors (age [18 to 64 years (inclusive); 65 to 74 years (inclusive)] and total number of treatment failures [2; 3 or more]) and baseline score as a covariate. For all model approaches, LS estimates of the treatment differences and 95% confidence intervals will be presented.

Additionally, for scales that have a minimum clinically important difference (MCID), the proportion of participants having improved by at least the MCID will be described at each visit and compared between study interventions using CMH chi-square test adjusting for age (18 to 64 years [inclusive]; 65 to 74 years [inclusive]) and total number of treatment failures (2; 3 or more). The same analysis will be conducted for the proportion of participants who deteriorate by

at least the MCID. The MCIDs used in the analysis will be documented in the Statistical Analysis Plan.

Time to event parameters (eg, time to improvement by at least MCID) will be analyzed by the Kaplan-Meier method and study interventions will be compared using a 2-sided log-rank test for the full analysis set. Time to event will be summarized with median, 25th and 75th percentile (if estimable). Confidence intervals of 25th, 50th, and 75th percentile of time to event will also be provided. Hazard ratios and their confidence intervals will be estimated using Cox proportional hazard models stratified by age (18 to 64 years [inclusive]; 65 to 74 years [inclusive]) and number of previous treatment failures (2; 3 or more).

9.4.3. Other Secondary/Exploratory Endpoints

Subgroup analyses will be performed for age (18 to 64 years [inclusive]; 65 to 74 years[inclusive]) and total number of treatment failures (2; 3 or more), as well as sex and severity of depression. Analysis by geographical region may also be provided.

Details regarding the other secondary and exploratory analyses will be provided in the Statistical Analysis Plan.

9.4.4. Safety Analyses

All safety analyses will be made on the Safety Population defined in Section 9.3.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using MedDRA. Intervention-emergent AEs are AEs occurring or worsening in severity after the start of study intervention. All reported intervention-emergent AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group. In addition, comparisons between intervention groups will be provided if appropriate.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue intervention due to an AE, or who experience a severe or a SAE. Adverse events reported occurring after study intervention discontinuation will be tabulated.

Intervention-emergent AEs of special interest will be summarized separately, grouped in the MedDRA based categories specified in Section 8.3.7.

Vital Signs

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

Nasal Examination

Abnormalities observed during the targeted nasal examinations at screening and post-baseline will be summarized and listed by treatment group.

C-SSRS

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

9.4.5. Other Analyses

Biomarker and Pharmacogenomic (DNA and RNA) Analyses

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

9.5. Interim Analysis

Not applicable.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

5HT	5-hydroxytryptamine
AD	Antidepressant
ADE	adverse device effect
AE	adverse event
AUC	area under the plasma concentration-time curve
AUC_{∞}	area under the plasma concentration-time curve from time 0 to infinity
CGI-C	Clinical Global Impression – Change
CGI-S	Clinical Global Impression – Severity
CL_{CR}	creatinine clearance
C_{max}	maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus Infectious 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
DNA	deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
ECG	Electrocardiogram
eCRF	electronic case report form
ECT	electroconvulsive therapy
eDC	electronic data capture
EQ-5D-5L	European Quality of Life (EuroQoL) Group, 5-Dimension, 5-Level (questionnaire)
EQ-VAS	EuroQoL Group: visual analogue scale
EuroQoL	European Quality of Life
FDA	Food and Drug Administration
FT4	free thyroxine
GCP	Good Clinical Practice
HPA	hypothalamic–pituitary–adrenal
IB	Investigator's Brochure
ICF	informed consent form
ICMJE	International Committee of Medical Journal Editors
ICH	International Council on Harmonisation
IDS-C30	Inventory of Depressive Symptomatology – Clinician-rated, 30 item
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISO	International Organization for Standardization
IV	Intravenous
IWRS	interactive web response system
LS	least squares
LOCF	last observation carried forward
MADRS	Montgomery-Asberg Depression Rating Scale
MCID	minimum clinically important difference
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview
NMDA	N-methyl-D-aspartate
NRI	non-responder imputation
NSAID	non-steroidal anti-inflammatory drug
PCP	Phencyclidine
PHQ-9	Patient Health Questionnaire, 9-item
PQC	product quality complaint
PRO	patient-reported outcome
QLDS	Quality of Life in Depression Scale
QTP	Quetiapine
RNA	ribonucleic acid

SADE	serious adverse device effect
SAE	serious adverse event
SBP	systolic blood pressure
SDS	Sheehan Disability Scale
SF-36	36-item Short-Form Health Survey
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
TSH	thyroid stimulating hormone
WPAI:D	Work Productivity and Activity Impairment: Depression
XR	extended-release

Definitions of Terms

Electronic source system	Contains data traditionally maintained in a hospital or clinic record to document medical care or data recorded in an eCRF as determined by the protocol. Data in this system may be considered source documentation.
Esketamine Arm	Participants will receive treatment with esketamine nasal spray (28 mg [initial dose for elderly participants 65 to 74 years of age and adults of Japanese ancestry; may be used throughout the study in these populations; may be uptitrated in 28 mg increments], 56 mg [initial dose for adult participants aged 18 to 64 years and may be used for all age groups throughout the study], or 84 mg [maximum dose esketamine nasal spray may be uptitrated to]) in combination with continuing SSRI/SNRI.
Comparator Arm	Participants will receive treatment with a continuing SSRI/SNRI augmented with quetiapine XR as per the SmPC (or local equivalent, if applicable). In adult participants aged 18 to 64 years, the initial dose is 50 mg/day on Days 1-2, 150 mg/day on Days 3-4 [lowest effective dose]; a further dose increase to 300 mg/day as of Day 5 will be based on individual participant evaluation. In elderly participants aged 65 to 74 years, the initial dose is 50 mg/day on Days 1-3, 100 mg/day on Days 4-7, and 150 mg/day on Day 8; a further dose increase to 300 mg/day will be based on individual participant evaluation no earlier than Day 22.
Baseline	Day 1 randomization visit

10.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed according to the Schedule of Activities by the central (hematology, chemistry, and screening pregnancy test) and local (urinalysis) laboratories:

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	-hemoglobin -hematocrit -red blood cell (RBC) count	-white blood cell (WBC) count with differential -platelet count
Clinical Chemistry (fasting, at least 8 hours)	-sodium -potassium -chloride -bicarbonate -blood urea nitrogen (BUN) -creatinine -glucose -total cholesterol -high-density lipoprotein cholesterol -triglycerides -low-density lipoprotein cholesterol	-aspartate aminotransferase (AST) -alanine aminotransferase (ALT) -gamma-glutamyltransferase (GGT) -alkaline phosphatase -creatine phosphokinase (CPK) -calcium -phosphate -albumin -total protein -total bilirubin -magnesium
Routine Urinalysis	Dipstick -specific gravity -pH -glucose -protein -blood -ketones -bilirubin -urobilinogen -nitrite -leukocyte esterase	Sediment (if dipstick result is abnormal) -red blood cells -white blood cells -epithelial cells -crystals -casts -bacteria
Screening Tests	• Serum Pregnancy Testing for women of childbearing potential only	
Thyroid Tests	• Thyroid-stimulating hormone (TSH) • Free thyroxine (FT4), only if required for abnormal TSH (refer to Exclusion criteria)	

The following will be performed at the site/local:

- Urine drug screen at baseline (Day 1): barbiturates, methadone, opiates, cocaine, cannabinoids, PCP, and amphetamine/methamphetamine; positive result(s) on Day 1 prior to randomization is exclusionary (1 retest is allowed; see Section 5.4).
- Urine pregnancy tests at baseline (Day 1) and all subsequent visits as per the Schedule of Activities.

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

REGULATORY AND ETHICAL CONSIDERATIONS

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current International Council on Harmonisation (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

- Sponsor-approved participant recruiting materials
- 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.

Approval for the collection of optional samples for research and for the corresponding ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

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
- If applicable, new or revised participant recruiting materials approved by the sponsor
- 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 AEs 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 4.2.10, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.10.

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.

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. Participants who are rescreened (see Section 5.4) are required to sign a new ICF.

Participants will be asked for consent to provide optional samples for research (where local regulations permit). After informed consent for the study is appropriately obtained, the participant will be asked to sign and personally date a separate ICF indicating agreement to participate in the optional research components. Refusal to participate in either optional research component will not result in ineligibility for the study. A copy of this signed ICF will be given to the participant.

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.

Exploratory DNA, RNA, pharmacodynamic, biomarker, pharmacokinetic, and immunogenicity research is not conducted under standards appropriate for the return of data to participants. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

LONG-TERM RETENTION OF SAMPLES FOR ADDITIONAL FUTURE RESEARCH

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand esketamine, to understand depression, to understand differential intervention responders, and to develop tests/assays related to esketamine or depression. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section 7.2.1, Withdrawal From the Use of Research Samples).

PUBLICATION POLICY/DISSEMINATION OF CLINICAL STUDY DATA

All information, including but not limited to information regarding esketamine or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including 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, 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.

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. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study.

The sponsor will review 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.

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.

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 AEs and follow-up of AEs; 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 early withdrawal from the study, if applicable.

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

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

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

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

The minimum source documentation requirements for Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician containing full documentation of each treatment with antidepressive(s) and the current treatment with antidepressive(s) for the current moderate to severe depressive episode:
  - Substance name
  - Period during which it was taken by participant at least at recommended therapeutic dosage according to SmPC (see Appendix 7 List of Previous Antidepressive Treatments) (duration and/or start/stop dates of this period); ie, excluding periods where the substance was given at a dose lower than the recommended therapeutic dose according to SmPC
  - Highest dose received by participant
  - Assessment of nonresponse: based on treating physician and participant's feedback, was the amount (%) of improvement in depression he/she reported when they feel it was working at its best above or below 25%
  - Documentation of any overlap that qualifies as combination or augmentation

  or
- Complete history of medical notes at the site (including information specified above)

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

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.

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. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records). 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.

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.

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.

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 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 esketamine nasal spray development

10.4. Appendix 4: 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 (and as applicable per randomly assigned study intervention arm), the prohibited medications listed in the following table are prohibited from 1 week (or 5 half-lives, whichever is longer) prior to the first dose of study intervention (ie, esketamine nasal spray or quetiapine XR, both in combination with continuing SSRI/SNRI) 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 nasal treatment session or for 2 hours after the nasal treatment session for participants in the esketamine treatment arm.	Safety
Amantadine	N	N		PD interaction
Anorexiants (eg, phentermine, phendimetrazine)	N	N		Safety
Anti-cholinergic medications (eg, Atropine, Benztropine, Biperiden)	N	N	As quetiapine has a moderate to strong affinity for several muscarinic receptor subtypes, concomitantly used with other medicines with anti-cholinergic effects can contributes to occurrence of ADR reflecting anti-cholinergic effects (eg, decreased intestinal motility and risk for intestinal obstruction)	Safety
Anticholinesterase inhibitors	N	N		Participant population is excluded
Anticonvulsants	N	N	Participants with seizures are excluded. Use as adjunctive treatment for MDD is prohibited. – Note: Anticonvulsants used for indications other than seizures may be allowed (eg, valproate for migraine; pregabalin).	Safety and PD interaction

Drug Class	Episodic Use (As Needed)	Continuous Use	Comments	Reason for Prohibition
Antidepressants (ADs) (*other than continuing SSRI/SNRI as described in Section 6.1.3*)	N	N	– If a participant is taking a monoamine oxidase inhibitor (MAOI) at screening, there must be a minimum wash-out interval of 2 weeks prior to the first dose of study intervention. – Even if used for indications other than MDD (eg, trazodone for sleep), the use of any ADs other than specified as study intervention is not permitted during treatment with study intervention.	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 for participants in the esketamine arm. 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
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. 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. Pseudoephedrine-containing oral products should not be used within 12 hours prior to a nasal treatment session.	Safety and PD interaction

Drug Class	Episodic Use (As Needed)	Continuous Use	Comments	Reason for Prohibition
CYP3A4 inducers - potent	N	N	Participants may not take a known potent inducer of hepatic CYP3A activity within 2 weeks of the first administration of study intervention until at least 24 hours after the last dose of study intervention. Examples (not all-inclusive): amiodarone, efavirenz, nevirapine, barbiturates, carbamazepine, glucocorticoids, modafinil, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort.	PK
CYP3A4 inhibitors	N	N	Participants may not take a known potent inhibitor of hepatic CYP3A activity within 2 weeks of the first administration of study intervention until at least 24 hours after the last dose of study intervention. Examples (not all-inclusive): erythromycin, clarithromycin, nefazodone, HIV-protease inhibitors, azole-antifungal agents; grapefruit juice.	
Dextromethorphan	N	N		PD interaction
Diphenhydramine	Y	N	Prohibited within 12 hours prior to the start of each nasal treatment session in the esketamine arm. 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

Drug Class	Episodic Use (As Needed)	Continuous Use	Comments	Reason for Prohibition
Medications that cause electrolyte imbalance or QT-prolongation (corrected according to Fridericia's formula (QTcF): ≥450 msec (males); ≥470 msec (females) eg, Antiarrhythmics (quinidine, procainamide, disopromide, dofetilide, ibutilide, sotalol), Antihistamines (terfenadine, astemizole), Neuroleptic, (haloperidol, droperidol, thioridazine, chlorpromazine), Antibiotics (levofloxacin, moxifloxacin, erythromycin, clarithromycin), Antimalarials (quinine, halofantrine), Antiprotozoal (pentamidine), Antifungal (azole group)	N	N	Reported interaction with quetiapine.	Safety
Memantine	N	N		PD interaction
Methyldopa	N	N		Safety and PD Interaction
Metyrosine	N	N		Safety and PD interaction
Non-steroidal anti-inflammatory drugs (NSAIDs)	Y	Y	Participants should not take within 24 hours before biomarker blood sample collection at Day 1 and Week 8 visits.	
Non-vitamin K antagonist oral anticoagulation agents (eg, dabigatran, rivaroxaban, apixaban)	N	N		Safety
Opioids	N	N	Note: With Sponsor approval, brief treatment with opiates may be allowed for treatment of acute injuries etc.	PD interaction
Psychostimulants (eg, amphetamines, methylphenidate)	N	Y	Prescribed psychostimulants taken for indications other than MDD 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 in the esketamine arm. • Within 12 hours prior to visits in the comparator arm (minimize differences in study intervention arms related to PROs)	Cardiovascular safety
Reserpine	N	N		PD interaction
Scopolamine	N	N		PD interaction
St. John's wort	N	N		PD interaction and PK

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

10.5. Appendix 5: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

ADVERSE EVENT DEFINITIONS AND CLASSIFICATIONS

Adverse Event

An AE is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. An AE 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 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 AEs 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 AE 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 SAE based on ICH and European Union Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening
  (The 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 AE 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 AE 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 AE will be determined by whether or not it is listed in the IB. For quetiapine XR and the SSRIs/SNRIs, the expectedness of an AE will be determined by whether or not it is listed in the SmPC (if applicable).

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 AEs.

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.

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).

SPECIAL REPORTING SITUATIONS

Safety reporting situations for 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
- 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 SAE should be recorded on the SAE page of the eCRF.

PROCEDURES

All Adverse Events

All AEs, 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 AE to study therapy. All measures required for AE 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 SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study 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)

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

- Hospitalizations not intended to treat an acute illness or AE (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 SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.
- For convenience the investigator may choose to hospitalize the participant for the duration of the intervention period.

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 SAE.

CONTACTING SPONSOR REGARDING SAFETY

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

PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, 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.

Contacting Sponsor Regarding Product Quality

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

Esketamine-Specific Reporting Requirements for PQCs

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

10.6. Appendix 6: Contraceptive and Barrier Guidance and Collection of Pregnancy Information

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.5, Pregnancy and Appendix 5 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential

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) **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
• Vasectomized partner *(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.)*
USER DEPENDENT **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] – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] – oral – injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study 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. 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. c) Male condom and female condom should not be used together (due to risk of failure with friction).

10.7. Appendix 7: List of Previous Antidepressive Treatments

The below list reflects the minimum recommended therapeutic dosage of possible previous antidepressive treatments. In addition, according to Section 5.1 Inclusion Criteria, antidepressive treatments in the current moderate to severe depressive episode must have been given at an adequate dosage for an adequate duration and must have been uptitrated to the maximum tolerated dose, determined on a patient-by-patient basis.

Substance name	Minimal Therapeutic Dose adult	Minimal Therapeutic Dose elderly	Substance class	Recoded class for ESCAPE-TRD
citalopram	20 mg/d	10 mg/d	Selective Serotonin Reuptake Inhibitors (SSRIs)	SSRIs
escitalopram	10 mg/d	5 mg/d	Selective Serotonin Reuptake Inhibitors (SSRIs)	SSRIs
fluoxetine	20 mg/d	20 mg/d	Selective Serotonin Reuptake Inhibitors (SSRIs)	SSRIs
fluvoxamine	100 mg/d	100 mg/d	Selective Serotonin Reuptake Inhibitors (SSRIs)	SSRIs
paroxetine	20 mg/d	20 mg/d	Selective Serotonin Reuptake Inhibitors (SSRIs)	SSRIs
sertraline	50 mg/d	50 mg/d	Selective Serotonin Reuptake Inhibitors (SSRIs)	SSRIs
desvenlafaxine	60 mg/d	60 mg/d	Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)	SNRIs
duloxetine	50 mg/d	50 mg/d	Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)	SNRIs
levomilnacipran	100 mg/d	100 mg/d	Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)	SNRIs
milnacipran	40 mg/d	20 mg/d	Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)	SNRIs
venlafaxine/ venlafaxine XR	150 mg/d	75 mg/d	Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)	SNRIs
agomelatine	25 mg/d	25 mg/d	Other Antidepressants	Other ADs
bupropion	300 mg/d	150 mg/d	Other Antidepressants	Other ADs
mianserin	30 mg/d	30 mg/d	Other Antidepressants	Other ADs
mirtazapine	15 mg/d	15 mg/d	Other Antidepressants	Other ADs
nefazodone	300 mg/d	300 mg/d	Other Antidepressants	Other ADs
opipramol	150 mg/d	150 mg/d	Other Antidepressants	Other ADs
reboxetine	8 mg/d	4 mg/d	Other Antidepressants	Other ADs
tianeptine	37.5 mg/d	37.5 mg/d	Other Antidepressants	Other ADs
trazodone	300 mg/d	200 mg/d	Other Antidepressants	Other ADs
vilazodone	40 mg/d	30 mg/d	Other Antidepressants	Other ADs
vortioxetine	10 mg/d	5 mg/d	Other Antidepressants	Other ADs
amitriptyline	150 mg/d	100 mg/d	Tricyclic Antidepressants	Other ADs
amitriptylinoxid	90 mg/d	45 mg/d	Tricyclic Antidepressants	Other ADs
amoxapine	150 mg/d	100 mg/d	Tricyclic Antidepressants	Other ADs
clomipramine	150 mg/d	100 mg/d	Tricyclic Antidepressants	Other ADs
clomipramine ret.	75 mg/d	50 mg/d	Tricyclic Antidepressants	Other ADs

Substance name	Minimal Therapeutic Dose adult	Minimal Therapeutic Dose elderly	Substance class	Recoded class for ESCAPE-TRD
desipramine	150 mg/d	100 mg/d	Tricyclic Antidepressants	Other ADs
doxepin	150 mg/d	100 mg/d	Tricyclic Antidepressants	Other ADs
imipramine	150 mg/d	100 mg/d	Tricyclic Antidepressants	Other ADs
maprotiline	150 mg/d	100 mg/d	Tricyclic Antidepressants	Other ADs
nortriptyline	75 mg/d	50 mg/d	Tricyclic Antidepressants	Other ADs
noxiptiline	100 mg/d	100 mg/d	Tricyclic Antidepressants	Other ADs
pipofezine	150 mg/d	100 mg/d	Tricyclic Antidepressants	Other ADs
protriptyline	30 mg/d	20 mg/d	Tricyclic Antidepressants	Other ADs
trimipramine	150 mg/d	100 mg/d	Tricyclic Antidepressants	Other ADs
isocarboxazid	30 mg/d	20 mg/d	Monoamine Oxidase Inhibitors (MAOIs)	Other ADs
moclobemide	300 mg/d	300 mg/d	Monoamine Oxidase Inhibitors (MAOIs)	Other ADs
phenelzine	45 mg/d	30 mg/d	Monoamine Oxidase Inhibitors (MAOIs)	Other ADs
pirlindole	200 mg/d	100 mg/d	Monoamine Oxidase Inhibitors (MAOIs)	Other ADs
selegiline	10 mg/d	10 mg/d	Monoamine Oxidase Inhibitors (MAOIs)	Other ADs
selegiline patch	6 mg/24 hrs	6 mg/24 hrs	Monoamine Oxidase Inhibitors (MAOIs)	Other ADs
tranylcypromine	30 mg/d	20 mg/d	Monoamine Oxidase Inhibitors (MAOIs)	Other ADs
aripiprazole	5 mg/d	5 mg/d	Atypical antipsychotics	NA
brexpiprazole	1 mg/d	1 mg/d	Atypical antipsychotics	NA
olanzapine	10 mg/d	5 mg/d	Atypical antipsychotics	NA
quetiapine	150 mg/d	150 mg/d	Atypical antipsychotics	NA
risperidone	4 mg/d	2 mg/d	Atypical antipsychotics	NA
lithium	Regular serum testing should be conducted to assess if dose was in the recommended therapeutic range. Recommended plasma level 0.8-1.0 mmol/L.			NA

10.8. Appendix 8: 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. Key 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 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 on-site monitoring visits.

Screening and Randomization

- For sites already initiated and where screening and randomization is ongoing, all screening and randomization activities should be stopped immediately in the event a participant's safety or study procedures cannot be sufficiently assured.
- Screening and randomization activities should not be restarted until the situation resolves to an acceptable level as mutually agreed by the site staff and sponsor.
- The participants who are in screening period but not yet randomized would have the possibility to be rescreened when the screening and randomization will restart.

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 as soon as the participant has passed the 8-week- acute phase of the study and after consultation with the sponsor. Reduction of visit frequency from weekly to every other week, is allowed for esketamine treatment arm during the maintenance phase 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.
- Dispensing of quetiapine to participant home may be allowed if permitted by local regulation.
- 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 patient's source notes as well as the eCRF. Missed study intervention dosing does not result in automatic withdrawal from the study.

Protocol Assessments

- MADRS rating in this study should be conducted by an independent 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 not allowed 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.
- In the event laboratory samples cannot be collected by Covance (eg, due to temporary COVID-19-related restrictions), local laboratory tests may be performed at the discretion of Principal Investigator. Local laboratory results should be reviewed to confirm any abnormalities and if considered clinically significant to be added as AEs in the eCRF.

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 investigator in consultation with the sponsor prior to resuming study drug.

10.9. Appendix 9: Protocol Amendment History

This is the first protocol amendment for the study. The PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE for the current amendment is located directly before the Table of Contents.

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INVESTIGATOR AGREEMENT

JNJ-54135419 (esketamine)
Clinical Protocol 54135419TRD3013 Amendment 1

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 MD

Institution: J&J Bulgaria

Signature: PPD Date: 8 October, 2020
(Day Month Year)

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

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Status: Approved, Date: 8 October 2020