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Inclusion Criteria

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

1. At the time of signing the informed consent form (ICF), subject must be a man or woman 18 (or older if the minimum legal age of consent in the country in which the study is taking place is >18) to 64 years of age, inclusive.
2. At the start of the screening/prospective observational phase, subject must meet the DSM-5 diagnostic criteria for single-episode MDD (if single-episode MDD, the duration must be ≥2 years) or recurrent MDD, without psychotic features, based upon clinical assessment and confirmed by the MINI.
3. At the start of the screening/prospective observational phase subject must have had non-response (≤25% improvement) to ≥1 but ≤5 (if current episode is >2 years, upper limit is applicable to only the last 2 years) oral antidepressant treatments in the current episode of depression, assessed using the MGH-ATRQ and confirmed by documented records (eg, medical/pharmacy/prescription records or a letter from a treating physician, etc.). In addition, the subject is taking a different oral antidepressant treatment (on the MGH-ATRQ) for at least the previous 2 weeks at or above the minimum therapeutic dose.
    - For specific tricyclic antidepressants which are ongoing and being taken at a dose below the MGH-ATRQ minimum therapeutic dose, a blood level that is within the therapeutic (antidepressant) range, is acceptable to establish the adequacy of the antidepressant treatment.
    - Subjects must be adherent to the continued oral antidepressant treatment medication(s) through the screening/prospective observational phase, as documented on the PAQ. Missing ≥4 days of antidepressant medication in the prior 2-week period will be considered as inadequate adherence.
    - Subjects who are non-responders to their current oral antidepressant medication(s) from the screening/prospective observational phase (as assessed by independent, remote raters) may be eligible for randomization if all other entry criteria are met. Non-response at the end of the screening/prospective observational phase is defined as ≤25% improvement in the MADRS total score from Week 1 to Week 4 and a MADRS total score of ≥28 on Week 2 and Week 4.
4. At the start of the screening/prospective observational phase, subject must have an IDS-C_{30} total score of ≥34.
5. The subject's current major depressive episode, depression symptom severity (Week 1 MADRS total score ≥28 required), and antidepressant treatment response in the current depressive episode, must be confirmed using a Site Independent Qualification Assessment.
6. Subject must be medically stable on the basis of physical examination, medical history, vital signs (including blood pressure), pulse oximetry, and 12-lead ECG

performed in the screening/prospective observational phase. If there are any abnormalities that are not specified in the inclusion and exclusion criteria, the determination of their clinical significance must be determined by the investigator and recorded in the subject's source documents and initialed by the investigator.

7. Subject must be medically stable on the basis of clinical laboratory tests performed in the screening/prospective observational phase. If the results of the serum chemistry panel, hematology, or urinalysis are outside the normal reference ranges, the subject may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for the population under study. This determination must be recorded in the subject's source documents and initialed by the investigator.

   – Subjects with a pre-existing history of thyroid disease/disorder who are treated with thyroid hormones must be on a stable dosage for 3 months prior to the start of the screening/prospective observational phase.

   – For any subject (regardless of thyroid history), if the thyroid-stimulating hormone (TSH) value is out of range, a free thyroxine (FT4) will be conducted. If the FT4 value is abnormal and considered to be clinically significant (after discussion with the medical monitor), the subject is not eligible.

8. Subject must be comfortable with self-administration of intranasal medication and be able to follow the intranasal administration instructions provided.

9. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

   A woman must be either:

   a. Not of childbearing potential defined as:

      - postmenopausal
        A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy, however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

      - permanently sterile
        Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

   b. Of childbearing potential and

      - practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly)

        Examples of highly effective contraceptives include
        - user-independent methods:

implantable progestogen-only hormone contraception associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); vasectomized partner; sexual abstinence (s*exual abstinence is considered a highly effective method **only** if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.*)

- user-dependent methods:
  combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, and transdermal; progestogen-only hormone contraception associated with inhibition of ovulation: oral and injectable

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method.

- agrees to use a highly effective method throughout the study and for at least 6 weeks after the last dose of study drug.

Note: If the childbearing potential changes after start of the study (eg, woman who is not heterosexually active becomes active), a woman must begin a highly effective method of birth control, as described throughout the inclusion criteria.

10. A woman of childbearing potential must have a negative highly sensitive serum (β-human chorionic gonadotropin [β-hCG]) at the start of the screening/prospective observational phase and a negative urine pregnancy test must be obtained before the first dose of study drug on Day 1 of the double-blind induction phase prior to randomization.
11. During the study (ie, from Day 1 of the double-blind induction phase, prior to randomization) and for a minimum of 1 spermatogenesis cycle (defined as approximately 90 days) after receiving the last dose of intranasal study medication, a man who is sexually active with a woman of childbearing potential

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

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

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

Exclusion Criteria

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

1. The subject's depressive symptoms have previously demonstrated non-response to:
   - Esketamine or ketamine in the current major depressive episode per clinical judgment, or
   - All of the oral antidepressant treatment options available in the respective country for the double-blind induction phase (ie, duloxetine, escitalopram, sertraline, and venlafaxine XR) in the current major depressive episode (based on MGH-ATRQ), or
   - An adequate course of treatment with electroconvulsive therapy (ECT) in the current major depressive episode, defined as at least 7 treatments with unilateral/bilateral ECT.
2. Subject has received vagal nerve stimulation (VNS) or has received deep brain stimulation (DBS) in the current episode of depression.
3. Subject has a current or prior DSM-5 diagnosis of a psychotic disorder or MDD with psychotic features, bipolar or related disorders (confirmed by the MINI), obsessive compulsive disorder (current only), intellectual disability (DSM-5 diagnostic codes 317, 318.0, 318.1, 318.2, 315.8, and 319), autism spectrum disorder, borderline personality disorder, antisocial personality disorder, histrionic personality disorder, or narcissistic personality disorder.
4. Subject has homicidal ideation/intent, per the investigator's clinical judgment, or has suicidal ideation with some intent to act within 6 months prior to the start of the screening/prospective observational phase, per the investigator's clinical judgment or based on the C-SSRS, corresponding to a response of "Yes" on Item 4 (active suicidal ideation with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent) for suicidal ideation on the C-SSRS, or a history of suicidal behavior within the past year prior to the start of the screening/prospective observational phase. Subjects reporting suicidal ideation with intent to act or suicidal behavior prior to the start of the double-blind induction phase should be excluded.

5. Subject has a history of moderate or severe substance or alcohol use disorder according to DSM-5 criteria, except nicotine or caffeine, within 6 months before the start of the screening/prospective observational phase.

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

6. Subjects with a current or past history of seizures (uncomplicated childhood febrile seizures with no sequelae are not exclusionary).
7. Subject has an UPSIT total score ≤18, indicative of anosmia, during the screening/prospective observational phase.
8. Subject has one of the following cardiovascular-related conditions:

    - Cerebrovascular disease with a history of stroke or transient ischemic attack
    - Aneurysmal vascular disease (including intracranial, thoracic, or abdominal aorta, or peripheral arterial vessels)
    - Coronary artery disease with myocardial infarction, unstable angina, or revascularization procedure (eg, coronary angioplasty or bypass graft surgery) within 12 months before the start of the screening/prospective observational phase. Subjects who have had a revascularization performed >12 months prior to screening and are clinically stable and symptom-free, per investigator's clinical judgment, can be included.
    - Hemodynamically significant valvular heart disease such as mitral regurgitation, aortic stenosis, or aortic regurgitation.
    - New York Heart Association (NYHA) Class III-IV heart failure of any etiology.

9. Subject has a history of uncontrolled hypertension despite diet, exercise, or antihypertensive therapy at the start of the screening/prospective observational phase or any past history of hypertensive crisis or ongoing evidence of uncontrolled hypertension defined as a supine systolic blood pressure (SBP) >140 mmHg or diastolic blood pressure (DBP) >90 mmHg during screening/prospective observational phase which continues to be above this range with repeated testing during this phase. Note: On Day 1 of the double-blind induction phase prior to randomization a supine SBP >140 mmHg or DBP >90 mmHg is exclusionary.

    - A potential subject may have his/her current antihypertensive medication(s) adjusted during the screening/prospective observational phase and be re-evaluated to assess their blood pressure control. The subject must be on a stable regimen for at least 2 weeks before Day 1 of the double-blind induction phase.

10. Subject has a current or past history of significant pulmonary insufficiency/condition or with an arterial blood oxygen saturation (SpO_2) of <93% at the start of the screening/prospective observational phase or Day 1 prior to randomization.

11. Subject has clinically significant ECG abnormalities at the start of the screening/prospective observational phase or on Day 1 of the double-blind induction phase prior to randomization, defined as:

    - During screening, a QT interval corrected according to Fridericia's formula (QTcF): ≥450 msec; if the QTcF is prolonged on the initial ECG, the average QTcF of three ECGs, recorded 4 minutes apart, must not be ≥450 msec.
    - On Day 1 (predose), a QT interval corrected according to Fridericia's formula (QTcF): ≥450 msec based on the site-evaluated ECG; if the QTcF is prolonged on the initial ECG, the average QTcF of three ECGs, recorded 4 minutes apart, must not be ≥450 msec.
    - Evidence of 2nd and 3rd degree AV block, complete left bundle branch block (LBBB), or complete right bundle branch block (RBBB).
    - Features of new ischemia.
    - Arrhythmia (except premature atrial contractions [PACs] and premature ventricular contractions [PVCs])

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

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

    - Repeat of screening test for abnormal ALT and AST is permitted once during the screening period provided per investigator discretion and provided there is an alternative explanation for the out of range value.
    - For elevations in bilirubin if, in the opinion of the investigator and agreed upon by the sponsor's medical officer, the elevation in bilirubin is consistent with Gilbert's disease, the subject may participate in the study.

14. Subject has positive test result(s) for drugs of abuse (including barbiturates, methadone, opiates, cocaine, phencyclidine, and amphetamine/methamphetamine) at the start of the screening/prospective observational phase or Day 1 of the double-blind induction phase prior to randomization.

    - Subjects who have a positive test result at screening due to prescribed psychostimulants (eg, amphetamine, methylphenidate, etc.) taken for an indication other than MDD are permitted to continue to take this medication during the study in accordance with Attachment 1.
    - Otherwise, subjects who have a positive test result at screening due to prescribed/over-the-counter opiates or barbiturates may be permitted to continue in the screening/prospective observational phase if the medication is

discontinued at least 1 week or 5 half-lives, whichever is longer, before Day 1 of the double-blind induction phase (prior to randomization) in accordance with Attachment 1 restrictions. The result of the Day 1 (prior to randomization) test for drugs of abuse must be negative for the subject to be randomized.

  - Retesting is not permitted for positive test result(s), except for reasons stated above.

- Prior intermittent use of cannabinoids prior to the start of the screening/prospective observational phase is not exclusionary as long as the subject does not meet the criteria for substance use disorder. A positive test for cannabinoids at the start of the screening/prospective observational phase is not exclusionary, however, a positive test result for cannabinoids predose on Day 1 of the double-blind induction phase is exclusionary.

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

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

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

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

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

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

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

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

23. Subject has received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 60 days before the start of the screening/prospective observational phase, or has participated in 2 or more MDD or other psychiatric condition clinical interventional studies (with different investigational medication) in the previous 1 year before the start of the screening/prospective observational phase, or is currently enrolled in an investigational interventional study.

24. Subject is a woman who is pregnant, breast-feeding, or planning to become pregnant while enrolled in this study or within 6 weeks after the last dose of intranasal study drug.

25. Subject has a diagnosis of acquired immunodeficiency syndrome (AIDS). Human immunodeficiency virus (HIV) testing is not required for this study.

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

27. Subject has had major surgery, (eg, requiring general anesthesia) within 12 weeks before the start of the screening/prospective observational phase, or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study.

    Note: Subjects with planned surgical procedures to be conducted under local anesthesia may participate.

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

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

Prohibitions and Restrictions

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

- Refer to the Inclusion Criteria and Exclusion Criteria for information regarding contraception requirements.
- Subjects who were taking benzodiazepines at dosages equal to or less than the equivalent of 6 mg/day of lorazepam and/or permitted non-benzodiazepine sleep medications (eg, zolpidem, zaleplon) during the screening/prospective observational phase can continue these medications during the induction phase. No dose increases beyond the equivalent of 6 mg/day of lorazepam or new benzodiazepine medications are permitted during the induction phase, with the exception of the use of permitted

benzodiazepine rescue medication. Benzodiazepines and non-benzodiazepine sleeping medication (eg, zolpidem, zaleplon, eszopiclone, and ramelteon) are prohibited within 12 hours prior to the start of each intranasal treatment session or cognition testing.

- A positive urine drug screen for use of phencyclidine (PCP), or cocaine from Day 1 of the induction phase through the final visit in the double-blind induction phase will lead to discontinuation.
- Subjects must abstain from using alcohol within 24 hours before and after each intranasal treatment session. If a subject appears intoxicated, dosing should not occur (delayed per the permitted visit window; see the Time and Events Schedule).
- On all intranasal study drug dosing days, all subjects must remain at the clinical study site until study procedures have been completed and the subject is ready for discharge. Subjects should be accompanied by a responsible adult when released from the clinical study site. Subjects must not drive a car or work with machines for 24 hours after study drug dosing.
- ECT, DBS, transcranial magnetic stimulation (TMS), and VNS are prohibited from study entry through the end of the double-blind induction phase.
- Subjects receiving psychotherapy (including cognitive behavioral therapy; CBT) can continue receiving psychotherapy; however, CBT must have been ongoing for the last 3 months prior to the screening/prospective observational phase. With the exception of new CBT, which is prohibited, new psychotherapy is allowed during this study. Any change in existing therapy or new therapy must be documented on the concomitant therapies form.

Additional Evaluations to Ensure Adequate Selection of Patients with TRD and Independent Confirmation of Eligibility

PAQ

Subjects' adherence to their oral antidepressant treatment regimen during the screening/prospective observational phase was assessed using the Patient Adherence Questionnaire (PAQ), a brief, 2-item subject-reported outcome measure that was developed to assess how often the subject has taken, and whether he or she has made any changes to his/her antidepressant treatment regimen in the last 2 weeks. To document adherence on the PAQ and determine eligibility for the study, a subject must have been adherent to the continued oral antidepressant treatment medication(s) through the screening/prospective observational phase; missing ≥4 days of antidepressant medication in the prior 2-week period was considered inadequate adherence. The total score was based on the response selected to Question 1 ("How often have you taken your medication [or medications] during the last 2 weeks?"), and was interpreted as 0 (I have taken my medications every day without missing a day) to 1 (I have missed taking my medications one, two, or three days)=adherent, and 2 (I have only missed taking my medication on four days) or more=nonadherent.

SIQA
Site Independent Qualification Assessment An independent clinical reviewer (psychiatrist/psychologist) performed the SIQA in the screening/prospective observational phase for all subjects to confirm diagnosis of depression and eligibility for the study. The SIQA is a tool to facilitate subject selection for MDD clinical studies, and was used to ensure enrollment of subjects who have symptoms that reflect the current state of illness, to ensure that these symptoms can be reliably measured with appropriate measurement tools, and to minimize placebo response. The independent clinical reviewer evaluated the subject's MADRS, MINI, MGH-ATRQ, C-SSRS, IDS-C30, and CGI-S assessments at screening; medical history; and concomitant therapies to determine whether a subject was eligible to participate in the study. In addition to confirming there was documented non-response to at least 1 antidepressant agent on the MGH-ATRQ at screening, the SIQA was used to confirm the adequacy of the prospective ongoing oral antidepressant medication in terms of dose (at least the minimum therapeutic dose on the MGH-ATRQ) and duration (ongoing at least 2 weeks prior to study entry).

Prestudy and Concomitant Therapy

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

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

Any medication that is listed on the MGH-ATRQ and is being taken at the start of the screening/prospective observational phase for an indication other than depression (eg, insomnia) should be continued during the screening/prospective observational phase but must be discontinued before the start of the double-blind induction phase.

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

Subjects should continue to take their permitted concomitant medications (eg, antihypertensive medications) at their regular schedule; however, restrictions as outlined

in Table S1 (below) should be taken into account. Of note, if a subject has routinely taken his/her oral antihypertensive medications in the morning on dosing days, the morning dose should be taken prior to intranasal dosing.

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

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

Instructions in Study Protocol to Investigators Regarding the Selection of the Oral Antidepressant

On Day 1 of the double-blind induction phase, a new, open-label oral antidepressant treatment will be initiated in all subjects. Each subject will be assigned to receive 1 of 4 oral antidepressant medications from 2 different classes of antidepressant treatments, an SSRI (escitalopram or sertraline) or an SNRI (duloxetine or venlafaxine XR).

The antidepressant medication will be assigned by the investigator based on review of MGH-ATRQ and relevant prior antidepressant medication information.

These 2 classes were selected because they are the most commonly prescribed antidepressant classes in this population and are generally well-tolerated. The oral antidepressant treatment assigned will be one that the subject has not previously had a non-response to in the current depressive episode, has not been previously intolerant to (lifetime), and is available in the participating country.

TABLE S1. Prohibited Concomitant Medications with Intranasal Study Medication (Esketamine or Placebo)

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

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

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

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

Drug Class	Episodic Use (as needed)	Continuous Use	Comments	Reason for Prohibition
Amantadine	N	N		PD interaction
Anorexiants (eg, phentermine, phendimetrazine)	N	N		Safety
Anticholinesterase inhibitors	N	N		Subject population is excluded
Anticonvulsants	N	N	Subjects with seizures are excluded. Use as adjunctive treatment for major depressive disorder (MDD) is prohibited. – Note: Anticonvulsants used for indications other than seizures may be allowed (eg, valproate for migraine; pregabalin)	Safety and PD interaction

Drug Class	Episodic Use (as needed)	Continuous Use	Comments	Reason for Prohibition
Antidepressants (*other than the specific antidepressant started in the induction phase of the study*)	N	N	– Only 1 of the 4 predefined oral antidepressant treatment options are permitted – If a subject is taking a monoamine oxidase inhibitor (MAOI) during the screening/prospective observational phase, there must be a minimum washout interval of 2 weeks prior to the first dose of intranasal study medication. – Even if used for other indications (eg, trazodone for sleep), the use of any medication listed on the ATRQ is not permitted during the treatment phase.	Safety and PD interaction
Antipsychotics	N	N		PD interaction
Benzodiazepines (at dosages less than or equal to the equivalent of 6 mg/day lorazepam) and non-benzodiazepine sleeping medication (including: zolpidem, zaleplon, eszopiclone, and ramelteon)	Y	Y	Prohibited within 12 hours prior to the start of each intranasal treatment session or cognition testing	Safety and PD interaction
Benztropine	Y	N	Prohibited if use is continuous and prohibited within 12 hours prior to the start of cognition testing	Safety and PD interaction.
Chloral hydrate, melatonin, valerian	N	N		Safety and PD interaction
Clonidine	N	N		Safety and PD interaction
Corticosteriods (systemic)	Y	N	Inhaled, intranasal, topical, and ophthalmic steroids are not prohibited. Intermittent IM/IV corticosteroids are permitted (chronic use prohibited)	PD interaction
Cough/cold preparations/nasal solutions containing vasoconstrictors, decongestants	Y	Y	Intranasally-administered decongestants (vasoconstrictors) should not be used from 1 hour prior to each intranasal study medication administration. Pseudoephedrine- containing oral products should not be used within 12 hours prior to an intranasal treatment session.	Safety and PD interaction

Drug Class	Episodic Use (as needed)	Continuous Use	Comments	Reason for Prohibition
CYP3A4 inducers - Potent	N	N	Subjects may not take a known potent inducer of hepatic CYP3A activity within 2 weeks of the first administration of intranasal study medication until at least 24 hours after the last intranasal dose of study medication. Examples (not all-inclusive): Efavirenz, nevirapine, barbiturates, carbamazepine, glucocorticoids, modafinil, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort	PK
Dextromethorphan	N	N		PD interaction
Diphenhydramine	Y	N	Prohibited within 12 hours prior to the start of each intranasal treatment session	Safety
Ketanserin	N	N		Safety
Lithium	N	N		PD interaction
Memantine	N	N		PD interaction
Methyldopa	N	N		Safety and PD Interaction
Metyrosine	N	N		Safety and PD interaction
Non-vitamin K antagonist oral anticoagulation agents (eg, dabigatran, rivaroxaban, apixaban	N	N		Safety
Opioids	N	N		PD interaction
Psychostimulants (eg, amphetamines, methylphenidate, and modafinil, armodafinil)	N	Y	Prescribed psychostimulants taken for indications other than MDD can be continued but must not be taken within 12 hours prior to the intranasal treatment session or for 2 hours after the intranasal treatment session.	Cardiovascular safety
ADHD medications (eg, atomoxetine, guanfacine)	N	Y	Can be continued but must not be taken within 12 hours prior to the intranasal treatment session or for 2 hours after the intranasal treatment session.	Safety
Reserpine	N	N		PD interaction
Scopolamine	N	N		PD interaction
St. John’s Wort	N	N		PD interaction and PK

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: N, Prohibited; PD, pharmacodynamics; PK, pharmacokinetics; Y, Permitted, with restrictions (please refer to the column labeled "Comments" for additional guidance).

Rescue Medications

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

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

Guidance on Blood Pressure Monitoring on Intranasal Treatment Session Days

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

- If subsequent to fulfilling the inclusion and exclusion criteria on Day 1 (i.e., applicable for all other intranasal treatment session days after Day 1), a subject's pre-dose systolic blood pressure (SBP) is >140 mmHg and/or diastolic blood pressure (DBP) is >90 mmHg, it is recommended to repeat the blood pressure measurement after subject rests in sitting or recumbent position. If after rest and repeated measurements, pre-dose SBP is >140 mmHg and/or DBP is >90 mmHg, then dosing should be postponed and the subject scheduled to return on the following day or within the given visit window. If the blood pressure elevation still persists on the next visit, the subject will be scheduled for a consultation by cardiologist, other specialist, or primary care physician, prior to further dosing.
- If at any postdose time point on the dosing day, the SBP is ≥180 mmHg but <200 mmHg and/or the DBP is ≥110 mmHg but <120 mmHg, further intranasal dosing should be interrupted and the subject should be referred to a cardiologist, other specialist, or primary care physician for a follow-up assessment.
    - After the assessment by a cardiologist, other specialist, or primary care physician, if recommended by the referring doctor and considered appropriate according to the clinical judgment for the subject to continue in the study, the subject may continue with intranasal dosing if the pre-dose blood pressure at the next scheduled visit is within the acceptable range (see bullet point above).
- If at any postdose time point on the dosing day the SBP is ≥200 mmHg and/or the DBP is ≥120 mmHg, the subject must discontinue from further dosing and the subject should be referred to a cardiologist, other specialist or primary care physician for a follow-up assessment.

During the double-blind phase, at 1.5 hours postdose, if the SBP is ≥160 mmHg and/or the DBP ≥100 mmHg, assessments should continue every 30 minutes until:

- blood pressure is <160 mmHg SBP and <100 mmHg DBP, or
- in the investigator's clinical judgment, the subject it is clinically stable and can be discharged from the study site, or
- the subject is referred for appropriate medical care, if clinically indicated, or
- if the blood pressure remains ≥180 mmHg SBP and/or ≥110 mmHg DBP, 2 hours after dosing, the subject should be referred for immediate medical treatment.

TABLE S2. Intranasal Treatment Administration During the Double-Blind Phase

	Time of Intranasal Device Administration[c]		
Intranasal Treatment	**0[a]**	**5 minutes**	**10 minutes**
Intranasal Device[b]	1st	2nd	3rd
Placebo	1 spray of placebo to each nostril	1 spray of placebo to each nostril	1 spray of placebo to each nostril
Esketamine 56 mg	1 spray of esketamine to each nostril	1 spray of esketamine to each nostril	1 spray of placebo to each nostril
Esketamine 84 mg	1 spray of esketamine to each nostril	1 spray of esketamine to each nostril	1 spray of esketamine to each nostril

a. Time 0 is defined as the time of administration of the first intranasal spray to one nostril from the first intranasal device.
b. One device will be used at each time point. Each individual intranasal device contains 2 sprays. The intranasal devices containing esketamine deliver 14 mg per spray, for a total of 28 mg per individual device (ie, 2 sprays).
c. The 3 intranasal devices for each intranasal treatment session should be administered in the medication kit order provided by the IWRS

TABLE S3. Dose Titration of Esketamine Nasal Spray

Day	Dose	Dose Titration Guidance
Day 1	56 mg	
Day 4	56 or 84 mg	The dose could remain at 56 mg or be increased to 84 mg, as determined by the investigator based on efficacy and tolerability.
Days 8 and 11	56 or 84 mg	The dose could remain the same or be increased to 84 mg (if the previous dose was 56 mg) or be reduced to 56 mg (if the previous dose was 84 mg) as determined by the investigator based on efficacy and tolerability.
Day 15	56 or 84 mg	A dose reduction from 84 mg to 56 mg was permitted if required for tolerability; no dose increase was permitted on Day 15.
Days 18, 22 and 25	56 or 84 mg	The dose was to remain unchanged. If there was no intranasal treatment session on Day 15, a dose reduction from 84 mg to 56 mg was permitted on Day 18 if required for tolerability; no dose increase was permitted.

TABLE S4. Oral Antidepressant Titration Schedule for Double-Blind Phase

	Titration Schedule			
Oral Antidepressant	**Week 1 (Starting Day 1)**	**Week 2 (Starting Day 8)**	**Week 3 (Starting Day 15)**	**Week 4 (Starting Day 22)**
Duloxetine	60 mg[a]	60 mg	60 mg	60 mg
Escitalopram	10 mg	20 mg	20 mg	20 mg
Sertraline	50 mg	100 mg	150 mg	200 mg
Venlafaxine XR	75 mg	150 mg	225 mg	225 mg

[a] Patients should be initiated with 60 mg/day. Patients that have in the past shown increased sensitivity towards serotonin reuptake inhibitors (SSRI)/norepinephrine reuptake inhibitors (SNRI) can, at the discretion of the treating physician, be started on a 30 mg dose and up-titrated into the therapeutic range of 60 mg by the start of Week 2.

Use of Benzodiazepines During the Double-blind Phase

- Patients who were taking benzodiazepines at dosages equal to or less than the equivalent of 6 mg/day of lorazepam and/or permitted non-benzodiazepine sleep medications (e.g., zolpidem, zaleplon) during the screening/prospective observational phase can continue these medications during the double-blind phase.
- No dose increases beyond the equivalent of 6 mg/day of lorazepam or new benzodiazepine medications are permitted during the double-blind phase, with the exception of the use of permitted benzodiazepine rescue medication.
- Benzodiazepines and non-benzodiazepine sleeping medication (e.g., zolpidem, zaleplon, eszopiclone, and ramelteon) are prohibited within 12 hours prior to the start of each intranasal treatment session or cognition testing.

Assessment Instruments

Sheehan Disability Scale

The SDS was used to assess the key secondary objective of functional impact and associated disability. The SDS is a subject-reported outcome measure and is a 5 item questionnaire which has been widely used and accepted for assessment of functional impairment and associated disability (Leon et al., 1997; Sheehan et al., 1996). The first 3 items assess disruption of (1) work/school, (2) social life, and (3) family life/home responsibilities on a scale from 0 (not at all) to 10 (extremely). The score for the first 3 items are summed to create a total score of 0-30 where a higher score indicates greater impairment. It also has one item on days lost from school or work and one item on days when underproductive. The recall period for this study is 7 days.

Leon AC, Olfson M, Portera L, Farber L, Sheehan DV. Assessing psychiatric impairment in primary care with the Sheehan Disability Scale. Int J Psychiatry Med. 1997;27(2):93-105.

Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. Int Clin Psychopharmacol. 1996;11 Suppl 3:89-95.

Patient Health Questionnaire – 9-Item

The PHQ-9 is a 9-item, subject-reported outcome measure that was used to assess depressive symptoms (Spitzer et al., 1999). The scale scores each of the 9 symptom domains of the DSM-5 MDD criteria, and it has been used both as a screening tool and a measure of response to treatment for depression. Each item is rated on a 4-point scale (0=not at all, 1=several days, 2=more than half the days, and 3=nearly every day). The subject's item responses are summed to provide a total score (range of 0 to 27) with higher scores indicating greater severity of depressive symptoms. The recall period is 2 weeks.

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

Generalized Anxiety Disorder 7-Item Scale

The 7-item subject-reported GAD-7 was used to measure the secondary objective of symptoms of anxiety. The GAD-7 is a brief and validated measure of overall anxiety. Each item is rated on a 4-point scale (0=not at all; 1=several days; 2=more than half the days; 3=nearly every day) (Spitzer et al., 2006). Item responses are summed to yield a total score (range of 0 to 21), with higher scores indicating more anxiety. The recall period is 2 weeks.

Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med. 2006;166(10):1092-1097.

European Quality of Life – 5 Dimension – 5 Level

The EQ-5D-5L is a standardized instrument used as a measure of health outcome, primarily designed for self-completion by respondents. It consists of the EQ-5D-5L descriptive system and the European Quality of Life – Visual Analogue Scale (EQ-VAS). The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each of the 5 dimensions is divided into 5 levels of perceived problems (Level 1 indicating no problem, Level 2 indicating slight problems, Level 3 indicating moderate problems, Level 4 indicating severe problems, and Level 5 indicating extreme problems). The subject selects an answer for each of the 5 dimensions considering the response that best matches his or her health "today." The responses are used to generate a health state description, and

individual health state descriptions are used to obtain a health status index using crosswalk value sets. Health status index is anchored at 0 (health state value equal to dead) and 1 (full health). Changes in health status index on the order of 0.03 to 0.07[1] are recognized as a threshold for meaningful change for an individual subject (Gerhards et al., 2011; Walters & Brazier, 2005). The EQ-VAS self-rating records the respondent's own assessment of his or her overall health status at the time of completion, on a scale of 0 (the worst health you can imagine) to 100 (the best health you can imagine). Changes in EQ-VAS on the order of 7 to 10[1] are recognized as a threshold for meaningful change for an individual subject (Pickard et al., 2007).

Gerhards SA, Huibers MJ, Theunissen KA, de Graaf LE, Widdershoven GA, Evers SM. The responsiveness of quality of life utilities to change in depression: a comparison of instruments (SF-6D, EQ-5D, and DFD). Value Health. 2011;14(5):732-739.

Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. Qual Life Res. 2005;14(6):1523-1532.

Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes. 2007;5:70.

Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS was performed to assess potential suicidal ideation and behavior. The C-SSRS is a low-burden measure of the spectrum of suicidal ideation and behavior that was developed to assess severity and track suicidal events through any treatment (Posner et al., 2007). It is a clinical interview providing a summary of both suicidal ideation and behavior that can be administered during any evaluation or risk assessment to identify the level and type of suicidality present. The C-SSRS can also be used during treatment to monitor for clinical worsening.

The C-SSRS events are categorized into scores ranging from 0 (no event that can be assessed on the basis of C-SSRS) to 10 (completed suicide). The maximum score assigned for each subject was also summarized into one of 3 categories: no suicidal ideation or behavior (0), suicidal ideation (1-5), suicidal behavior (6-10).

Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry. 2007;164:1035-1043.

[1] Although these values are based on an earlier version of the instrument, they are applicable to the EQ-5D-5L evaluation in this study.

Clinician-Administered Dissociative States Scale (CADSS)

The CADSS is an instrument for the measurement of present-state dissociative symptoms (Bremner et al., 1998), and was administered to assess treatment-emergent dissociative symptoms. The CADSS consists of 23 subjective items, divided into 3 components: depersonalization, derealization, and amnesia. Participant's responses are coded on a 5-point scale (0=not at all through to 4=extremely). The CADSS has excellent inter-rater reliability and internal consistency.

Bremner JD, Krystal JH, Putnam FW, et al. Measurement of dissociative states with the Clinician-Administered Dissociative States Scale (CADSS). J Trauma Stress. 1998;11(1):125-136

Brief Psychiatric Rating Scale (BPRS)

The BPRS is an 18-item rating scale that is used to assess a range of psychotic and affective symptoms, rated from both observation of the subject and the subject's own report (Overall & Gorham 1962). It provides a rapid and efficient evaluation of treatment response in clinical drug studies and in clinical settings (Rugani et al., 2012).

Only the 4-item positive symptom subscale BPRS+ (ie, suspiciousness, hallucinations, unusual thought content, and conceptual disorganization) was administered in this study to assess potential treatment-emergent psychotic symptoms. It is highly sensitive to change, and excellent inter-rater reliability can be achieved with training and a standard interview procedure.

Overall JE; Gorham D R. The Brief Psychiatric Rating Scale. Psychol Rep. 1962;10:799-812.

Rugani F, Bacciardi S, Rovai L, et al. Symptomatological features of patients with and without ecstasy use during their first psychotic episode. Int. J. Environ. Res. Public Health. 2012;9(7):2283-2292.

Global Assessment of Discharge Readiness (CGADR)

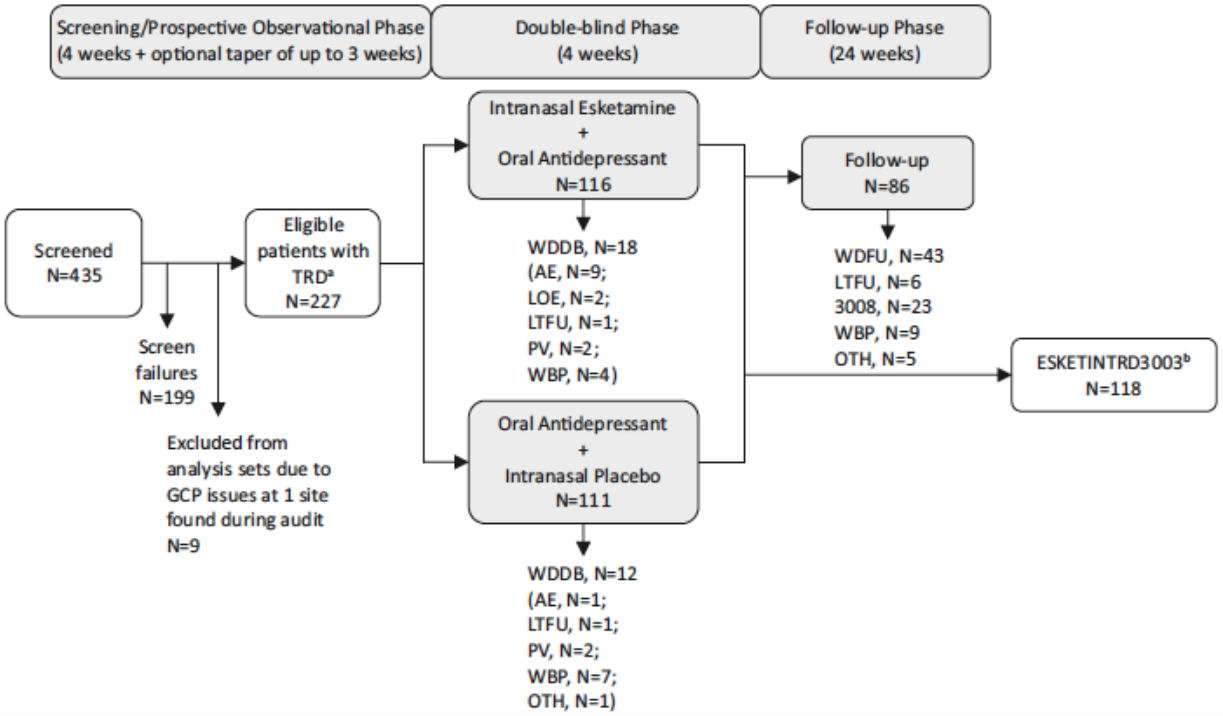
The CGADR was used to measure the subject's current clinical status and is the clinician's assessment of the subject's readiness to be discharged from the study site. The clinician answered "Yes" or "No" to the question "Is the subject considered ready to be discharged based on their overall clinical status (e.g., sedation, blood pressure, and other adverse events)?"

Physician Withdrawal Checklist; 20-Item (PWC-20)

The PWC-20 was administered to assess potential withdrawal symptoms following cessation of intranasal esketamine treatment. The PWC-20 is a 20-item simple and accurate method to assess potential development of discontinuation symptoms after stopping of study medication. The PWC-20 is a reliable and sensitive instrument for the assessment of discontinuation symptoms (Rickels et al., 2008) Discontinuation symptoms occur early and disappear rather swiftly, depending upon speed of taper, daily medication dose, and drug elimination half-life.

Rickels K, Garcia-Espana F, Mandos L, Case GW. Physician Withdrawal Checklist (PWC-20). J Clin Psychopharmacol. 2008;28(4):447–451.

FIGURE S1. Disposition of Patients



3008 = entered Janssen-sponsored Study TRD3008 (NCT02782104); AE = adverse event; GCP = Good Clinical Practice; LOE = lack of efficacy; LTFU = lost to follow-up; N = number of patients; OTH = other reason for withdrawal; PV = protocol violation; TRD = treatment-resistant depression; WBP = withdrawal by patient; WDDB = withdrawal from double-blind phase; WDFU = withdrawn from follow-up phase.

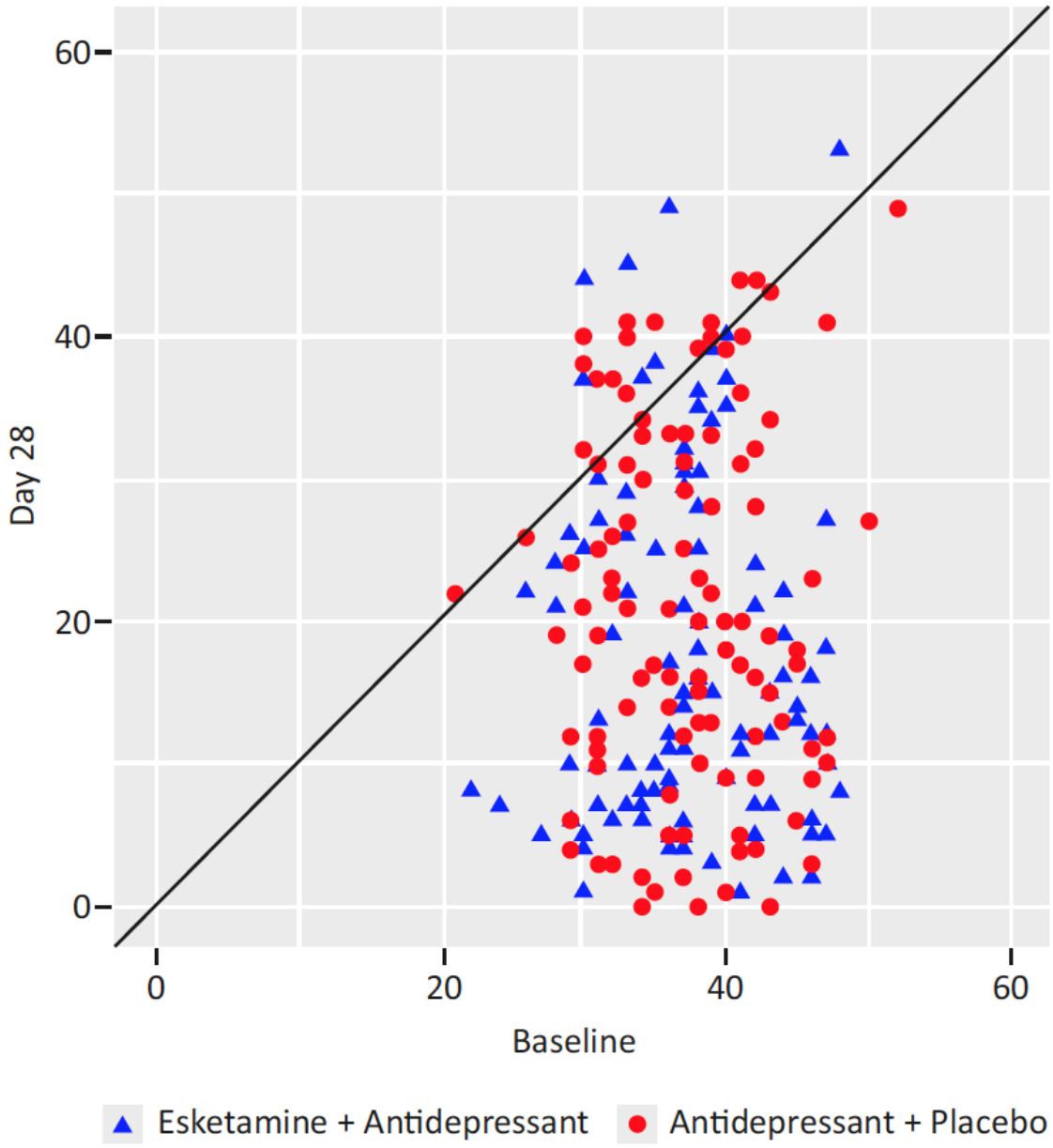
a. Only patients with non-response to ≥2 oral antidepressants prior to randomization were eligible to participate in the study.

b. Only responders (define as ≥50% reduction in MADRS total score from baseline to end of the 28-day double-blind phase were eligible to continue to Janssen-sponsored Study TRD3003 (NCT02493868).

Sensitivity Analysis on the Primary Endpoint

A delta adjustment tipping point sensitivity analysis was performed to evaluate the robustness of the MMRM analysis to increasing deviations from the missing at random assumption. For each delta adjustment scenario, the "tipping point", the smallest delta adjustment value at which conclusions change from favorable to intranasal esketamine plus oral antidepressant (i.e., significant at the two-sided $p < 0.05$ level) to unfavorable (acceptance of the null hypothesis of no treatment difference), was identified. The delta adjustment to the imputed changes in MADRS total score for the intranasal esketamine plus oral antidepressant group was equal to a 9.0 point increase, and the delta adjustment for the oral antidepressant plus intranasal placebo group was equal to 0. This indicates that if the missing at random assumption does not hold and the missing changes in MADRS total score for the intranasal esketamine plus oral antidepressant group worsen after discontinuation, then conclusions continue to favor intranasal esketamine plus oral antidepressant over oral antidepressant plus intranasal placebo up until the point the missing changes in MADRS total scores for the intranasal esketamine plus oral antidepressant group are 9.0 points worse after discontinuation than expected if they were missing at random. This indicates that the results of the primary analysis were robust. In addition to the tipping point analysis, a jump to reference (i.e., imputing missing values from the comparator group) and analysis of covariance using last observation carried forward (LOCF), baseline observation carried forward (BOCF), and worst observation carried forward (WOCF) were performed with the results being consistent with the primary analysis.

FIGURE S2. MADRS Total Score by Patient: Day 28 Versus Baseline



Note: The primary analysis was based on an MMRM analysis, which utilized all observed case data collected for a patient at each visit, not just the baseline and day 28 values. Figure S2 only includes completers.

TABLE S5. Key Secondary Efficacy Endpoints in Double-Blind Phase

	Esketamine + Antidepressant		Antidepressant + Placebo	
Early Onset of Sustained Clinical Response[a]				
N	114			109
Yes, n (%)	9	(7.9%)	5	(4.6%)
Generalized Cochran-Mantel-Haenszel test[b]				
2-sided p-value	0.321[c]			
Odds ratio[d] (95% CI)	1.79	(0.57; 5.67)		
Sheehan Disability Scale Total Score				
Baseline				
N	111			104
Mean (SD)	24.0	(4.07)	24.2	(4.38)
Change from baseline to day 28				
N	86			85
Mean (SD)	-13.6	(8.31)	-9.4	(8.43)
MMRM analysis[e]				
Difference of LS means[f] (SE)	-4.0	(1.17)		
95% CI on difference	-6.28; -1.64			
Effect size (95% CI)	0.48	(0.17, 0.78)		
Patient Health Questionnaire Total Score				
Baseline				
N	114			109
Mean (SD)	20.2	(3.63)	20.4	(3.74)
Change from baseline to day 28				
N	104			100
Mean (SD)	-13.0	(6.42)	-10.2	(7.80)
MMRM analysis[e]				
Difference of LS means[f] (SE)	-2.4	(0.88)		
95% CI on difference	-4.18; -0.69			
Effect size (95% CI)	0.34	(0.06, 0.61)		

CI = confidence interval; CMH = generalized Cochran-Mantel-Haenszel; LS = least squares; MADRS = Montgomery-Asberg Depression Rating Scale; MMRM = mixed model for repeated measures; PHQ-9 = Patient Health Questionnaire; SDS = Sheehan Disability Scale; SE = standard error

a. Onset of clinical response defined as ≥50% improvement from baseline in MADRS total score with onset by day 2 that was maintained to day 28. Patients were allowed one excursion (non-response) on days 8, 15, or 22, provided the score was ≥25% improvement. Patients with missed assessments or who discontinued early were not considered to have onset of clinical response.
b. CMH test for mean score difference between treatments, adjusting for country and class of oral antidepressant (SNRI or SSRI).
c. Esketamine + antidepressant vs. antidepressant + placebo, the analysis could be considered statistically significant at the 2-sided 0.050 level only if the MADRS total score analysis was also significant.
d. Odds of achieving onset of clinical response on esketamine + antidepressant divided by the odds of achieving onset of clinical response on antidepressant + placebo.
e. Test for treatment effect was based on MMRM with change from baseline as the response variable and the fixed effect model terms for treatment (esketamine + antidepressant, antidepressant + placebo), day, country, class of antidepressant (SNRI or SSRI), and treatment-by-day, and baseline value as a covariate.
f. Esketamine + antidepressant minus antidepressant + placebo.

Note: SDS total score ranges from 0 to 30; a higher score indicates greater impairment. PHQ-9 total score ranges from 0 to 27; a higher score indicates greater depression. Negative change in SDS total score and PHQ-9 total score indicates improvement, and a negative difference for each favors esketamine.

TABLE S6. Clinical Global Impression–Severity (CGI-S): Change From Baseline to End Point of the Double-Blind Phase

	Esketamine + Antidepressant N = 114	Antidepressant + Placebo N = 109
Baseline		
N	113	109
Median (Range)	5.0 (4; 7)	5.0 (4; 7)
Change from baseline to endpoint		
N	111	109
Median (Range)	-2.0 (-5; 1)	-2.0 (-5; 1)
2-sided p-value[a]	0.034[b]	

LS = least squares;
(a) Test for treatment effect is based on analysis of covariance (ANCOVA) model on ranks of change from baseline as the response variable and factors for treatment (intranasal esketamine plus oral antidepressant, oral antidepressant plus intranasal placebo), country, and class of oral antidepressant (SNRI or SSRI), and baseline value (unranked) as a covariate.
(b) p-value is descriptive and not inferential as this endpoint was not part of the serial gatekeeping approach to control type 1 error.
Note: CGI-S score ranges from 1(normal, not at all ill) to 7 (among the most extremely ill patients). Values of 0 (not assessed) are excluded from analysis.
Note: Negative change in score indicates improvement.

EuroQol-5 Dimension-5 Level (EQ-5D-5L) Results

Health outcome improved in both treatment groups based on mean [SD] change in the EQ-5D-5L health status index (0.288 [0.2317] and 0.231 [0.2506]) and in the EQ-5D-5L VAS score (29.1 [26.32] and 20.9 [26.60] for the esketamine plus antidepressant and antidepressant plus placebo groups, respectively).

Narrative for Patient Who Died During the Trial

One patient in the esketamine plus antidepressant group experienced multiple injuries following a road traffic (motorbike) accident on day 16 of the double-blind phase and subsequently died on day 55, 40 days after the last dose of esketamine. The motor vehicle accident with fatal outcome occurred ~28 hours after the patient's last dose of esketamine. Information on drug levels at the time of death is not available, as it was not collected in the emergency room. This patient underwent pre-dose cognitive testing evaluation, which included reaction time measurement on the day of the final dosing preceding the accident, with normal results. The patient did not experience other adverse events. No history of suicidal behavior and no suicidal ideations (CSSRS was 0 at all timepoints) were reported. In the serious adverse event (SAE) report narrative provided by the site, the verbatim description of the event was: "The accident was not patient's fault, but he ended up falling down and hitting a tree." The investigator assessed the road traffic accident as doubtfully related to esketamine or antidepressant. An autopsy was

performed, however the report was not shared with investigator or Sponsor based on the family's wishes.

The Sponsor's internal Safety Management Team (a product-based, cross-functional collaborative team responsible for review, assessment, and evaluation of Medical Safety data arising from any source) also reviewed the case as part of the Safety Oversight and, based on the available evidence, considered it not related to the study treatment. Similarly, the case was reviewed by an Independent Data Monitoring Committee (IDMC) established for the esketamine phase 3 TRD studies

Esketamine has a short half-life and is rapidly cleared from the plasma (which tightly parallels the rates of the drop in brain concentrations and receptor occupancy), therefore it seems unlikely that esketamine played a role in this accident. Moreover, we conducted two formal studies of the effects of esketamine nasal spray on driving, which supported the safety of driving on the day following esketamine dosing. Per protocol, patients were discharged from the clinical site accompanied by a responsible adult and were not allowed to drive a car or operate machinery within 24 hours following an intranasal session.

Local Nasal Tolerability Results

Few patients had evidence of symptoms on nasal examination (2, 1.9% in the esketamine plus antidepressant group and 5 [4.9%] in the antidepressant plus placebo group). Likewise, most patients (75 [65.8%] and 92 [84.4%] in the respective groups) reported no nasal symptoms or only mild symptoms for individual items on the Nasal Symptom Questionnaire.

Physician Withdrawal Checklist (PWC-20) Results

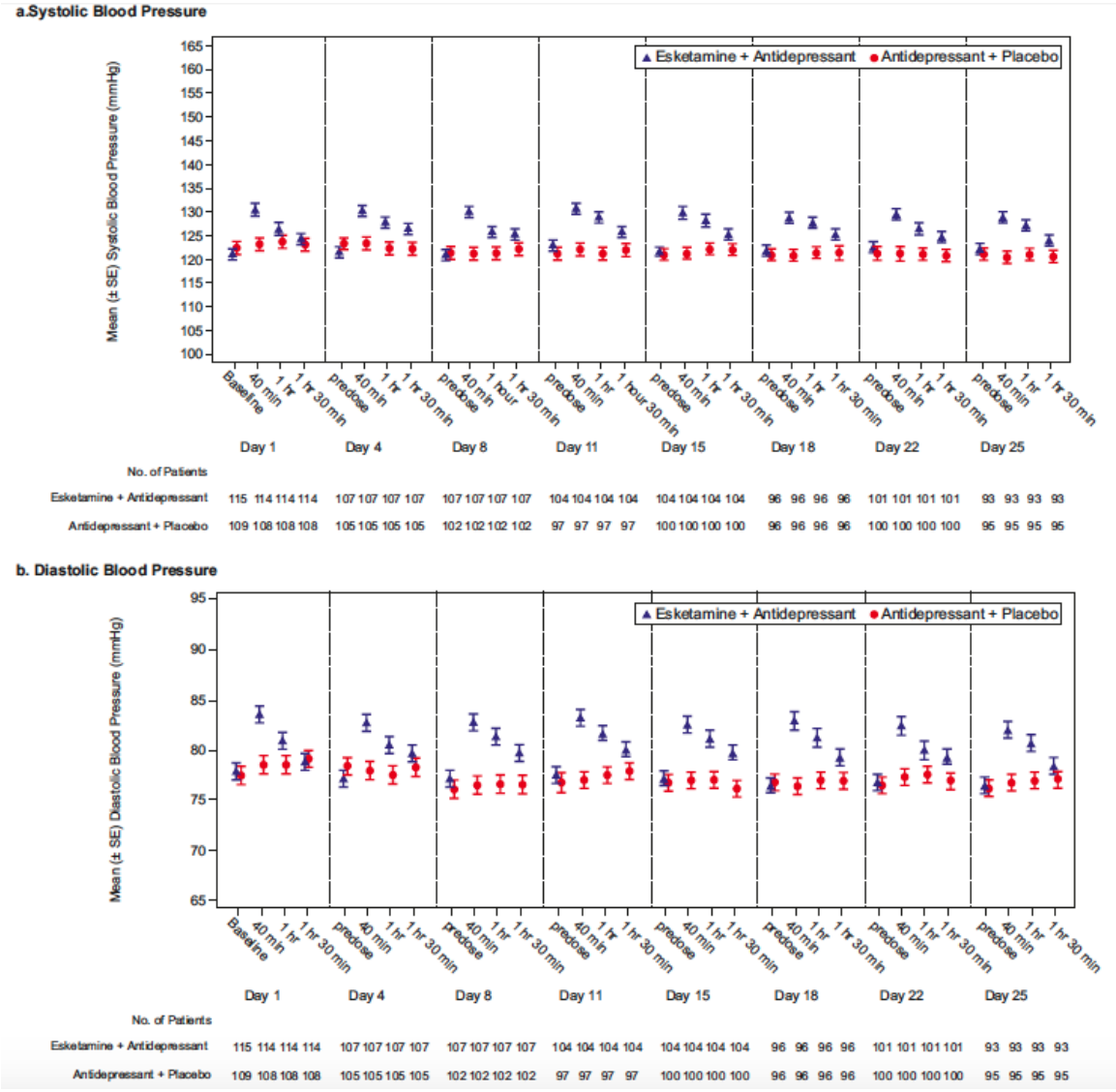
The PWC-20 was administered to assess potential withdrawal symptoms following cessation of intranasal treatment. The categories of withdrawal symptom status were no symptom; improved; symptom present, unchanged; and new or worsened symptom.

- At the 1-week follow-up visit, the most frequently reported (≥25.0%) new or worsened symptoms were:
  - In the intranasal esketamine plus oral antidepressant group (n=24): fatigue-lethargy-lack of energy (8 [33.3%] patients); weakness (7 [29.2%] patients); dysphoric mood-depression, loss of appetite, and restlessness-agitation (6 [25.0%] patients each)
  - In the oral antidepressant plus intranasal placebo group (n=41): insomnia (12 [29.3%] patients); irritability, and dysphoric mood-depression (11 [26.8%] patients each).
- At the 2-week follow-up visit, the most frequently reported (≥25.0%) new or worsened symptoms:
  - In the intranasal esketamine plus oral antidepressant group (n=17): fatigue-lethargy-lack of energy (6 [35.3%] patients); restlessness-agitation, and anxiety-nervousness (5 [29.4%] patients each)
  - In the oral antidepressant plus intranasal placebo group (n=30): insomnia (13 [43.3%] patients); difficulty concentrating/remembering (12 [40.0%]

patients); muscle aches or stiffness (11 [36.7%] patients); poor coordination and irritability (9 [30.0%] patients); loss of appetite, dysphoric mood-depression, diaphoresis, and weakness (8 [26.7%] patients each).

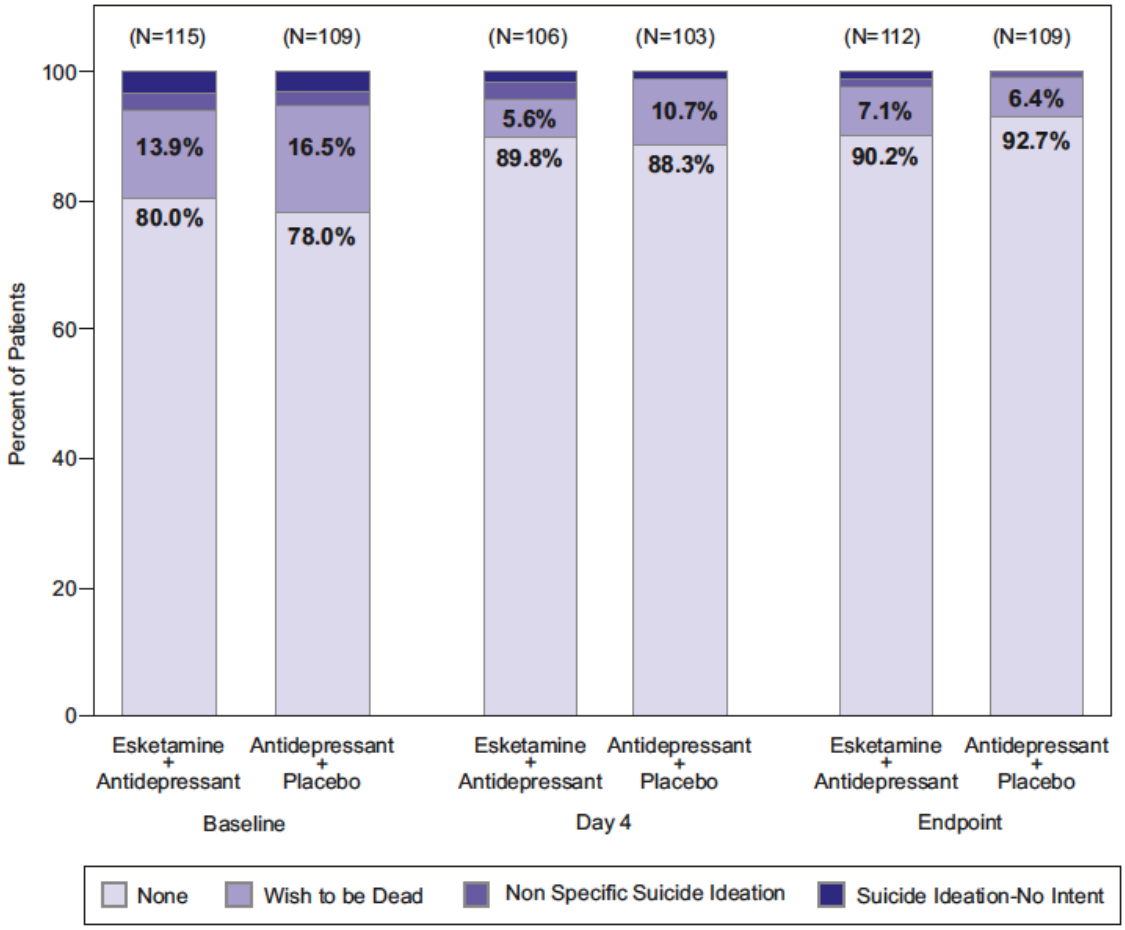
The changes in withdrawal symptoms assessed by the PWC-20 after cessation of treatment with intranasal esketamine plus oral antidepressant were consistent with observed changes in symptoms of depression and anxiety. No clear evidence of withdrawal was observed 2 weeks after cessation of treatment with intranasal esketamine plus oral antidepressant.

FIGURE S3. Mean (±SE) Blood Pressure Over Time in the Double-Blind Phase



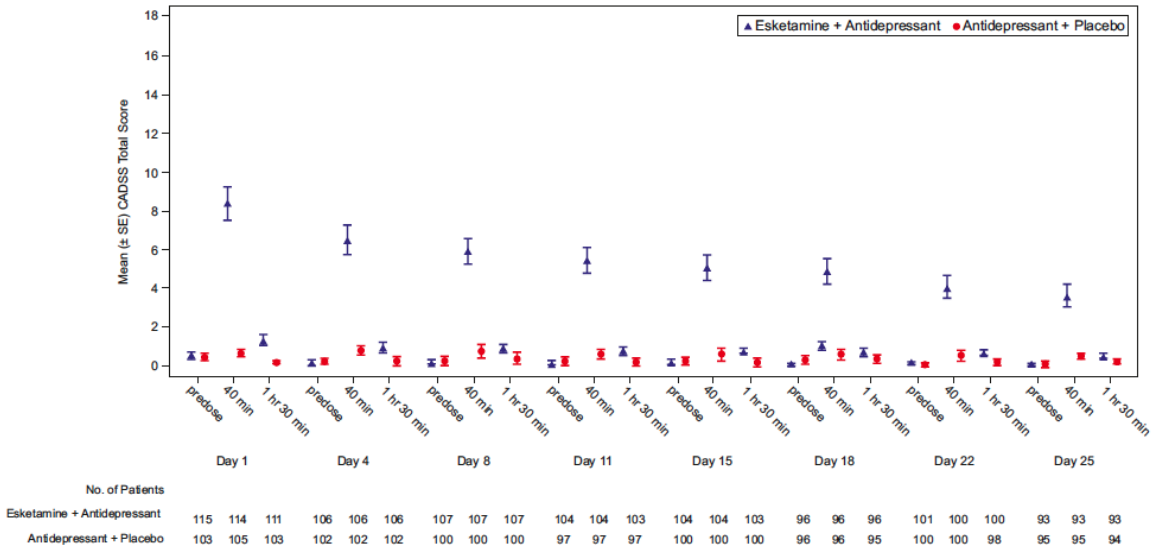
SE = standard error

FIGURE S4. Incidence of C-SSRS Scores at Baseline, Day 4 and Endpoint of the Double-Blind Phase



C-SSRS = Columbia-Suicide Severity Rating Scale
Note: None = C-SSRS score of 0; Wish to be Dead = C-SSRS score of 1; Non-Specific Suicide Ideation = C-SSRS score of 2; Suicide Ideation - No Intent = C-SSRS score of 3

FIGURE S5. Mean (±SE) CADSS Total Score Over Time in the Double-Blind Phase



CADSS = Clinician-Assessed Dissociative Symptom Scale; SE = standard error

Outlier Data for Sedation, Dissociation, and Treatment-Emergent Blood Pressure Increase

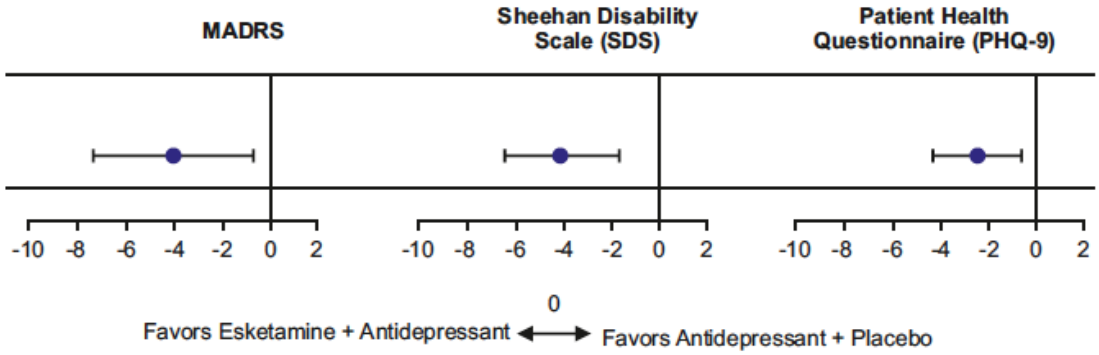
Of those who experienced moderate to severe sedation (score of 0, 1, or 2 on the Modified Observer's Assessment of Alertness/Sedation [MOAA/S]), there was no participant where onset of sedation was reported after 1.5 hours postdose. Only one esketamine-treated patient reported MOAA/S score of 2 in the first dosing session with onset at 20 minutes postdose and resolution (MOAA/S = 5) at 71 minutes postdose.

Review of the data for dissociation (based on the Clinician Administered Dissociative States Scale [CADSS]) indicated that onset of symptoms of dissociation (i.e., CADSS total score >4) was typically seen within the first 40 minutes and resolved by 1.5 hours.

With regard to treatment-emergent blood pressure elevation (using a cut-off of ≥160 mmHg systolic or a diastolic of ≥90 mmHg), all patients who reached these values had done so by 1.5 hours postdose.

All patients were ready for discharge by 3 hours post-dose, with the exception of 3 esketamine-treated patients who reported discharge readiness at 3 hours postdose (reported only at a single visit for each) due to adverse events of feeling drunk, feeling abnormal, and dizziness/nausea for one patient each.

FIGURE S6. MADRS, SDS, and PHQ-9: LS Mean Change from Baseline



The Montgomery-Asberg Depression Rating Scale (MADRS) is a clinician-rated scale designed to measure depression severity and detects changes due to antidepressant treatment. 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 Sheehan Disability Scale (SDS) is a 5-item questionnaire, which has been widely used and accepted for assessment of functional impairment and associated disability. The first 3 items assess disruption of (1) work/school, (2) social life, and (3) family life/home responsibilities on a scale from 0 (not at all) to 10 (extremely). The score for the first 3 items are summed to create a total score of 0-30 where a higher score indicates greater impairment. It also has one item on days lost from school or work and one item on days when underproductive. The recall period for this study is 7 days.

The PHQ-9 is a 9-item patient-reported outcome measure used to assess depressive symptoms. Each item is rated on a 4-point scale (0 = not alt all, 1 = several days, 2 = more than half the days, and 3 = nearly every day). The patient's item responses are summed to provide a total score (range of 0 to 27) with higher scores indicating greater severity of depressive symptoms.