

Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. List of Institutional Review Boards and Independent Ethics Committees

BELGIUM

Ethisch Comité OLV Ziekenhuis Aalst
UZ Brussel IRB, Comité D'éthique Hospitalo-Facultaire (Liège)
AZ St.-Jan Brugge, Sint-Franciskusziekenhuis IRB (Heusden-Zolder)
AZ Sint-Lucas IRB (Bruge)
Comite D Ethique Cliniques Universitaires de Mont Godinne (Yvoi)

BRAZIL

Comitê de Ética em Pesquisa do Investiga - Instituto de Pesquisas (Campinas, SP)
National Committee of Ethics in Research (CONEP) (Brasilia)
Comite de Etica em Pesquisa - Instituto de Psiquiatria da Universidade Federal do Rio de Janeiro
Comitê de Ética em Pesquisa da Faculdade de Medicina do Abc (Santo Andre)
Comite de Etica em Pesquisa do hospital Universitario Walter Cantidio (Fortaleza)
Comite de Etica em Pesquisa do Hospital Universitario Sao Jose - Faculdade de Ciencias Medicas de Mi (Belo Horizonte)
Comite de Etica em Pesquisa em Seres Humanos da Faculdade de Medicina de Sao Jose do Rio Preto
CEP do Instituto de Educacao e Pesquisa da Associacao Hospitalar Moinhos de Vento (Porto Alegre)
Comite de Etica em Pesquisa do Instiruto de Neurologia de Curitiba
Comite de Etica em Pesquisa em Seres Humanos Da Universidade De Passo Fundo
Comite de Etica em Pesquisa da Unifesp/EPM (São Paulo)
Comissao de Etica Para Analise de Projetos de Pequisa - CAPpesq-HCFMUSP (São Paulo)
Comite de Etica em Pesquisa do Hospital das Clínicas da Universidade Federal De Goias
Comite de Etica em Pesquisas do Hospital Pro-Cardiaco (Rio de Janeiro)
Cep do Hospital de Clinicas de Porto Alegre – Hcpa / Ufrgs (Porto Alegre)

CANADA

Royal Ottawa Health Care Group (ON)
UBC Clinical Research Ethics Board (CREB) (Vancouver, BC)
Queen's University, Health Sciences and Affiliated Hospitals Research Ethics Board (Kingston, ON)
CAMH Research Ethics Board (Toronto, ON)
Comite d'Ethique de la Recherche Institut Universitaire en Sante Mentale Douglas (Montreal, QC)
Conjoint Health Research Ethics Board (Calgary, Alberta)

CZECH REPUBLIC

Etická komise BIALBI s.r.o. (Litomerice)
Eticka komise pro multicentricke klinicke hodnoceni Fakultni nemocnice v Motole (Praha)
Etická komise NUDZ (Klecany)
Etická komise NZZ CLINTRIAL, s.r.o. (Praha)
MEC FN Brno
Eticka Komise Nestatniho Zdravotnickeho Zarizeni Research Site, s.r.o. (Plzen)

ESTONIA

Tallinn Medical Research Ethics Committee

FRANCE

CPP EST-IV (Strasbourg)

GERMANY

Landesamt für Gesundheit und Soziales Berlin Geschäftsstelle der Ethik-Kommission des Landes Berlin

Ethik-Kommission bei der Landesärztekammer Rheinland-Pfalz

Ethik-Kommission der Ärztekammer Nordrhein (Düsseldorf)

Ethik-Kommission der Medizinischen Fakultät der Martin-Luther-Universität Halle-Wittenberg

Ethikkommission bei der Bayerischen Landesärztekammer (München,)

Ethikkommission des Landes Berlin

Ethikkommission der Sächsischen Landesärztekammer (Dresden)

HUNGARY:

Medical Research Council Ethics Committee for Clinical Pharmacology (Budapest)

ITALY

Comitato Etico Regione Toscana - Area Vasta Sud-Est (C.E.A.V.S.E.) (Siena)

Comitato etico Catania 1

Comitato Etico Interaziendale Azienda Ospedaliero un. San Luigi Gonzaga di Orbassano

Comitato Etico dell'Università "La Sapienza" Sezione Azienda Ospedaliera Sant'Andrea (Roma)

Comitato Etico "Università Federico II" di Napoli

MEXICO

Comité de etica en Investigación del Mexico Centre for Clinical Research SA de CV (Mexico City)

Comité de Etica en Investigación Centro Hospitalario VICOR SA de CV (Guadalajara)

Comité de ética en Investigación del Instituto Jalisco de Investigación Clínica (Guadalajara)

Comité de ética en Investigación de Winsett Rethman S.A. de C.V. (Monterrey)

Comité de Etica en Investigación del Hospital La Mision SA de CV (Monterrey)

Comité de la Clínica Bajío CLINBA, S.C. (Guanajuato)

Comité de ética en Investigación del Hospital Aranda de la Parra S.A. de C.V. (Leon)

Comité de Ética en Investigación "Hospital Ignacio Morones Prieto" (San Luis Potosi)

Comité de Ética en Investigación de la Facultad de Medicina y Hospital Universitario de la Univers (Monterrey)

Comité de Etica en Investigación del Hospital La Mision SA de CV (Monterrey)

POLAND

Komisja Bioetyczna przy OIL w Warszawie

SLOVAKIA

Etická komisia Bratislavského samosprávneho kraja

Nezávislá etická komisia Banskobystrického samosprávneho kraja

Etická komisia Nemocnice s poliklinikou sv. Barbory Rožnava

Eticka komisia Presovskeho samospravného kraja
Eticka komisia Liptovskej nemocnice s poliklinikou MUDr. Ivana Stodolu

SPAIN

CEIC Parc de Salut Mar (Barcelona)

SWEDEN

Regionala Etikprövningsnämnden i Lund

TURKEY

Mersin University Medical Faculty Ethics Committee
Sisli Etfal Research and Training Hospital Clinical Research Ethics Committee (Istanbul)

UNITED STATES

Sterling Institutional Review Board (Atlanta, GA)
Duke University Health System Institutional Review Board (Durham, NC)
KU Human Subjects Committee 2 (Wichita, KS)
Sharp HealthCare IRB (San Diego, CA)
Western Institutional Review Board (Puyallup, WA)
Office of Regulatory Affairs (Philadelphia, PA)
Hartford Hospital IRB (Hartford, CT)
Baylor College of Medicine IRB (Houston, TX)
Partners Human Research Committee (Boston, MA)
UT Southwestern IRB (Dallas, TX)
Committee for the Protection of Human Subjects in Research, Office of Human Subjects, UMass
Medical (Worcester, MA)
Loyola University of Chicago Health Sciences Division IRB (Maywood, IL)
Johns Hopkins Medicine Institutional Review Boards, Office of Human Subjects Research
(Baltimore, MD)
New York State Psychiatric Institutional Review Board (New York, NY)
University of Virginia Institutional Review Board for Health Science Research (Charlottesville, VA)
Butler Hospital IRB (Providence, RI)
Rush University Medical Center IRB (Chicago, IL)
Quorum Review IRB (Seattle, WA)
Creighton University Institutional Review Board (Omaha, NE)

eAppendix 2. Patient Inclusion and Exclusion Criteria

Inclusion Criteria:

Direct-Entry Patients

The following criteria apply only to those patients entering directly into the study. Each potential patient must satisfy all of the following criteria to be enrolled in the study.

1. At the time of signing the informed consent form (ICF) the patient, a man or woman, must be 18 (or older if the minimum legal age of consent in the country in which the study is taking place is >18) to 64 years of age, inclusive.
2. At the start of the screening/prospective observational phase, each patient must meet Diagnostic and Statistical Manual of Mental Disorders - fifth edition (DSM-5) diagnostic criteria for single-episode MDD (if single-episode MDD, the duration must be ≥ 2 years) or recurrent MDD, without psychotic features, based on clinical assessment and confirmed by the Mini International Neuropsychiatric Interview (MINI).
3. At the start of the screening/prospective observational phase, patient must have had non-response ($\leq 25\%$ 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 patient 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.
 - Patients 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.
 - Patients who are non-responders to their current oral antidepressant medication(s) from the screening/prospective observational phase (as assessed by independent, remote raters) may be eligible to continue to the open-label induction phase. Non-response at the end of the screening/prospective observational phase is defined as $\leq 25\%$ improvement in the MADRS total score from Week 1 to Week 4 and a MADRS total score of ≥ 28 on Week 2 and Week 4.
4. At the start of the screening/prospective observational phase, each patient must have an Inventory of Depressive Symptomatology, Clinician-rated, 30-item (IDS-C30) total score of ≥ 34 .
5. The patient'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 the Site Independent Qualification Assessment.
6. Patient must be medically stable on the basis of physical examination, medical history, vital signs (including blood pressure), pulse oximetry, and 12-lead ECG performed in the screening/prospective observational phase. If there are any abnormalities that are not specified in the inclusion and

exclusion criteria, their clinical significance must be determined by the investigator and recorded in the subject's source documents and initialed by the investigator.

7. Patient 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 patient 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 patient's source documents and initialed by the investigator.
 - Patients 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 patient (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 patient is not eligible.
8. Patient 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:

- o postmenopausal

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

- o permanently sterile

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

- b. Of childbearing potential and

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

Examples of highly effective contraceptives include

- ◆ user-independent methods:

implantable progestogen-only hormone contraception associated with inhibition of

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

◆ user-dependent methods:

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

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method.

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

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

10. 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 open-label induction phase prior to randomization.
11. During the study (ie, from Day 1 of the open-label induction phase, prior to intranasal dosing) and for a minimum of 1 spermatogenesis cycle (defined as approximately 90 days) after receiving the last dose of intranasal study medication, a man who is sexually active with a woman of childbearing potential
 - must be practicing a highly effective method of contraception with his female partner from those listed above (see examples of highly effective methods of contraception provided for female subjects).
 - must use a condom if his partner is pregnant.
 - must agree not to donate sperm.

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

Transfer-entry Patients

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

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

Note that the following criterion is intentionally not numbered sequentially:

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

Direct-Entry and Transfer-Entry Patients

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

13. Each subject must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.
14. Each subject must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and is willing to participate in the study.

Exclusion Criteria:

Direct-Entry Patients

The following exclusion criteria only apply to those subjects entering directly into the study:

1. Subject's depressive symptoms have previously not responded to any of the following:
 - Esketamine or ketamine in the current major depressive episode per clinical judgment, or
 - All of the oral antidepressant treatment options available in the respective country for the open-label induction phase (ie, duloxetine, escitalopram, sertraline, and venlafaxine XR) in the current major depressive episode (based on MGH-ATRQ), or
 - An adequate course of treatment with electroconvulsive therapy (ECT) in the current major depressive episode, defined as at least 7 treatments with unilateral/bilateral ECT.
2. 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 open-label 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. Subject has a current or past history of seizures (uncomplicated childhood febrile seizures with no sequelae are not exclusionary).
7. Subject has an UPSIT total score ≤ 18 , indicative of anosmia, in 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 (refer to Attachment 2).
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 open-label induction phase (prior to the first intranasal treatment session) a

supine SBP >140 mmHg or DBP >90 mmHg is exclusionary.

- A potential subject may have his/her current antihypertensive medication(s) adjusted during the screening/prospective observational phase and be re-evaluated to assess their blood pressure control. The subject must be on a stable regimen for at least 2 weeks before Day 1 of the open-label induction phase.
10. Subject has a current or past history of significant pulmonary insufficiency/condition or with an arterial blood oxygen saturation (SpO₂) of <93% at the start of the screening/prospective observational phase or Day 1 of the open-label induction phase prior to the first intranasal treatment session.
 11. Subject has clinically significant ECG abnormalities at the start of the screening/prospective observational phase or on Day 1 of the open-label induction phase prior to the first intranasal treatment session, defined as:
 - During screening, a QT interval corrected according to Fridericia's formula (QTcF): ≥ 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, or 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 ≥ 2 x the upper limit of normal or total bilirubin >1.5 times the ULN in the screening/prospective observational phase.
 - Repeat of screening test for abnormal ALT and AST is permitted once during the screening period provided per investigator discretion and provide there is an alternative explanation for the out of range value.
 - For elevations in bilirubin if, in the opinion of the investigator and agreed upon by the sponsor's medical officer, the elevation in bilirubin is consistent with Gilbert's disease, the subject may participate in the study.
 14. Subject has positive test result(s) for drugs of abuse (including barbiturates, methadone, opiates, cocaine, phencyclidine, and amphetamine/methamphetamine) at the start of the screening/prospective observational phase or Day 1 of the open-label induction phase prior to the first intranasal treatment session.
 - Subjects who have a positive test result at screening due to prescribed psychostimulants (eg,

amphetamine, methylphenidate, etc.), taken for an indication other than MDD, are permitted to continue to take this medication during the study in accordance with Attachment 1.

- Otherwise, subjects who have a positive test result at screening due to prescribed/over-the-counter opiates or barbiturates may be permitted to continue in the screening/prospective observational phase if the medication is discontinued at least 1 week or 5 half-lives, whichever is longer, before Day 1 of the open-label induction phase prior to the first intranasal treatment session, in accordance with Attachment 1 restrictions. The result of the Day 1 (prior to the first intranasal treatment session) test for drugs of abuse must be negative for the subject to have the first intranasal treatment session.
 - o Retesting is not permitted for positive test result(s), except for reasons stated above.
- Prior intermittent use of cannabinoids prior to the start of the screening/prospective observational phase is not exclusionary as long as the subject does not meet the criteria for substance use disorder. A positive test for cannabinoids at the start of the screening/prospective observational phase is not exclusionary; however, a positive test result for cannabinoids predose on Day 1 of the open-label induction phase is exclusionary.

15. 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. Criterion deleted per Amendment 2.
19. Subject has a history of malignancy within 5 years before the start of the screening/prospective observational phase (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy that, in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence).
20. Subject has known allergies, hypersensitivity, intolerance, or contraindications to esketamine/ketamine and/or its excipients or all of the available oral antidepressant treatment options for the open-label induction phase.
21. Subject has taken any prohibited therapies that would not permit dosing on Day 1, as noted in Section 8 (Prestudy and Concomitant Therapy) and Attachment 1.
22. Subject is taking a total daily dose of benzodiazepines greater than the equivalent of 6 mg/day of lorazepam at the start of the screening/prospective observational phase.
23. 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.

24. Subject has received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 60 days before the start of the screening/prospective observational phase, or has participated in 2 or more MDD or other psychiatric condition clinical interventional studies (with different investigational medication) in the previous 1 year before the start of the screening/prospective observational phase, or is currently enrolled in an investigational interventional study.
25. Subject is a woman who is pregnant, breast-feeding, or planning to become pregnant while enrolled in this study or within 6 weeks after the last dose of intranasal study drug.
26. Subject has a diagnosis of acquired immunodeficiency syndrome (AIDS). Human immunodeficiency virus (HIV) testing is not required for this study.
27. Subject has any condition or situation/circumstance for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.
28. Subject has had major surgery, (eg, requiring general anesthesia) within 12 weeks before the start of the screening/prospective observational phase, or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study.
 - Note: Subjects with planned surgical procedures to be conducted under local anesthesia may participate.
29. Subject is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.

Note that the following criterion is intentionally not numbered sequentially:

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

Transfer-Entry Patients

The following exclusion criteria apply to transfer-entry subjects:

30. Subject has any condition or situation/circumstance for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.
32. Transferred-entry subjects must meet the same criteria at the point of entry to this study as the direct-entry subjects at the same time point (ie, beginning of optimization phase).

NOTE: Investigators should ensure that all relevant study enrollment criteria have been met prior to Day 1 of the open-label induction phase (direct entry) or the start of the optimization phase (transferred entry). If a subject's status changes (including laboratory results or receipt of additional medical records) before the first dose of intranasal study drug is given in this study such that he or she no longer meets applicable eligibility criteria, then the subject should be excluded from participation in the study. Section 17.4 (Source Documentation) describes the required documentation to support meeting the enrollment criteria.

eAppendix 3. Columbia Suicide Severity Rating Scale (C-SSRS) Item Descriptions

Suicidal Ideation (1-5)

- 1: Wish to be Dead
- 2: Non-specific Active Suicidal Thoughts
- 3: Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
- 4: Active Suicidal Ideation with Some Intent to Act, without Specific Plan
- 5: Active Suicidal Ideation with Specific Plan and Intent

Suicidal Behavior (6-10)

- 6: Preparatory Acts or Behavior
- 7: Aborted Attempt
- 8: Interrupted Attempt
- 9: Actual Attempt (non-fatal)
- 10: Completed Suicide

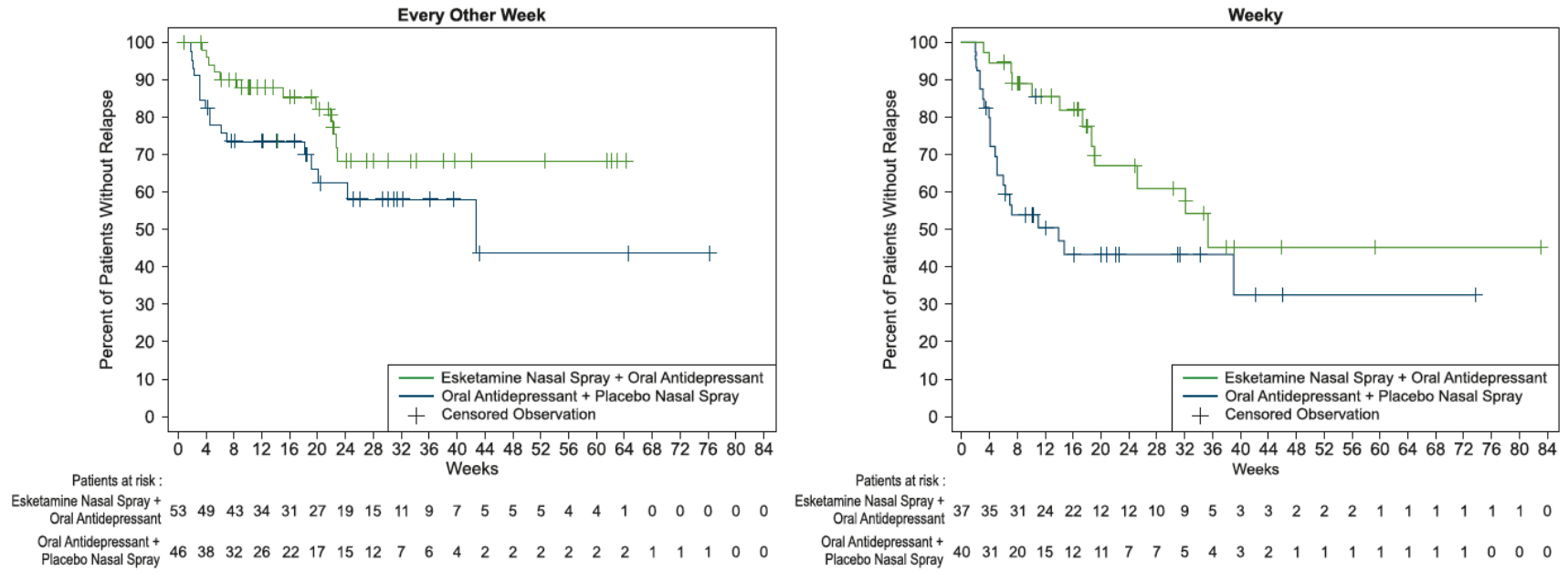
If no events qualify for a score of 1 to 10, a score of 0 will be assigned (0=“no event that can be assessed on the basis of C-SSRS”). Higher scores indicate greater severity.

eTable 1. Time-to-Relapse^a and Number (%) of Stable Remitters That Remained Relapse Free (Based on Stable Remission Defined as MADRS Total Score ≤ 10) in the Maintenance Phase

	Esketamine Nasal Spray + Oral Antidepressant	Oral Antidepressant + Placebo Nasal Spray
Number assessed	83	74
Number censored	66 (75.9%)	42 (56.8%)
Number of relapses	20 (24.1%)	32 (43.2%)
25% percentile (95% CI)	158.0 (130.0, 247.0)	35.0 (27.0, 103.0)
Median (95% CI)	NE	273.0 (126.0, NE)
75% percentile (95% CI)	NE	NE
Hazard ratio (95% CI) ^b	0.47 (0.27, 0.83)	
2-sided p-value ^c	0.005	

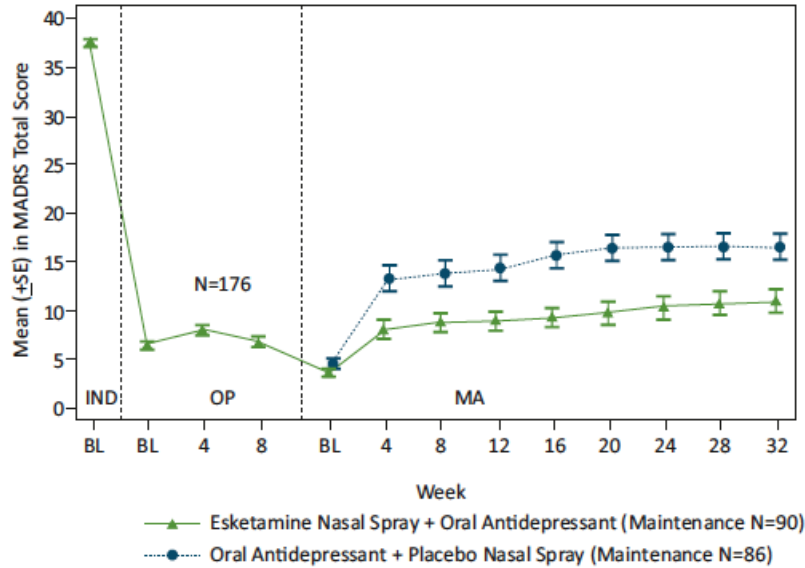
a. Based on Kaplan-Meier product limit estimates.

eFigure 1. Kaplan-Meier Estimates of Time to Relapse for Stable Remitters by Dosing Frequency in the Maintenance Phase

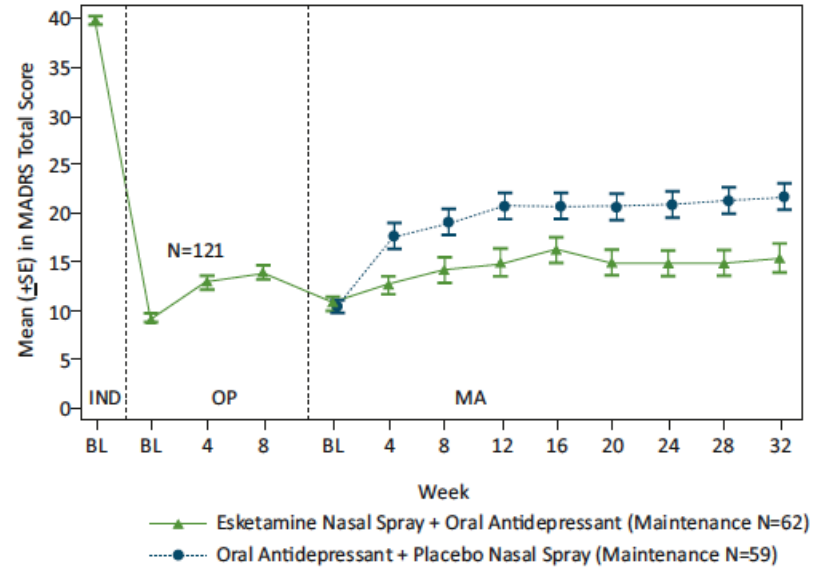


eFigure 2. Mean (\pm SE) in MADRS Total Score Over Time LOCF During the Induction, Optimization, and Maintenance Phases

A. Patients Who Were Stable Remitters



B. Patients Who Were Stable Responders



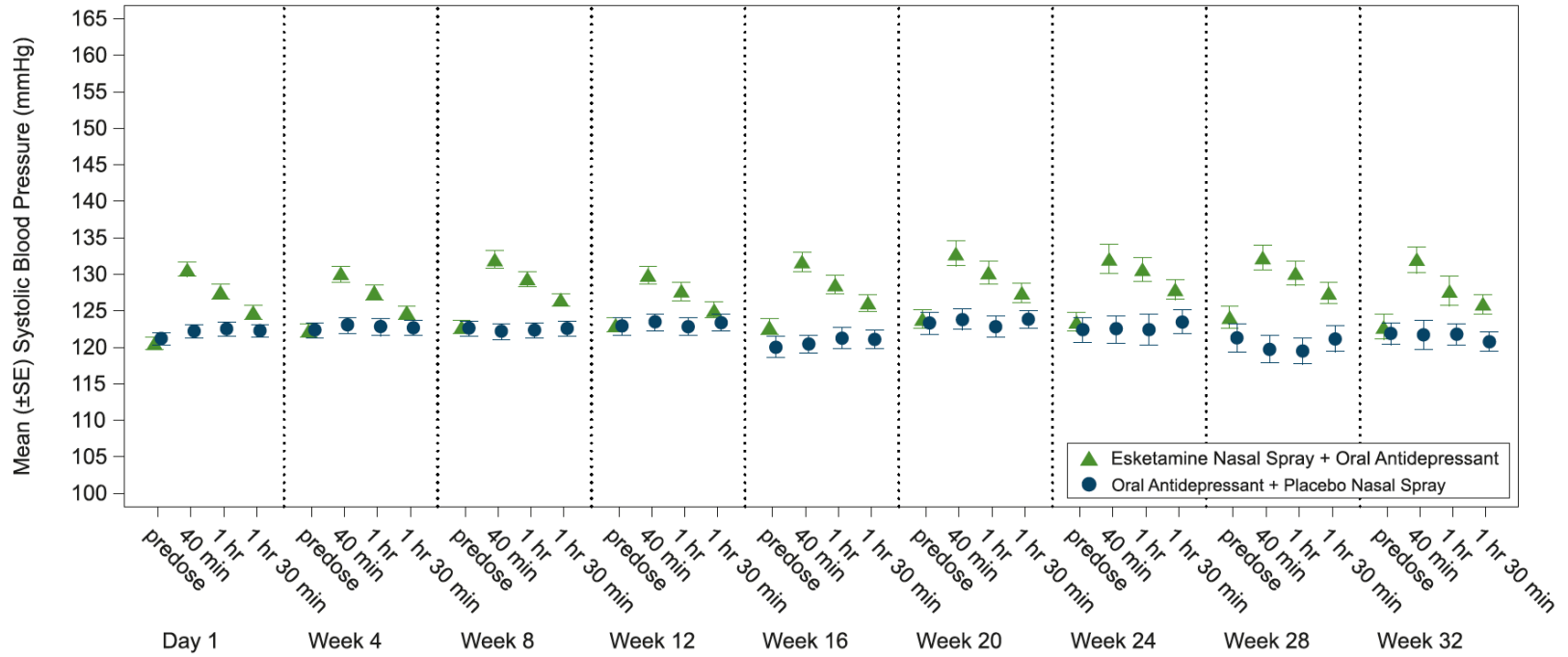
Abbreviations: IND=Induction, OP=Optimization, MA=Maintenance

LOCF = last observation carried forward; MADRS = Montgomery-Asberg Depression Rating Scale; SE = standard error

Note: Figures A and B only include data for stable remitters or stable responders on esketamine nasal spray who were randomized into the Maintenance Phase.

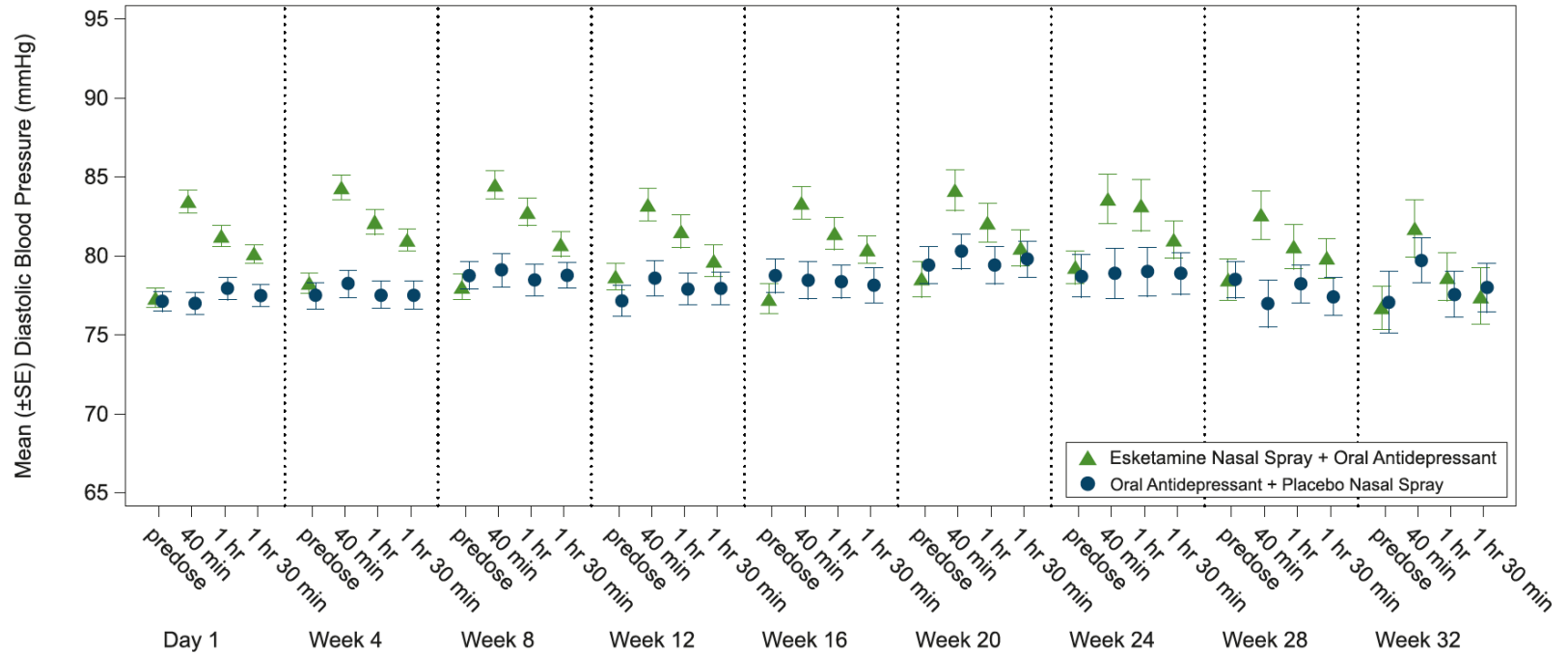
eFigure 3. Mean (\pm SE) Blood Pressure Over Time in the Maintenance Phase for Stable Remitters and Stable Responders

a. Systolic Blood Pressure



No. of Patients:	
Esketamine Nasal Spray + Oral Antidepressant	152 152 151 151 128 128 128 128 106 106 106 106 82 82 82 82 75 75 75 75 60 60 60 60 41 41 41 41 35 35 35 35 26 26 26 26
Oral Antidepressant + Placebo Nasal Spray	145 145 145 145 100 100 100 100 75 75 75 75 63 63 63 63 47 47 47 47 37 37 37 37 29 29 29 29 25 25 25 25 14 14 14 14

b. Diastolic Blood Pressure

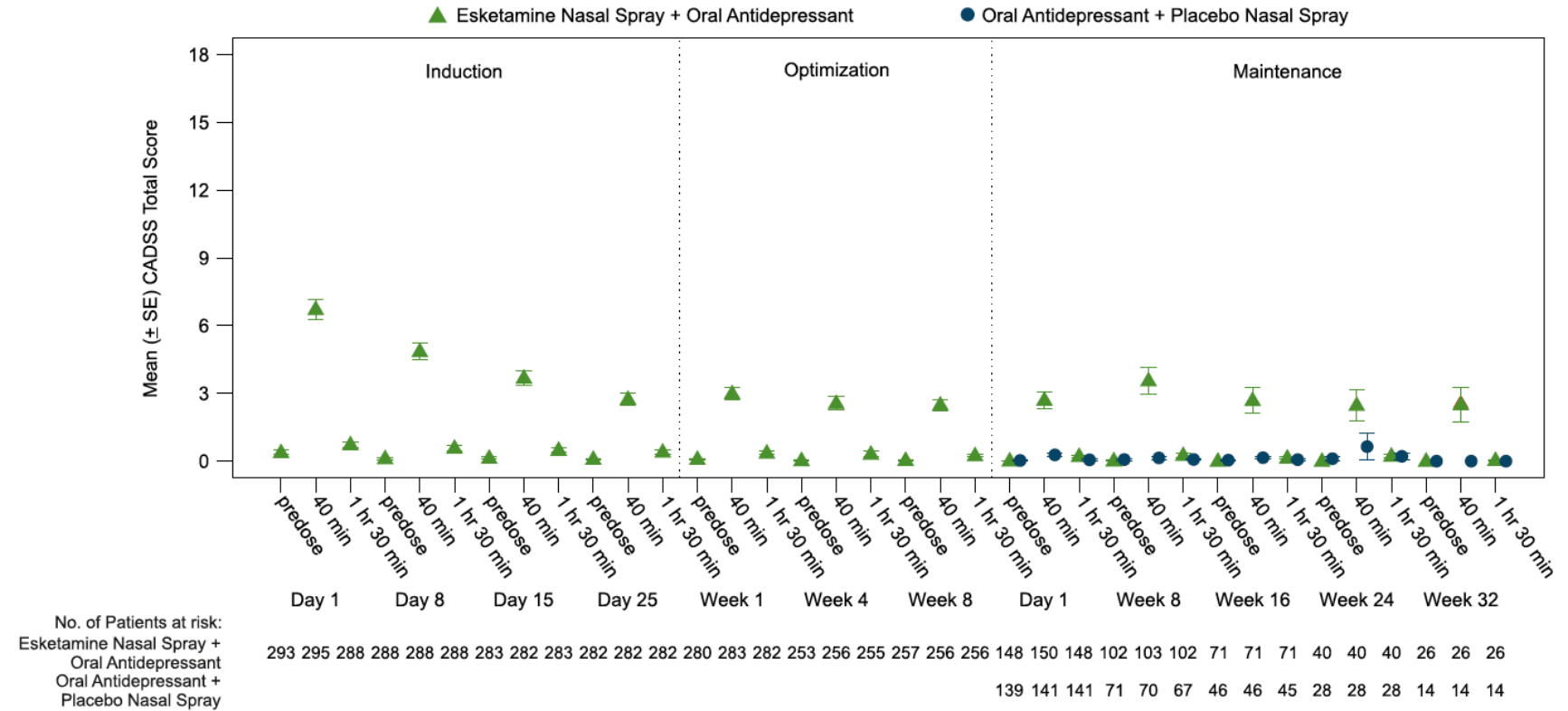


No. of Patients:

Esketamine Nasal Spray + Oral Antidepressant	152	152	151	151	128	128	128	128	106	106	106	106	82	82	82	82	75	75	75	75	60	60	60	60	41	41	41	41	35	35	35	35	26	26	26	26
Oral Antidepressant + Placebo Nasal Spray	145	145	145	145	100	100	100	100	75	75	75	75	63	63	63	63	47	47	47	47	37	37	37	37	29	29	29	29	25	25	25	25	14	14	14	14

SE = standard error

eFigure 4. Mean (\pm SE) CADSS Total Score Over Time During the Induction, Optimization, and Maintenance Phases for Stable Remitters and Stable Responders



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