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Supplementary Material

Article Title: Esketamine Nasal Spray for Rapid Reduction of Major Depressive Disorder Symptoms in Patients Who Have Active Suicidal Ideation With Intent: Double-Blind, Randomized Study (ASPIRE I)

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List of Supplementary Material for the article

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

BULGARIA
Ethics Committee for Clinical Trials

ESTONIA
Tallinn Medical Research Ethics Committee

GERMANY
Ethikkommission der Medizinischen Fakultät der Albert-Ludwigs-Universität Freiburg
Ethik-Kommission des Fachbereichs Medizin der Johann Wolfgang Goethe-Universität
Landesamt für Gesundheit Und Soziales Berlin Geschäftsstelle der Ethik-Kommission des Landes Berlin

HUNGARY
Central Ethics Committee Medical Research Council Ethics Committee for Clinical Pharmacology

KOREA
Chonnam National University Hospital IRB
Samsung Medical Center IRB
Kyung Hee University Medical Center IRB
Seoul National University Hospital IRB
Korea University Ansan Hospital IRB

MALAYSIA
Medical Research and Ethics Committee, Kompleks Institut Kesihatan Negara
Medical Research Ethics Committee, University Malaya Medical Centre

SOUTH AFRICA
Pharma Ethics

SPAIN
CEIC Hospital Universitari Vall d Hebron

TAIWAN
Institutional Review Board of Tri-Service General Hospital
Chung Shan Medical University Hospital IRB
Taipei Medical University Joint Institutional Review Board
Institutional Review Board, Taipei Veterans General Hospital

UNITED STATES
New York State Psychiatric Institutional Review Board (New York, NY)

Office of Research Integrity (Charleston, SC)
Rush University Medical Center Institutional Review Board (Chicago, IL)
Sterling Institutional Review Board (Atlanta, GA)
Univeristy of Louisville, Medical Center Institutional Review Board (Louisville, KY)
University at Buffalo Institutional Review Board (Buffalo, NY)
UT Southwestern Medical Center Institutional Review Board (Dallas, TX)
Western Institutional Review Board (Puyallup, WA)

Appendix 2. Patient Inclusion and Exclusion Criteria

Screening for eligible subjects should be performed within 48 hours prior to the first administration of intranasal study drug (if possible, screening should occur within 24 hours prior to the first administration of intranasal study drug).

Inclusion Criteria

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

1. Subject must be a man or woman, 18 to 64 years of age, inclusive.

2. Subject must meet Diagnostic and Statistical Manual of Mental Disorders (5th edition) (DSM-5) diagnostic criteria for MDD, without psychotic features, based upon clinical assessment and confirmed by the MINI.

3. Subjects must have current suicidal ideation with intent, confirmed by a "Yes" response to Question B3 [Think (even momentarily) about harming or of hurting or of injuring yourself: with at least some intent or awareness that you might die as a result; or think about suicide (ie, about killing yourself)?] AND Question B10 [Intend to act on thoughts of killing yourself?] obtained from the MINI. Note: the response to B3 must refer to the present, whereas the response to B10 may reflect the past 24 hours. If the screening period is longer than 24 hours, assessment of B3 and B10 of MINI must be repeated prior to randomization to confirm eligibility.

4. In the physician's opinion, acute psychiatric hospitalization is clinically warranted due to subject's imminent risk of suicide.

5. Subject has a MADRS total score of >28 predose on Day 1.

6. As part of standard of care treatment, subject agrees to be hospitalized voluntarily for a recommended period of 5 days after randomization (may be shorter or longer if clinically warranted in the investigator's opinion) and take prescribed noninvestigational antidepressant therapy(ies) for at least the duration of the double-blind treatment phase (Day 25).

7. Subject is comfortable with self-administration of intranasal medication and able to follow instructions provided.

8. Subject must be medically stable on the basis of physical examination, medical history, vital signs, and 12-lead ECG performed at screening. If there are abnormalities, the subject may be included only if the investigator judges the abnormalities to be not clinically significant. This determination must be recorded in the subject's source documents and initialed by the investigator.

Note: Subjects recovering from a recent suicide attempt may be eligible provided they are medically stable.

9. Subject must be medically stable on the basis of clinical laboratory tests performed by the local laboratory at screening. 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. This determination must be recorded in the subject's source documents and initialed by the investigator.
   - Incidental exclusionary laboratory values ("incidental" refers to duplicate results from a separate blood sample analyzed at the central laboratory that become available after the subject has satisfied the inclusion and exclusion criteria based on the local laboratory values) will be handled on a case-by-case basis to determine if the subject should be withdrawn from the study.

10. Contraceptive use by men or women should be consistent with local regulation regarding the use of contraceptive methods for subject participating in clinical studies.

    Before randomization, a woman must be either:

    a. Not of childbearing potential defined as:
    - postmenopausal (>45 years of age with amenorrhea for at least 12 months), permanently sterilized (eg, bilateral tubal occlusion/ligation procedures, hysterectomy, bilateral salpingectomy, bilateral oophorectomy); or otherwise be incapable of pregnancy

    b. Of childbearing potential and
    - practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly)
      Examples of highly effective contraceptives include
      - user-independent methods:
        implantable progestogen-only hormone contraception associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); vasectomized partner; sexual abstinence (sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)
      - user-dependent methods:
        combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, and transdermal; progestogen-only hormone contraception associated with inhibition of ovulation: oral and injectable

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

- 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.

11. A woman of childbearing potential must have a negative urine pregnancy test at screening.

12. During the study (ie, from Day 1 of the double-blind phase) and for a minimum of 1 spermatogenesis cycle (defined as approximately 90 days) after receiving the last dose of study drug, 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.

13. 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.

Note: Subjects with acute alcohol intoxication should not be screened (but can be screened once sober).

15. Each subject must sign a separate informed consent form if he or she agrees to provide an optional DNA sample for research (where local regulations permit). Refusal to give consent for the optional DNA research sample does not exclude a subject from participation in the study.

Exclusion Criteria

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

1. Subject has a current DSM-5 diagnosis of bipolar (or related disorders), antisocial personality disorder, or obsessive compulsive disorder.

2. Subject currently meets DSM-5 criteria for borderline personality disorder.

- Subjects not meeting full DSM-5 criteria for borderline personality disorder but exhibiting recurrent suicidal gestures, threats, or self-mutilating behaviors should also be excluded.

3. Subject has a current clinical diagnosis of autism, dementia, or intellectual disability.

4. Subject has a current or prior DSM-5 diagnosis of a psychotic disorder, or MDD with psychotic features.

5. Subject meets the DSM-5 severity criteria for moderate or severe substance or alcohol use disorder (except for nicotine or caffeine) within the 6 months before screening.
   - 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 any of the following conditions:
   - a history or current signs and symptoms of liver or renal insufficiency
   - clinically significant cardiac (including unstable coronary artery disease and congestive heart failure, tachyarrhythmias and recent myocardial infarction) or vascular, pulmonary, gastrointestinal, endocrine (including uncontrolled hyperthyroidism), neurologic (including current or past history of seizures except uncomplicated childhood febrile seizures with no sequelae), hematologic, rheumatologic, or metabolic (including severe dehydration/hypovolemia) disease.

7. Subject has uncontrolled hypertension (systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg) despite diet, exercise or a stable dose of antihypertensive treatment for at least 2 weeks at screening; or any past history of hypertensive crisis.
   - Subjects with conditions in which the elevation of blood pressure could be a serious risk (including unstable heart failure, severe cardiovascular disease, recent cerebral injury, increased intracranial pressure / intracranial mass lesion, intracranial bleeding or acute stroke, untreated glaucoma or perforating eye injury) are excluded.
   - An abnormal blood pressure value at screening can be repeated once after 5 minutes of relaxation for subject eligibility. On Day 1 of the double-blind phase prior to randomization, a supine or semi-supine systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg is exclusionary.
8. Subject has a positive urine test result(s) for phencyclidine (PCP), cocaine, or amphetamines (inclusive of amphetamine, methamphetamine [mAMP], and 3, 4-methylenedioxy-methamphetamine [MDMA]) at screening.
   - Subjects who have a positive test due to the appropriate use of prescribed opiates, benzodiazepines, or barbiturates may be eligible for study participation per clinician judgment. In addition, subjects who have a positive test for opiates, benzodiazepines, or barbiturates used without a prescription, may be considered eligible per clinician judgment and in consultation with the sponsor's medical monitor. Subjects known to be using heroin should be excluded from the study.

- Subjects who have a positive test due to opiates, benzodiazepines, or barbiturates taken in a suicide attempt (eg, overdose) may be eligible for study participation per clinician judgment and in consultation with the sponsor's medical monitor.
- Subjects, who have a positive test result at screening due to prescribed psychostimulants (eg. amphetamine, methylphenidate) that are permitted during the study in accordance with Attachment 1, are eligible for study participation.

9. Subject has a history of malignancy within 5 years before screening (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 to have minimal risk of recurrence).

10. 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.

11. Subject has known allergies, hypersensitivity, intolerance or contraindications to esketamine or ketamine or its excipients (refer to Investigator's Brochure for esketamine, Summary of Product Characteristics, US prescribing information).

12. Subject has taken any disallowed therapy(ies) as noted in Section 8, Prestudy and Concomitant Therapy, and Attachment 1.

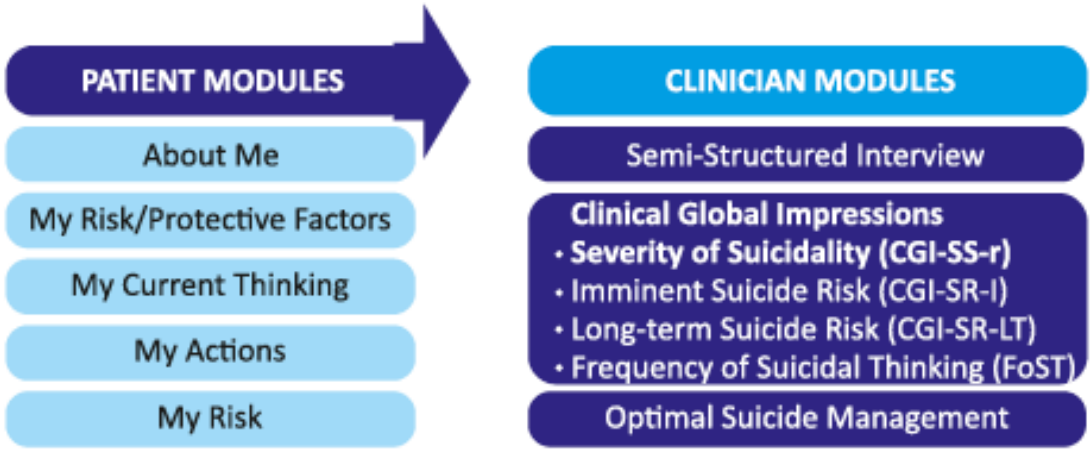
13. Subject has received an investigational drug (including esketamine, ketamine, or investigational vaccines) or used an invasive investigational medical device within 60 days before the planned first dose of study drug or is currently enrolled in an investigational study or was previously enrolled in this study or the Sponsor's other studies in this population, 54135419SUI3002 and ESKETINSUI2001.

14. Subject is a woman who is pregnant, breast-feeding, or planning to become pregnant while enrolled in this study or within 3 months after the last dose of study drug.

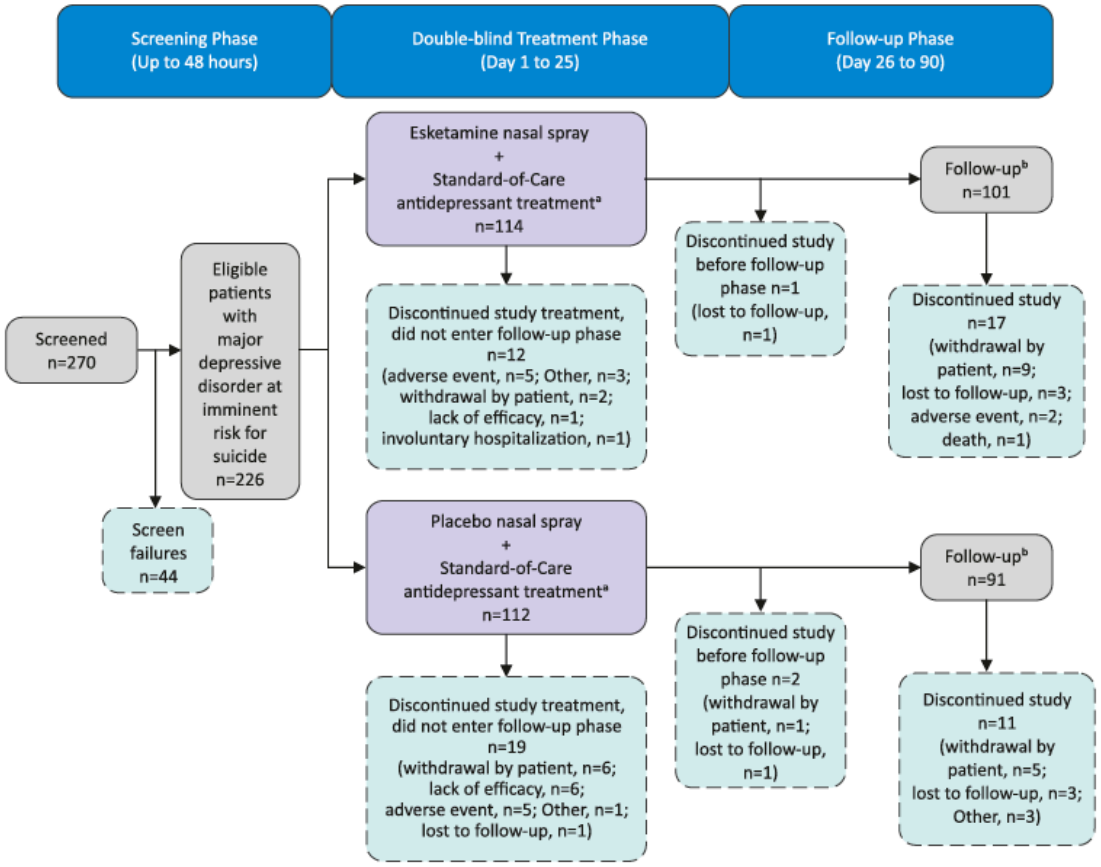
15. Subject has any situation or condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the wellbeing) or that could prevent, limit, or confound the protocol-specified assessments.

16. 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.

Supplementary Figure 1. **Suicide Ideation and Behavior Assessment Tool (SIBAT) Structure**

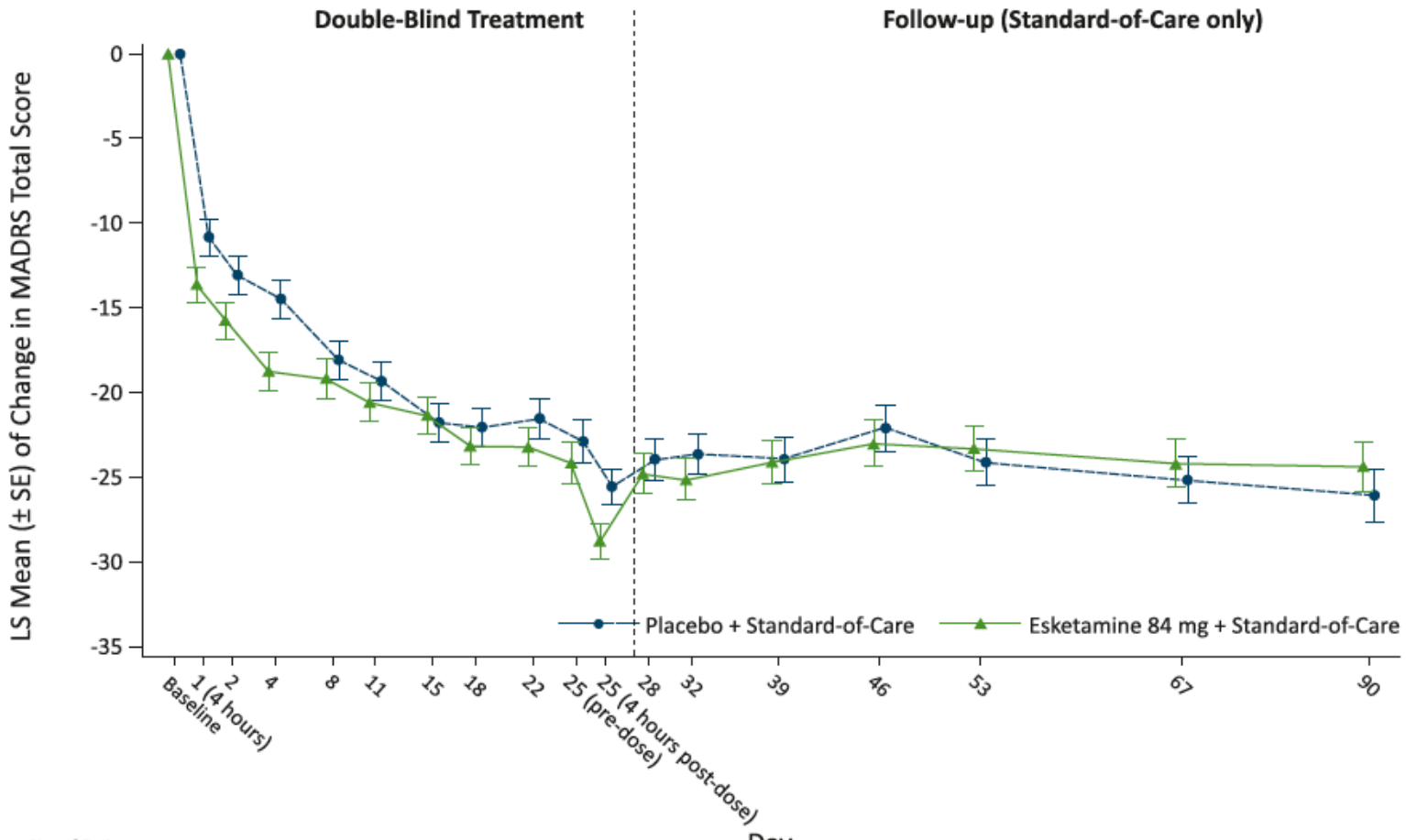


Supplementary Figure 2. Study Design and Disposition of Participants



[a]Standard antidepressant treatment was initiated or optimized on day 1.
[b]Patients who completed the double-blind phase and either entered the follow-up phase or provided adverse event data after the double-blind treatment phase.
Note: Two patients were not included in the efficacy analysis dataset due to discontinuing prior to receiving study drug or not providing postbaseline efficacy data.

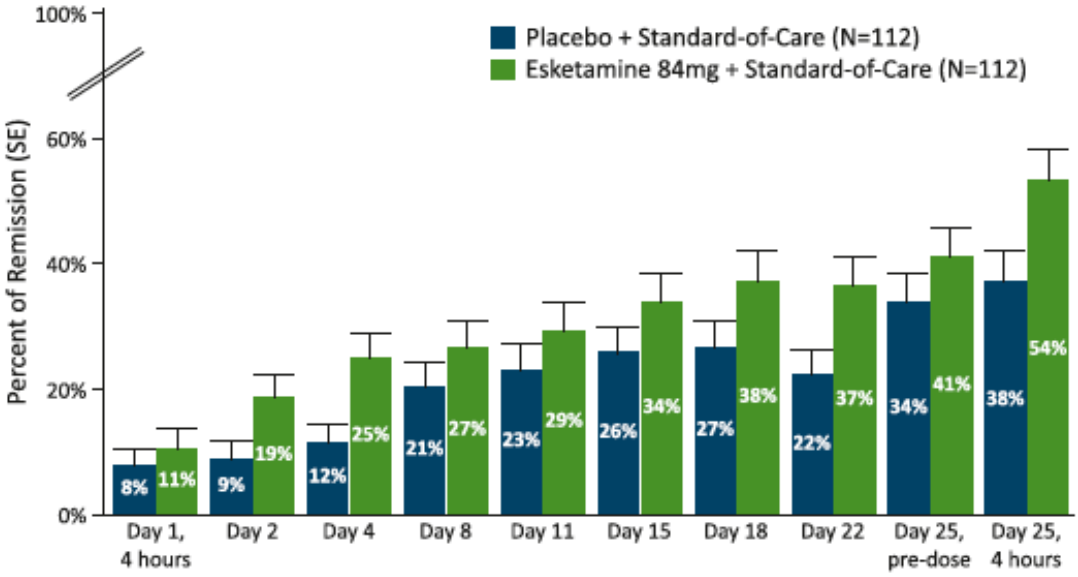
Supplementary Figure 3. Least-Square Mean Changes (±SE) from Baseline for MADRS Total Score During the Follow-up Phase (MMRM; Observed Cases)



No. of Patients																		
Placebo + Standard-of-Care	91	91	90	91	91	91	88	87	89	90	86	82	90	87	79	83	78	79
Esketamine 84 mg + Standard-of-Care	100	99	100	100	97	94	99	97	99	95	93	83	95	93	89	88	87	83

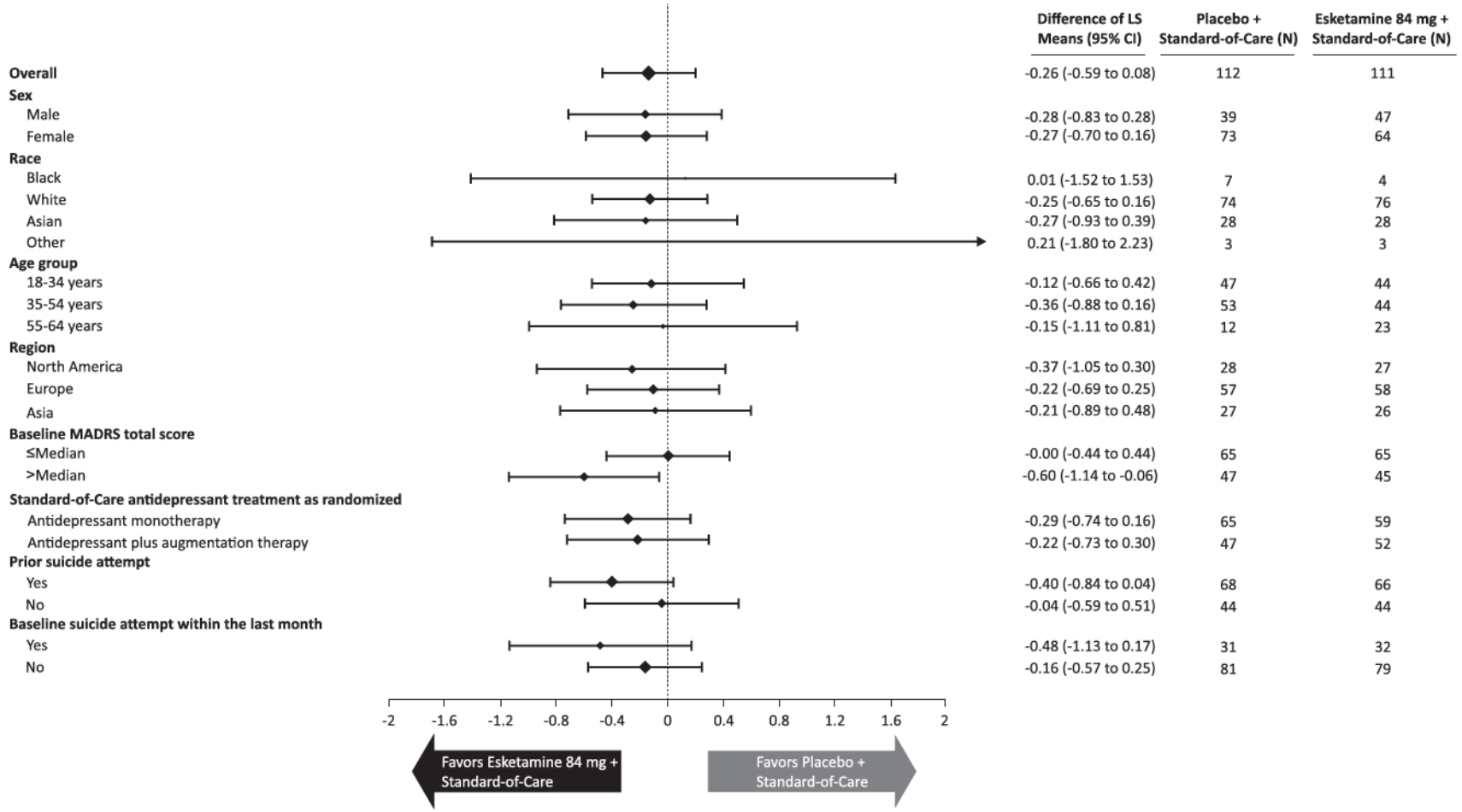
MADRS = Montgomery-Asberg Depression Rating Scale; MMRM = mixed-effects model using repeated measures; SE = standard error
Note: Negative change in score indicates improvement.

Supplementary Figure 4. MADRS Remission Rate During the Double-Blind Treatment Phase



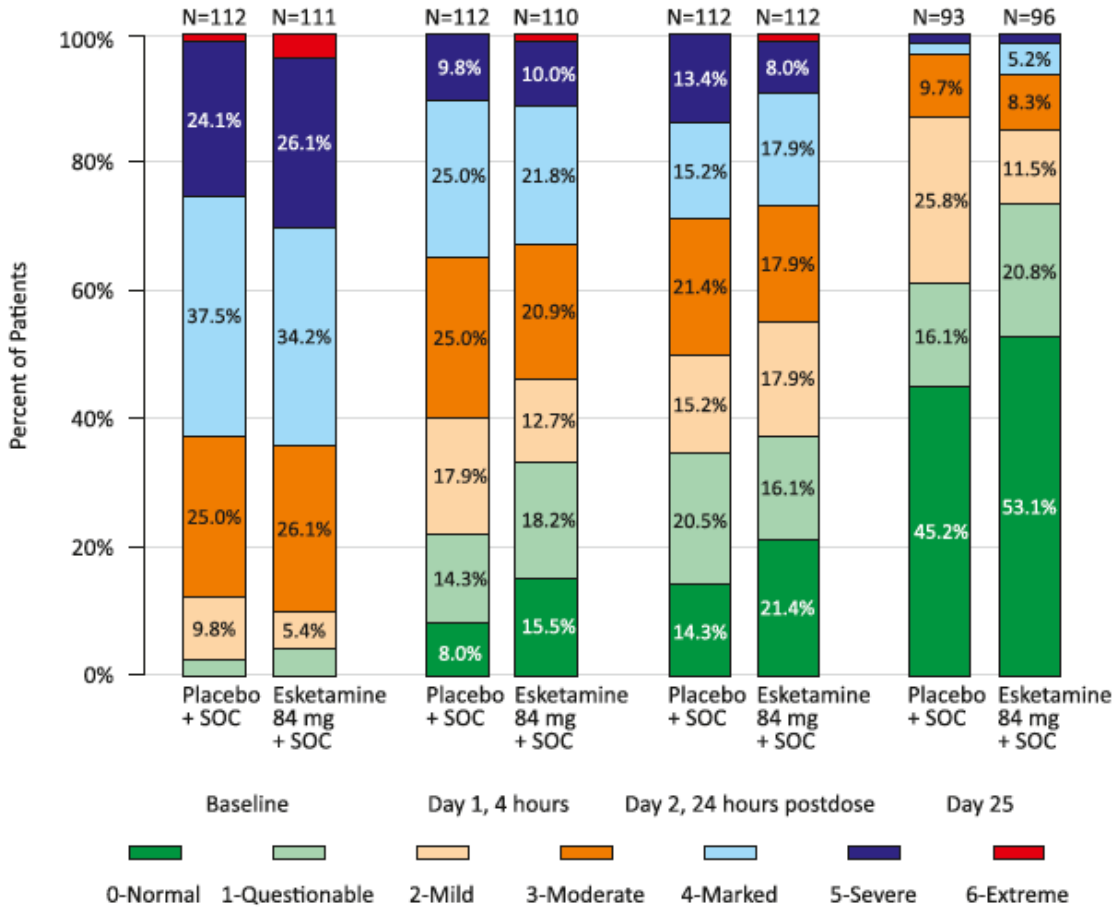
MADRS = Montgomery-Asberg Depression Rating Scale; MMRM = mixed-effects model using repeated measures
Remission defind as MADRS total score ≤12.
Notes: Negative change in score indicates improvement.
The remission rate during the follow-up phase on day 90 exceeded 45% in each treatment group.

Supplementary Figure 5. Forest Plot for CGI-SS-r Score: Least Squares Mean Treatment Difference of Change from Baseline (95% CI) to 24 Hours Post-First Dose by Subgroup (ANCOVA LOCF)



ANCOVA = analysis of covariance, CGI-SS-r = Clinical Global Impression – Severity of Suicidality – Revised, CI = confidence interval, LOCF = last observation carried forward, LS = least square

Supplementary Figure 6. Frequency Distribution of CGI-SS-r Score at Baseline, 4 and 24 Hours Post First Dose, and Day 25 (Observed Cases)



CGI-SS-r = Clinical Global Impression – Severity of Suicidality – Revised; SOC = Standard-of-Care

Supplementary Table 1. Summary of Most Frequently Reported[a] Adverse Events During the Follow-up Phase

	Number (%) of Patients	
	Placebo + Standard-of-Care[b] N = 91	Esketamine 84 mg + Standard-of-Care[b] N = 101
Depression	3 (3.3)	11 (10.9)
Headache	7 (7.7)	6 (5.9)
Depression suicidal	3 (3.3)	5 (5.0)
Suicidal ideation	5 (5.5)	5 (5.0)
Anxiety	9 (9.9)	3 (3.0)

[a] Most frequently reported is defined as ≥5% of patients in either treatment group. Events are presented in descending order in the esketamine group.

[b] This is the treatment assignment during the double-blind phase. During the follow-up phase, patients were only treated by standard-of-care antidepressant therapy.

Supplementary Table 2. Summary of Treatment-Emergent Serious Adverse Events[a] During the Double-Blind Phase

	Number (%) of Patients	
	Placebo + Standard-of-Care N = 112	Esketamine 84 mg + Standard-of-Care N = 113
Patients with ≥1 serious adverse events	6 (5.4)	4 (3.5)
Depression suicidal	1 (0.9)	2 (1.8)
Diabetic ketoacidosis	0	1 (0.9)
Depression	1 (0.9)	1 (0.9)
Suicide attempt	1 (0.9)	1 (0.9)
Suicidal ideation	2 (1.8)	0
Aggression	1 (0.9)	0
Hypertranaminasemia	1 (0.9)	0

[a] Events are presented in descending order in the esketamine group.

Supplementary Table 3. Summary of Serious Adverse Events[a] During the Follow-up Phase

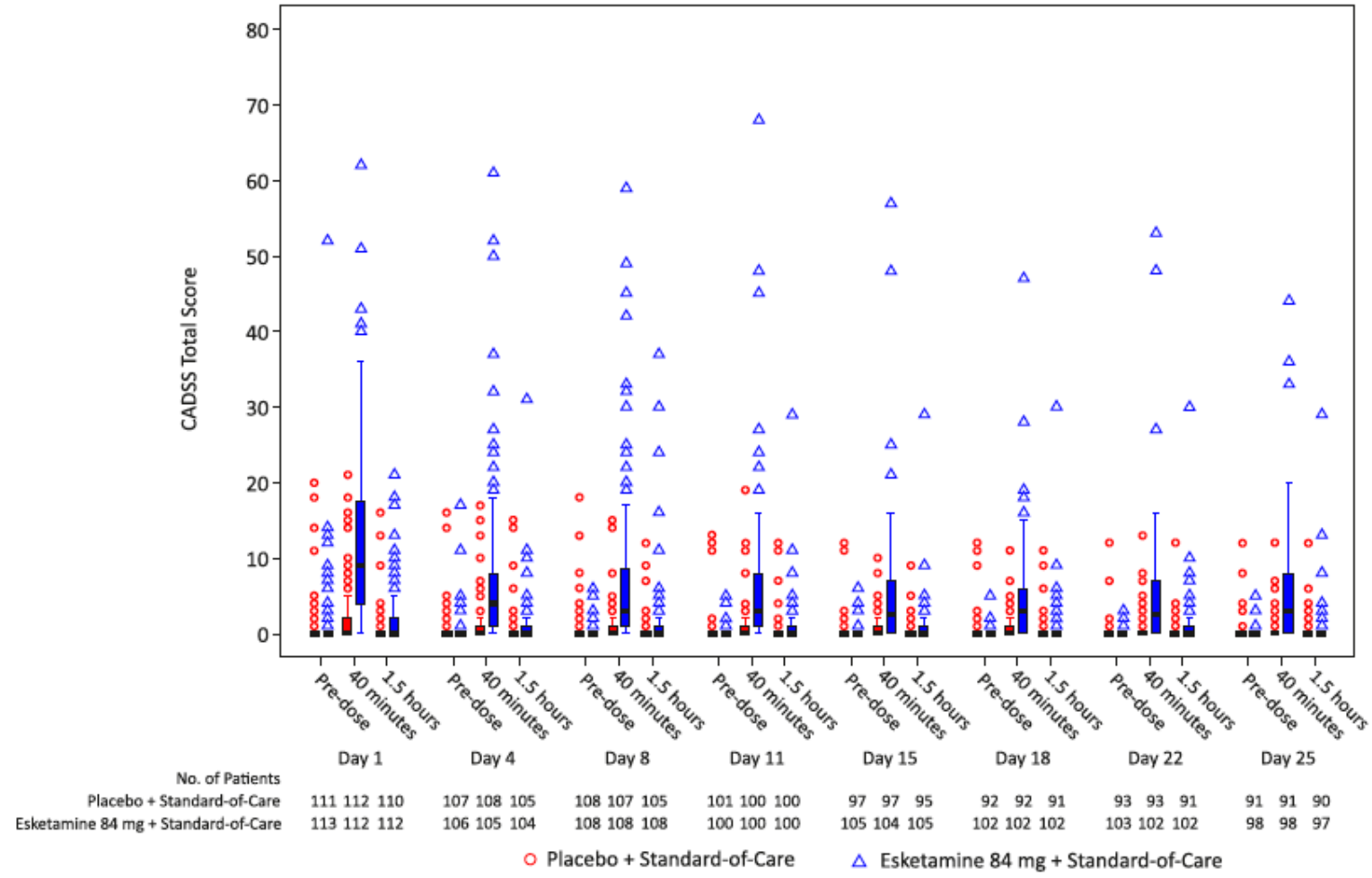
	Number (%) of Patients	
	Placebo + Standard-of-Care[b] N = 91	Esketamine 84 mg + Standard-of-Care[b] N = 101
Patients with ≥1 serious adverse events	10 (11.0)	13 (12.9)
Depression suicidal	3 (3.3)	5 (5.0)
Suicide attempt	2 (2.2)	3 (3.0)
Depression	1 (1.1)	2 (2.0)
Suicidal ideation	3 (3.3)	2 (2.0)
Completed suicide	0	1 (1.0)
Major depression	0	1 (1.0)
Rhabdomyolysis	1 (1.1)	0

[a] Events are presented in descending order in the esketamine group.
[b] This is the treatment assignment during the double-blind phase. During the follow-up phase, patients were only treated by standard-of-care antidepressant therapy.

Appendix 3. Adverse Events Leading to Discontinuation of Study Drug

Ten patients discontinued intranasal study drug prematurely due to an adverse event: 5 patients (4.4%) in the esketamine+standard-of-care group (due to: dizziness; hallucination visual; blood pressure increased and dissociation; headache and somnolence; confusional state, hypoesthesia, pharyngeal hypoesthesia, and sedation) and 5 patients (4.5%) in the placebo+standard-of-care group (due to: aggression; atrioventricular block first-degree; hypertransaminasemia; blood pressure diastolic increased; suicidal ideation).

Supplementary Figure 7. CADSS Total Score Box Plot Over Time During Double-Blind Treatment



CADSS = Clinician-administered Dissociative States Scale
Note: CADSS total score ranges from 0 to 92; a higher score indicates a more severe condition.
Any CADSS items scored zero at 40 minutes postdose did not need to be repeated at 1.5 hours postdose. The zero scores at 40 minutes were carried forward to 1.5 hours.
The lower boundary of the box is the 25th percentile, the higher boundary is the 75th percentile, and the solid line within the box marks the median. Whiskers below and above the box indicate the 1.5*interquartile range below the lower boundary (or the smallest value) and 1.5*interquartile range above the higher boundary (or the largest value). Outlying data points are extreme values

Supplementary Figure 8. Mean (±SE) Systolic and Diastolic Blood Pressure Over Time During Double-Blind Treatment