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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ABSTRACT

Objective: To compare esketamine to placebo, each in addition to standard-of-care treatment, for rapidly reducing major depressive disorder symptoms, including suicidal ideation.

Methods: This phase 3, double-blind, multicenter study (ASPIRE I), conducted between June 2017 and December 2018, enrolled 226 adults having major depressive disorder based on *Diagnostic and Statistical Manual of Mental Disorders* fifth edition (*DSM-5*) criteria, active suicidal ideation with intent, and need for psychiatric hospitalization. Patients were randomized 1:1 to esketamine 84 mg or placebo nasal spray twice-weekly for 4 weeks, each with comprehensive standard-of-care treatment (initial psychiatric hospitalization and newly initiated or optimized oral antidepressant[s] therapy). Change from baseline to 24 hours post–first dose in Montgomery-Asberg Depression Rating Scale (MADRS) total score (primary endpoint) was analyzed using analysis of covariance (ANCOVA), and change in Clinical Global Impression of Severity of Suicidality Revised version (CGI-SS-r; key secondary endpoint) score was analyzed using ANCOVA on ranks with treatment difference estimated using the Hodges-Lehmann estimate.

Results: Greater improvement in MADRS total score was observed with esketamine + standard-of-care versus placebo + standard-of-care at 24 hours (least-squares mean difference [SE]: −3.8 [1.39]; 95% CI, −6.56 to −1.09; 2-sided $P = .006$), as well as at earlier (4 hours) and later time points during 4-week double-blind treatment. The difference between groups in the severity of suicidality was not statistically significant (median of treatment difference [95% CI]: 0.0 [−1.00 to 0.00]; 2-sided $P = .107$). The most common adverse events among esketamine-treated patients were dizziness, dissociation, headache, nausea, and somnolence.

Conclusions: These findings demonstrate rapid and robust efficacy of esketamine nasal spray in reducing depressive symptoms in severely ill patients with major depressive disorder who have active suicidal ideation with intent.

Trial Registration: ClinicalTrials.gov identifier: NCT03039192

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Depression is the leading cause of disability worldwide and a major contributor to the overall global burden of disease.[1] Major depressive disorder (MDD) is the psychiatric diagnosis most commonly associated with suicide.[2,3] The reported prevalence of suicidal ideation in adult patients with MDD is as high as 60%, and the lifetime incidence of attempted suicide in this population ranges between 10% and 20%.[4,5] Further, the lifetime risk of completed suicide has been estimated to be 3.4% in this population.[6]

Suicidal ideation is a major risk factor for suicide in patients with depression.[7,8] The time between the onset of suicidal ideation and suicide attempt is often very short,[9] highlighting the need for immediate intervention. Patients with MDD who have active suicidal ideation with intent constitute a psychiatric emergency. These patients are often hospitalized to protect them from self-harm, although the benefits of hospitalization are often temporary. Moreover, while standard antidepressants effectively treat depressive symptomatology, including suicidal ideation,[10] they require 4–6 weeks to exert their full effect,[11,12] limiting their utility in crisis situations. Currently, there is no approved medication for emergency treatment of patients with depression who have active suicidal ideation with intent.[12,13]

Esketamine nasal spray was recently approved in the United States and European Union for treating treatment-resistant depression.[14,15] Esketamine (the *S*-enantiomer of ketamine), an *N*-methyl-D-aspartate (NMDA) receptor antagonist, is thought to confer antidepressant effects by transiently influencing glutamate transmission, increasing neurotrophic factor release, and stimulating synaptogenesis[16] through a primary mechanism that is distinct from that of conventional monoaminergic antidepressants.

Four small trials[17–20] including patients with MDD suggested that ketamine, administered intravenously, may rapidly decrease suicidal ideation. Further, in a phase 2 double-blind,

Clinical Points

- Currently, there is no approved medication for emergency treatment of patients with depression who have active suicidal ideation with intent.
- Esketamine nasal spray rapidly reduced depressive symptoms in adult patients with major depressive disorder who had moderate to severe depression and suicidal ideation with intent.

proof-of-concept study,[21] our research group reported that esketamine nasal spray compared with placebo nasal spray, given in addition to comprehensive standard-of-care treatment, resulted in statistically significant and clinically meaningful reduction in depressive symptoms at 4 and 24 hours after the first dose among depressed patients at imminent risk for suicide. The first phase 3 program consisting of 2 identically designed, fully powered global studies (ASPIRE I and ASPIRE II) was undertaken to confirm the antidepressant efficacy of esketamine in this population. The results of ASPIRE I are reported herein.

METHODS

Ethical Practices

Independent Review Boards and Ethics Committees (see Supplementary Appendix 1) approved the study protocol and amendments. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, consistent with Good Clinical Practices and applicable regulatory requirements. All patients provided written informed consent before participation. The study is registered at https://clinicaltrials.gov/ct2/show/NCT03039192.

Study Population

The study enrolled adults (18–64 years) with a diagnosis of MDD without psychotic features according to *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition (*DSM-5*),[22] and confirmed by the Mini-International Neuropsychiatric Interview (MINI).[23] Candidates were screened shortly after presenting to an emergency department or inpatient psychiatric unit. Eligibility criteria required that patients respond affirmatively to MINI questions B3 ("Think about suicide [killing yourself]?") and B10 ("Intend to act on thoughts of killing yourself in the past 24 hours?") within 24 hours of randomization, be in clinical need of acute psychiatric hospitalization due to imminent suicide risk, and have a Montgomery-Asberg Depression Rating Scale (MADRS)[24] total score >28 predose on day 1. Patients must have voluntarily agreed to comprehensive standard-of-care treatment, including initial hospitalization and initiation or optimization of a non-investigational antidepressant(s) treatment for at least the duration of double-blind treatment.

Certain psychiatric comorbidities were exclusionary (eg, current *DSM-5* diagnosis of bipolar disorder, obsessive-compulsive disorder, antisocial personality disorder, borderline personality disorder), as were moderate-to-severe *DSM-5* substance or alcohol use disorder within 6 months prior to screening, current or prior *DSM-5* diagnosis of psychotic disorder, and positive urine test result(s) for phencyclidine, cocaine, or amphetamines. A complete list of inclusion and exclusion criteria is presented in Supplementary Appendix 2.

Study Design

This double-blind, randomized, placebo-controlled, multicenter study was conducted from June 2017 to December 2018 at 51 study sites in the United States, Europe, Asia, and South Africa.

The study consisted of a 24- to 48-hour screening period to assess patients' eligibility, followed by 4-week double-blind treatment (days 1–25) given in the context of comprehensive standard-of-care, and then 9-week posttreatment follow-up (days 26–90). Patients were initially hospitalized in a psychiatric unit for a recommended 5 days, with shorter or longer hospitalizations permitted if clinically warranted per local standard practice.

Eligible patients were randomized (1:1), based on a computer-generated randomization schedule, to 84 mg esketamine nasal spray (referred to as *esketamine* hereafter) or matching placebo nasal spray (referred to as *placebo* hereafter), administered twice weekly. Randomization was balanced using randomly permuted blocks and stratified by study center and type of standard-of-care antidepressant (ie, monotherapy or antidepressant plus augmentation therapy) determined by the investigator.

Study Drug and Standard-of-Care Antidepressant Therapy

Intranasal study drugs were provided in disposable nasal spray devices with identical appearance and packaging. Each device contained 200 µL of solution and delivered 2 sprays of either esketamine (total of 28 mg of esketamine base) or placebo. The placebo solution contained a bittering agent to simulate the taste of esketamine solution, and the same number of devices (3) were administered to all patients at all sessions.

Patients self-administered study drug, under the supervision of a site staff member, twice weekly for 4 weeks. After day 1, a single dose reduction of esketamine (or placebo) from 84 mg to 56 mg was permitted for intolerance, with the 56-mg dose continued thereafter.

Standard-of-care oral antidepressant(s) treatment (either monotherapy or antidepressant + augmentation therapy) was initiated or optimized at the time of randomization on day 1 by the investigator based on clinical judgment and practice guidelines. Augmenting agents could consist of a second antidepressant, an atypical antipsychotic, or a mood stabilizer.

Dose titration/adjustments of standard-of-care antidepressant(s) occurred during the first 2 weeks of double-blind treatment, after which doses were to remain

stable. During the follow-up phase, patients were treated with standard-of-care antidepressant(s) managed per clinical judgment.

Efficacy Assessments

Depressive symptom severity was assessed using the Structured Interview Guide for MADRS[24] on day 1 (predose and 4 hours postdose), day 2 (~24 hours postdose), all subsequent visits (predose), at 4 hours postdose on day 25 during the double-blind phase, and at all visits during the follow-up phase (twice-weekly through day 39, weekly through day 53, and every other week through day 90). For the 4-hour version of the MADRS, the Reduced Sleep item was not assessed, but the scores for the Reduced Sleep item recorded predose on the same day were carried forward and included in the total score.

Efficacy related to suicidal ideation and behavior was assessed using the Suicide Ideation and Behavior Assessment Tool (SIBAT; see Supplementary Figure 1), a computerized instrument,[25] on all visit days during the double-blind (predose; 4 hours postdose on day 1) and follow-up phases. The SIBAT contains both patient- and clinician-reported modules, which include assessments of Clinical Global Impression of Severity of Suicidality Revised version (CGI-SS-r; rated from 0 [normal, not at all suicidal] to 6 [among the most extremely suicidal patients]), Clinical Global Impression of Imminent Suicide Risk (CGI-SR-I), and, clinician-rated and patient-reported Frequency of Suicidal Thinking (FoST).

Safety Assessments

Adverse events were monitored throughout the study. Vital signs were assessed and the Clinician Administered Dissociative States Scale (CADSS)[26] and Modified Observer's Assessment of Alertness Sedation (MOAA/S)[27] were administered at all dosing visits. The SIBAT was also utilized as a safety outcome.

To maintain the study blind, efficacy and safety assessments were performed by different raters who were trained and certified.

Statistical Methods

All randomized patients who received at least 1 dose of double-blind study medication were included in the safety analysis set. The full efficacy analysis set included all patients in the safety analysis set who had both a baseline and ≥ 1 postbaseline evaluation with the MADRS or CGI-SS-r. The follow-up analysis set included all patients who completed the double-blind treatment phase and either entered the follow-up phase or provided adverse event data after the double-blind treatment phase.

Sample Size Determination

Sample size was calculated based on an effect size of 0.45 for the change in MADRS total score between esketamine and placebo, a 2-sided significance level of .050, and a dropout rate of 5% at 24 hours. Approximately 112 patients were to be randomized to each treatment group to achieve 90% power.

Efficacy Endpoints and Analyses

Statistical analysis tests were conducted at a 2-sided .050 significance level. A fixed sequence approach was applied to adjust for multiplicity and to control type I error for the primary and key secondary efficacy endpoints (ie, secondary efficacy endpoint was tested only after rejecting the null hypothesis for the primary endpoint).

The primary efficacy endpoint—change in MADRS total score from baseline (day 1, predose) to 24 hours post–first dose (day 2)—was analyzed using the analysis of covariance (ANCOVA) model with treatment (placebo or esketamine 84 mg), standard-of-care antidepressant as randomized (monotherapy or antidepressant + augmentation therapy), and analysis center as factors and baseline MADRS total score as a continuous covariate. Missing day 2 MADRS total score was carried forward from 4 hours for 1 patient. A mixed model for repeated measures (MMRM) was used to explore the course of treatment effect over time for the MADRS total score during the double-blind and follow-up phases.

The key secondary endpoint—change in CGI-SS-r score from baseline to 24 hours after the first dose—was analyzed using an ANCOVA model on the ranks of change with the same factors (noted in the previous paragraph) and unranked baseline score as a covariate. The median of treatment difference was estimated using the Hodges-Lehmann estimate.

Prespecified subgroup analyses (shown in Figure 1 and Supplementary Figure 5) were conducted according to an ANCOVA model for the primary endpoint and key secondary endpoint (using unranked data), respectively.

Data for patients in remission (MADRS score ≤ 12) over time were summarized, and estimates of the treatment difference in proportions and 95% confidence intervals (CIs) were provided. Differences in least-squares means and 95% CIs were provided for other suicidality indices (CGI-SR-I, clinician- and patient-rated FoST, MADRS suicide item) based on ANCOVA modeling similar to that described for the primary analysis.

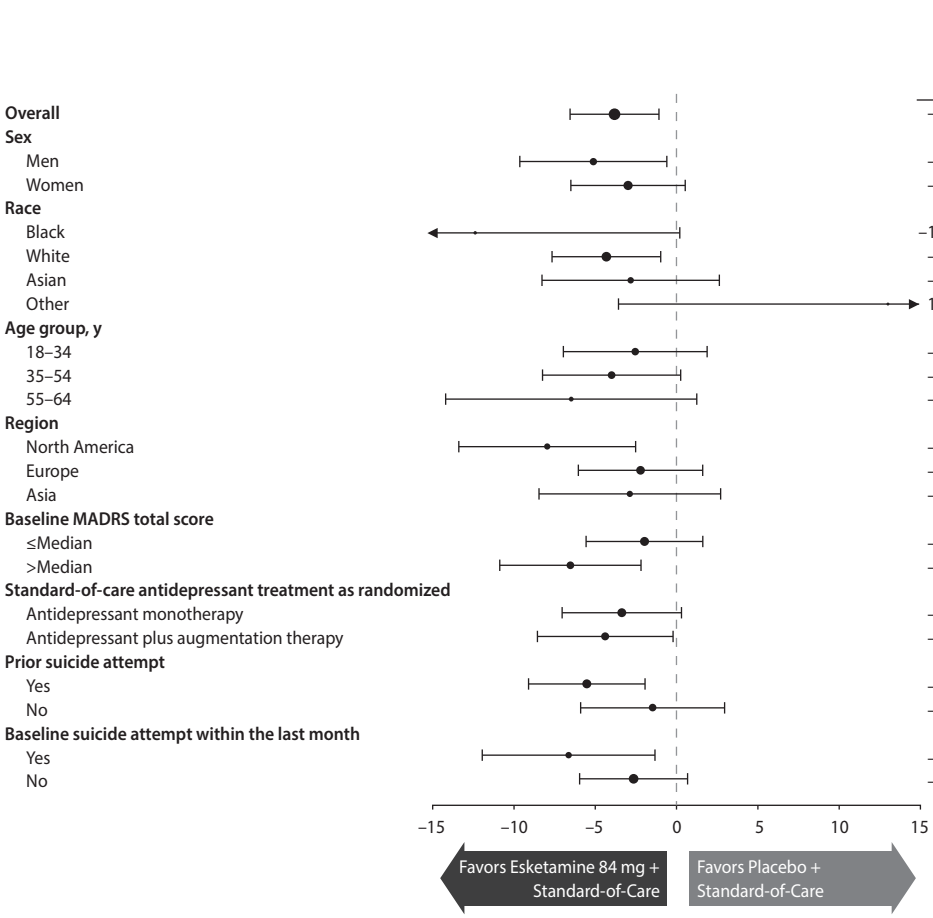
Frequency distributions or descriptive statistics were provided for adverse events, vital signs, and scores for clinician-reported outcomes (MOAA/S, CADSS).

RESULTS

Patients and Treatment

A total of 226 patients were randomized (114 and 112 to esketamine + standard-of-care and placebo + standard-of-care, respectively) (Supplementary Figure 2). Of the patients randomized to esketamine + standard-of-care, 1 was excluded from the safety analysis set and the full efficacy analysis set because the patient did not receive any dose of study drug. Another patient randomized to esketamine + standard-of-care was excluded from the full

Figure 1. Least-Squares Mean (95% CI) Treatment Difference of Change in MADRS Total Score From Baseline to 24 Hours Post–First Dose by Subgroup[a]



[a]Change in MADRS total score was analyzed using ANCOVA with LOCF. Negative change in score indicates improvement. Patients were hospitalized at the time of the primary endpoint; therefore, missing data were infrequent. Only 1 patient (in the placebo + standard-of-care group) did not have the day 2 MADRS total score; the MADRS total score was carried forward from 4 hours after the first dose (ie, LOCF).
[b]One patient in the esketamine 84 mg + standard-of-care group had missing MADRS data at baseline.
Abbreviations: ANCOVA = analysis of covariance, LOCF = last observation carried forward, LS = least squares, MADRS = Montgomery-Asberg Depression Rating Scale.

efficacy analysis set because the patient discontinued after the first dose of study agent on day 1 and did not provide any efficacy data after baseline (day 1, predose). Most randomized patients (esketamine + standard-of-care: 102/114 [89.5%]; placebo + standard-of-care: 93/112 [83.0%]) completed the double-blind treatment phase; 192 entered the follow-up phase, with 164 completing the day 90 follow-up visit.

The treatment groups were similar with respect to demographic and baseline clinical characteristics (Table 1), standard-of-care antidepressant use, and concomitant use of benzodiazepines. At baseline, mean MADRS total score was 41.1. The majority (60.1%) of patients reported a prior suicide attempt, 28.1% within the last month. The investigator rated most patients (88.8%) to be moderately to extremely suicidal, as measured by the CGI-SS-r. The most frequently reported standard-of-care antidepressant therapies were venlafaxine (24.9%), escitalopram (16.0%), duloxetine (15.6%), mirtazapine (15.6%), and quetiapine (14.2%). Approximately three-fourths of patients in the safety analysis dataset received ≥ 1 concomitant benzodiazepine during the double-blind treatment phase.

Efficacy Results

Symptoms of depression. In analysis of the primary endpoint, MADRS total score decreased (improved) from baseline to 24 hours after the first dose (day 2) in both the esketamine + standard-of-care (mean [SD]: −16.4 [11.95]) and placebo + standard-of-care groups (−12.8 [10.73]), with significantly greater improvement with esketamine (least-squares mean difference [SE]: −3.8 [1.39]; 95% CI, −6.56 to −1.09; 2-sided $P = .006$). The mean between-group difference [95% CI] in MADRS total score at 24 hours favored esketamine in most subgroups (Figure 1), notably so among patients with prior suicide attempt (−5.53 [−9.11 to −1.95]) and patients with more severe depressive symptoms (ie, MADRS total score > median) (−6.53 [−10.88 to −2.18]).

Table 1. Demographic and Baseline Characteristics (Full Efficacy Analysis Set)[a]

Parameter	Placebo + Standard-of-Care (n = 112)	Esketamine 84 mg + Standard-of-Care (n = 112)	Overall Sample (n = 224)
Age, mean (SD), y	37.9 (12.54)	40.8 (13.17)	39.3 (12.91)
Sex			
Female	73 (65.2)	65 (58.0)	138 (61.6)
Male	39 (34.8)	47 (42.0)	86 (38.4)
Race			
White	74 (66.1)	77 (68.8)	151 (67.4)
Asian	28 (25.0)	28 (25.0)	56 (25.0)
Black or African American	7 (6.3)	4 (3.6)	11 (4.9)
Other	3 (2.7)	3 (2.7)	6 (2.7)
MADRS total score,[b] mean (SD)	41.0 (6.29)	41.3 (5.87)	41.1 (6.07)
CGI-SS-r category,[c] n/total n[d] (%)			
Normal, not at all suicidal	0	0	0
Questionably suicidal	3/112 (2.7)	5/111 (4.5)	8/223 (3.6)
Mildly suicidal	11/112 (9.8)	6/111 (5.4)	17/223 (7.6)
Moderately suicidal	28/112 (25.0)	29/111 (26.1)	57/223 (25.6)
Markedly suicidal	42/112 (37.5)	38/111 (34.2)	80/223 (35.9)
Severely suicidal	27/112 (24.1)	29/111 (26.1)	56/223 (25.1)
Among the most extremely suicidal patients	1/112 (0.9)	4/111 (3.6)	5/223 (2.2)
Prior suicide attempt[e]			
Yes	68 (60.7)	66 (59.5)	134 (60.1)
No	44 (39.3)	45 (40.5)	89 (39.9)
Suicide attempt in the last month			
Yes	31 (27.7)	32 (28.6)	63 (28.1)
No	81 (72.3)	80 (71.4)	161 (71.9)
Standard-of-care antidepressant as randomized			
Antidepressant monotherapy	65 (58.0)	59 (52.7)	124 (55.4)
Antidepressant plus augmentation therapy[f]	47 (42.0)	53 (47.3)	100 (44.6)

[a]Values are shown as n (%) unless otherwise noted.
[b]One patient in the esketamine 84 mg + standard-of-care group had missing MADRS data at baseline.
[c]CGI-SS-r score ranges from 0 to 6; a higher score indicates a more severe condition. Scores are based on answers to the following question: "Considering your total clinical experience with suicidal patients and all information now available to you, how suicidal is this patient at this time?"
[d]One patient in the esketamine 84 mg + standard-of-care group had missing CGI-SS-r data at baseline.
[e]Prior suicide attempt data came from the Suicide Ideation and Behavior Assessment Tool (SIBAT). One patient in the esketamine 84 mg + standard-of-care group had missing SIBAT data at baseline.
[f]Patient received ≥ 2 medications for the treatment of depression.
Abbreviations: CGI-SS-r = Clinical Global Impression of Severity of Suicidality Revised version, MADRS = Montgomery-Asberg Depression Rating Scale.

The treatment effect of esketamine on depressive symptoms was observed starting at 4 hours after the first dose. Patients in both groups continued to improve over the double-blind treatment phase; the difference between treatment groups generally remained over time through day 25 (Figure 2). MADRS total scores were similar between groups and remained low throughout follow-up (Supplementary Figure 3).

The percentages of patients who achieved remission (MADRS total score ≤ 12) are presented in Supplementary Figure 4. The treatment difference (95% CI) was 9.8% (0.87 to 18.77) 24 hours post–first dose and 16.1% (3.20 to 28.94) on day 25, 4 hours postdose.

Severity of suicidality. At the 24-hour endpoint, patients in both treatment groups experienced improvement in the severity of their suicidality as measured by CGI-SS-r, though there was no statistically significant difference between treatment groups (2-sided $P = .107$). The Hodges-Lehmann estimate of the treatment difference (95% CI) was 0.0 (−1.00 to 0.00).

The estimated differences (95% CI) between treatment groups at 24 hours post–first dose with esketamine for the change in CGI-SS-r score were −0.40 (−0.84 to 0.04) for patients with a history of prior suicide attempt and −0.60 (−1.14 to −0.06) for patients with more severe depressive symptoms (Supplementary Figure 5).

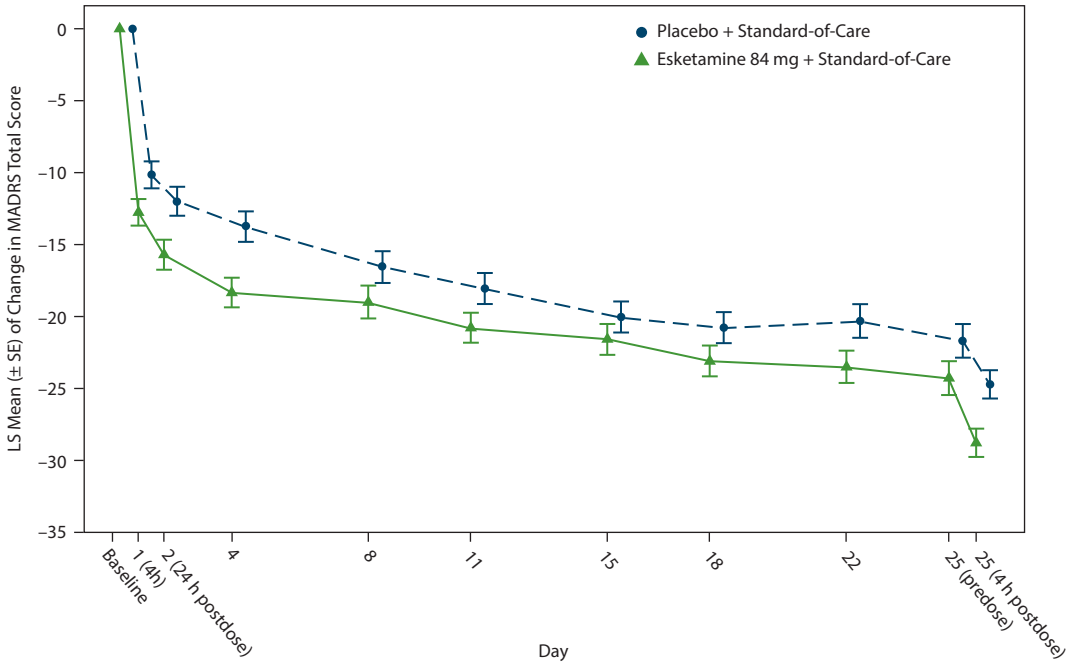
Improvement in severity of suicidality was also observed in both treatment groups at the end of double-blind treatment (Supplementary Figure 6). Results for other indices of suicidality are presented in Figure 3.

Safety Results

The adverse events most frequently reported during the double-blind treatment phase are shown in Table 2 (those most frequently reported during the follow-up phase, in Supplementary Table 1). Most events in the esketamine + standard-of-care (91.0%) and placebo + standard-of-care (70.3%) groups occurred on intranasal dosing days, and most of these (94.9%; and 85.7%, respectively) resolved on the same day. Twenty-one patients (18.6%) in the esketamine + standard-of-care group had a dose reduction to 56 mg due to intolerance, primarily on second dosing.

No deaths were reported during double-blind treatment. Serious adverse events are presented in Supplementary

Figure 2. Least-Squares Mean (± SE) Changes in MADRS Total Score From Baseline During the Double-Blind Treatment Phase[a]



No. of Patients											
Placebo + Standard-of-Care	112	112	111	110	108	103	99	94	92	92	88
Esketamine 84 mg + Standard-of-Care	111[b]	110	111	109	104	100	104	102	103	96	94

[a]MMRM analysis with observed cases. Negative change in score indicates improvement.
[b]One patient in the esketamine 84 mg + standard-of-care group had missing MADRS data at baseline.
Abbreviations: LS = least squares, MADRS = Montgomery-Asberg Depression Rating Scale, MMRM = mixed-effects model using repeated measures.

Table 2 and Supplementary Table 3, and events leading to discontinuation of study drug are summarized in Supplementary Appendix 3.

All depression- and suicide-related adverse events reported in the double-blind treatment phase were considered by the study site investigator as unrelated to esketamine. Suicide attempt was reported for 1 patient in each treatment group during the double-blind phase. Suicide-related serious adverse events during the follow-up phase—including 3 suicide attempts and 1 completed suicide among patients who had prior esketamine treatment and 2 suicide attempts among patients who had prior placebo treatment—were dispersed, without pattern or signal of rebound. The 1 patient who died by suicide in the follow-up phase, 3 days after receiving her last esketamine dose, had a history of 5 prior suicide attempts, the most recent in the month prior to randomization. All patients who attempted suicide during the study had also made an attempt within the month prior to randomization.

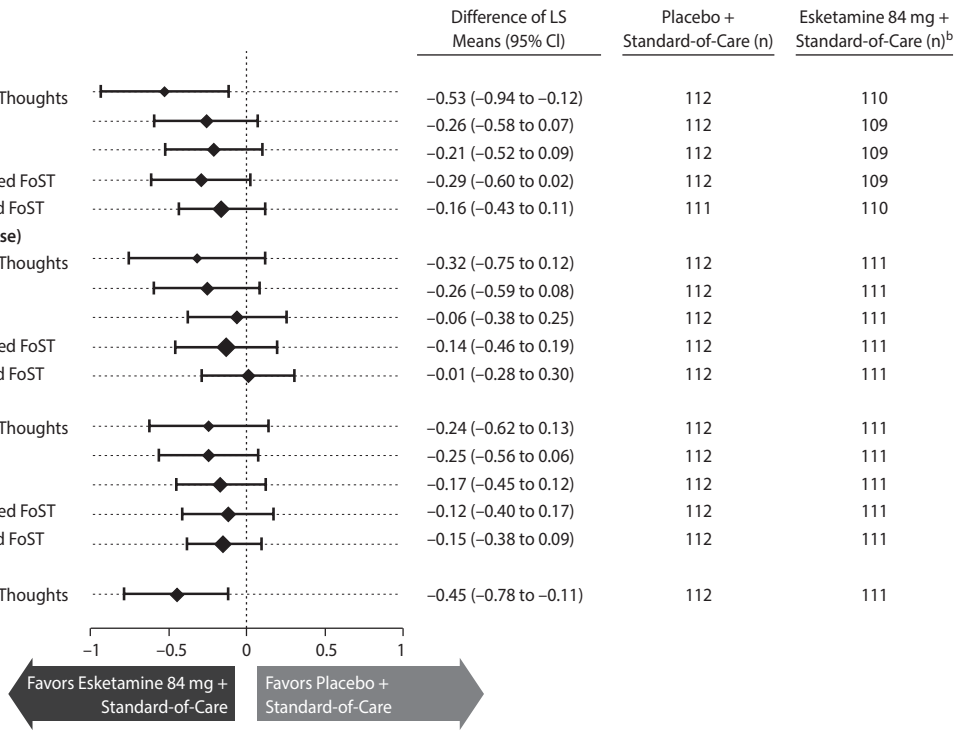
The results of assessments of CADSS and blood pressure are provided in Supplementary Figure 7 and Supplementary Figure 8, respectively. More patients in the esketamine + standard-of-care group (13/113 [11.5%]) had an MOAA/S score ≤ 3 (indicating moderate or greater sedation) at any time during the double-blind phase, versus placebo + standard-of-care (1/112 [0.9%]), and none of these patients required medical intervention.

DISCUSSION

This study is pivotal to the first global registration program of patients with MDD and active suicidal ideation with intent, a population typically excluded from antidepressant treatment trials[28] and for whom no approved pharmacologic treatment exists. The results of this phase 3 study demonstrate that esketamine nasal spray rapidly reduces depressive symptoms in this very ill, vulnerable population. The clinical benefit of esketamine is notable given the large nonspecific benefits afforded by the background of comprehensive standard-of-care,[29] consisting of initial inpatient psychiatric hospitalization and newly initiated or optimized antidepressant therapy. Specifically, improvement in MADRS total score was greater with esketamine than placebo starting at 4 hours post–first dose and continuing until the end of double-blind treatment, when the newly initiated or optimized antidepressant therapy had sufficient time to exert its effect.

In addition to the observed clear benefit of esketamine on depressive symptoms, patients in both the esketamine + standard-of-care and placebo + standard-of-care groups experienced rapid reduction in the severity of their suicidality, as measured by CGI-SS-r at 24 hours; however, the difference between treatment groups was not statistically significant. This may be due to the substantial

Figure 3. Least-Squares Mean (95% CI) Treatment Difference on CGI-SS-r and Other Suicidality Indices During the Double-Blind Treatment Phase[a]



[a]Change in suicidality indices score was analyzed using ANCOVA with LOCF.
[b]At baseline, 1 patient had missing MADRS data and another patient had missing CGI-SS-r data.
Abbreviations: ANCOVA = analysis of covariance, CGI-SR-I = Clinical Global Impression–Imminent Suicide Risk, CGI-SS-r = Clinical Global Impression of Severity of Suicidality Revised version, FoST = Frequency of Suicidal Thinking, LOCF = last observation carried forward, LS = least squares, MADRS = Montgomery-Asberg Depression Rating Scale.

Table 2. Summary of Most Frequently Reported[a] Treatment-Emergent Adverse Events During Double-Blind Phase

Adverse Event	Placebo + Standard-of-Care (n = 112)	Esketamine 84 mg + Standard-of-Care (n = 113)
Dizziness	10 (8.9)	40 (35.4)
Dissociation	4 (3.6)	33 (29.2)
Nausea	15 (13.4)	23 (20.4)
Headache	20 (17.9)	21 (18.6)
Somnolence	11 (9.8)	21 (18.6)
Blood pressure increased	6 (5.4)	19 (16.8)
Dysgeusia	11 (9.8)	16 (14.2)
Constipation	5 (4.5)	15 (13.3)
Vision blurred	5 (4.5)	10 (8.8)
Hypoesthesia	2 (1.8)	8 (7.1)
Vomiting	7 (6.3)	8 (7.1)
Insomnia	7 (6.3)	7 (6.2)
Sedation	2 (1.8)	7 (6.2)
Vertigo	1 (0.9)	7 (6.2)
Anxiety	10 (8.9)	6 (5.3)
Dizziness postural	2 (1.8)	6 (5.3)

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

impact of inpatient psychiatric hospitalization in diffusing the acute suicidal crisis. Further, comprehensive standard-of-care was enhanced by twice-weekly study visits with extensive clinical contact and permitted benzodiazepine use, all of which may have contributed to the rapid reduction of suicidality in both treatment groups.

Intravenous ketamine has been reported to rapidly reduce suicidal ideation, although most of these trials did not specifically select patients with active suicidal ideation and at imminent risk for suicide,[30] as required by our study. Although we also observed rapid treatment effect (4 hours post–first dose) with esketamine on measures of suicidality in a phase 2 proof-of-concept study with similar design and patient population,[21] those results were not confirmed in this phase 3 study. This lack of confirmation may be due to increased heterogeneity of the patient population and standard-of-care associated with a large global study.

Adverse events observed in this study are consistent with the established safety profile of esketamine nasal spray.[14,15] Sadly, 1 study patient, treated with esketamine during the double-blind phase, died by suicide during the follow-up phase. The patient had a history of multiple prior suicide attempts, including one within the month prior to randomization. This was the only completed suicide across the entire clinical development program in over 500 patients who had active suicidal ideation with intent. This low number of completed suicides very likely reflects the comprehensive clinical care and close follow-up patients received during the study.

Study Limitations

Conducting clinical trials in a population of patients with MDD who have active suicidal ideation and intent presents

unique methodological challenges, including parsing the benefits of hospitalization, as well as the care, attention, and expectancy bias that accompanies participation in research.[31] In the study of this high-risk patient population, these methodological challenges may be inevitable to ensure ethical practice and patient safety. Also noteworthy are potential regional differences in the standard-of-care treatment provided in this global study. As esketamine has known transient sedative and dissociative effects, patients themselves may have been unblinded. To mask the bitter taste of esketamine, a bittering agent was added to the placebo nasal spray. To ensure that efficacy raters were not unblinded, different raters were used to perform efficacy and safety assessments.

CONCLUSIONS

Taken together, our findings suggest esketamine nasal spray may address the unmet need for a rapid-acting antidepressant in patients with MDD and active suicidal ideation with intent, for which there is no approved pharmacologic treatment.

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Potential conflicts of interest: **Drs Fu**, **Ionescu**, **Li**, **Lim**, **Hough**, **Drevets** and **Canuso** and **Ms Lane** are employees of Janssen Research & Development, LLC. **Dr Manji** is an employee of Janssen Research & Development, LLC and is an inventor on patents that are directed to this technology, are assigned to Icahn School of Medicine at Mount Sinai, Yale University, and the National Institutes of Health (NIH), and are exclusively licensed to Janssen; however, he does not receive any direct financial benefit therefrom. **Dr Sanacora** has received consulting fees from Allergan, Alkermes, Axsome Therapeutics, Boehringer Ingelheim, Biohaven, Clexio Biosciences, Epiodyne, Intra-Cellular Therapies, Janssen, Merck, Navitor, NeruoRx, Novartis, Noven, Otsuka, Perception Neuroscience, Praxis Therapeutics, Sage, Taisho, Valeant, and Vistagen Therapeutics over the last 24 months. He has also received additional research contracts from Johnson & Johnson and Merck over the last 36 months. Free medication was provided to Dr Sanacora for an NIH-sponsored study by Sanofi-Aventis. In addition, he holds shares in BioHaven Pharmaceuticals Holding Company and is a co-inventor on the patent "Glutamate agents in the treatment of mental disorders" (Patent number: 8778979) and a US Provisional Patent Application No. 047162-7177P1 (00754) filed on August 20, 2018, by Yale University Office of Cooperative Research OCR 7451 US01. Dr Sanacora's employer, Yale University, has a financial relationship with Janssen Pharmaceuticals and may in the future receive financial benefits from this relationship. The University has put multiple measures in place to mitigate this institutional conflict of interest. Questions about the details of these measures should be directed to Yale University's Conflict of Interest office.

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Disclaimer: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Additional information: The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. Requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

Supplementary material: Available at PSYCHIATRIST.COM.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Suicide section. Please contact Philippe Courtet, MD, PhD, at pcourtet@psychiatrist.com.

See supplementary material for this article at PSYCHIATRIST.COM.

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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)

Author(s): Dong-Jing Fu, MD, PhD; Dawn F. Ionescu, MD; Xiang Li, PhD; Rosanne Lane, MAS; Pilar Lim, PhD; Gerard Sanacora, MD, PhD; David Hough, MD; Husseini Manji, MD; Wayne C. Drevets, MD; and Carla M. Canuso, MD

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List of Supplementary Material for the article

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Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

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.

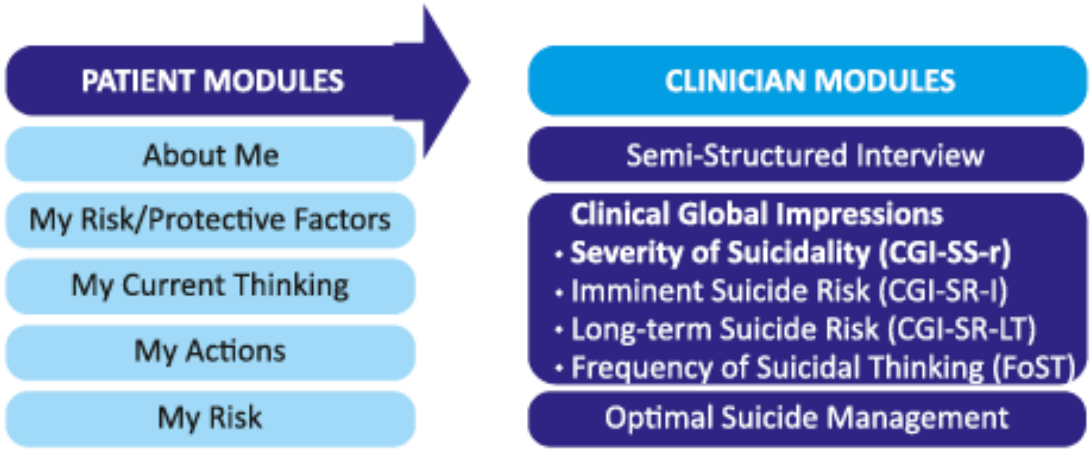
13. Subject has received an investigational drug (including esketamine, ketamine, or investigational vaccines) or used an invasive investigational medical device within 60 days before the planned first dose of study drug or is currently enrolled in an investigational study or was previously enrolled 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.

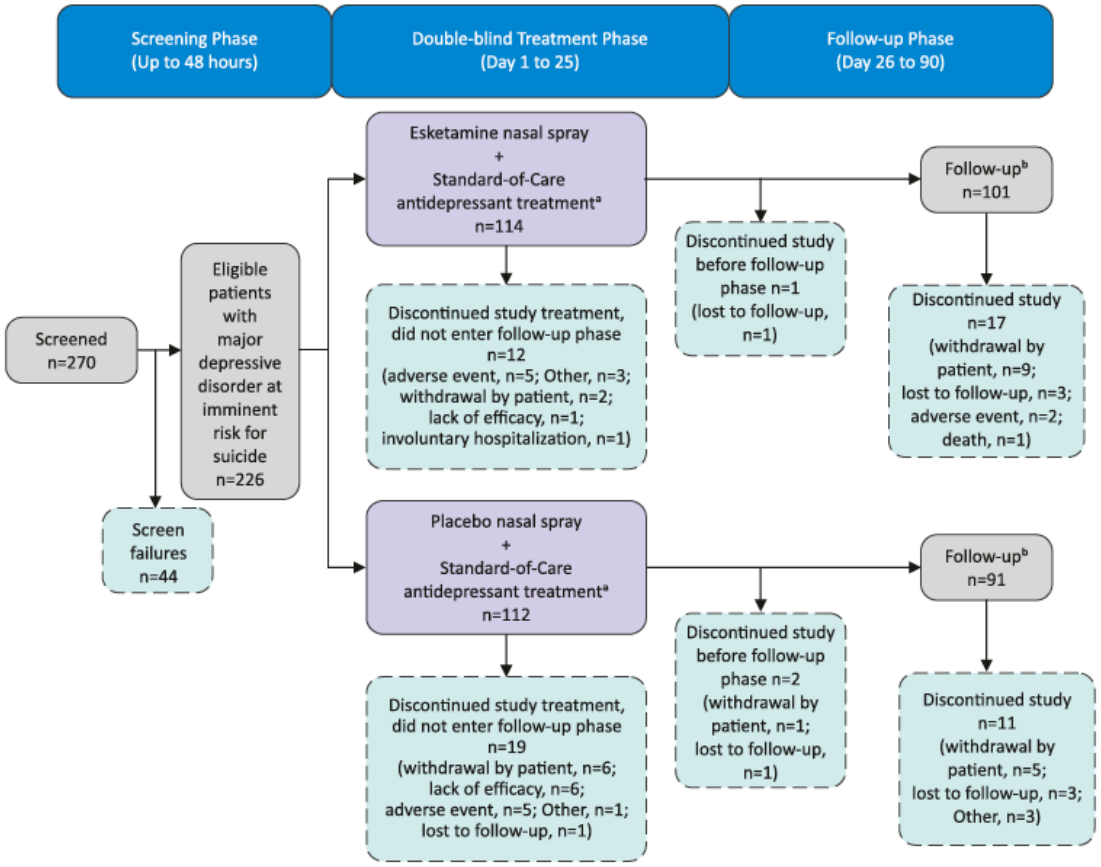
15. Subject has any situation or condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the wellbeing) or that could prevent, limit, or confound the protocol-specified assessments.

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**

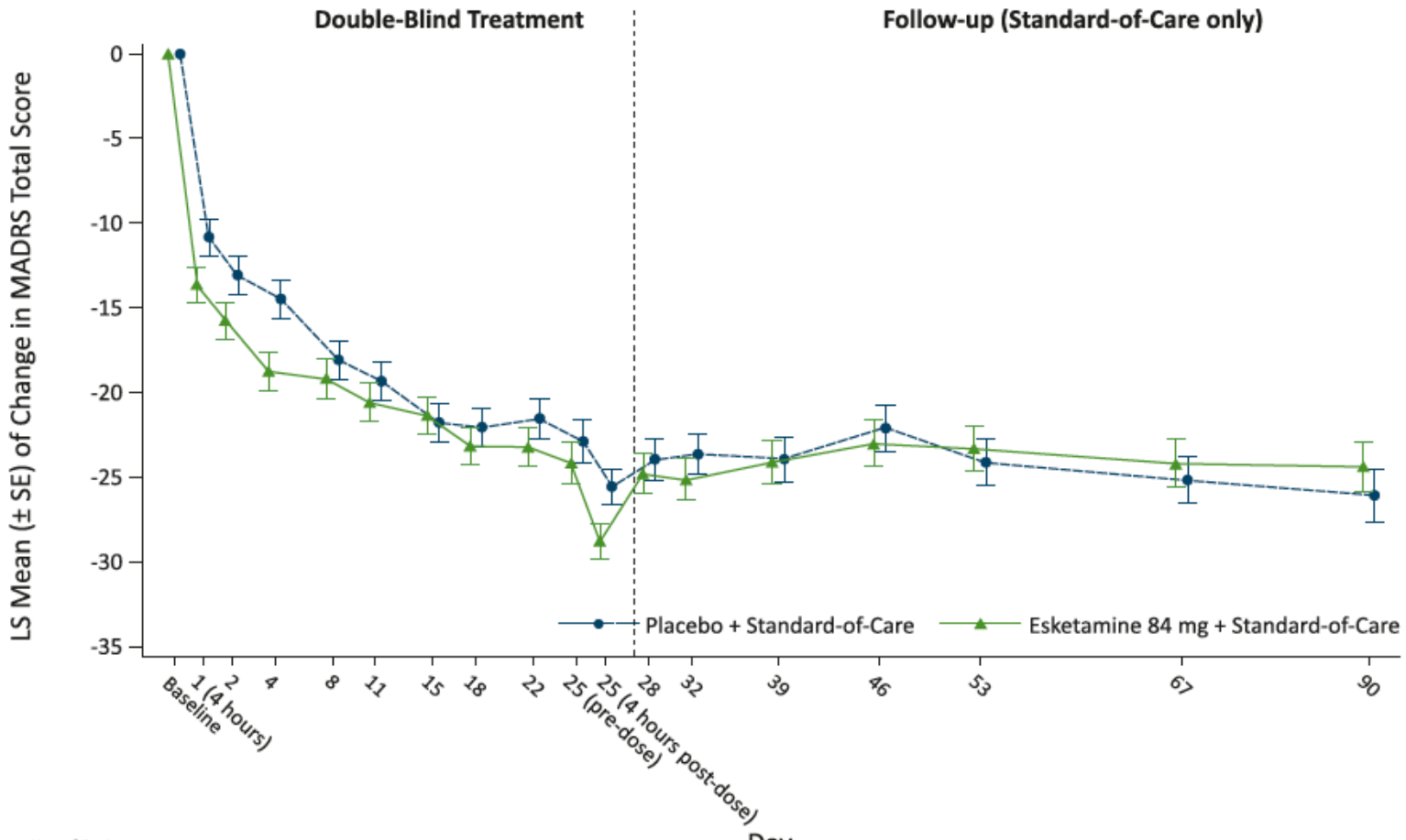


Supplementary Figure 2. Study Design and Disposition of Participants



[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.

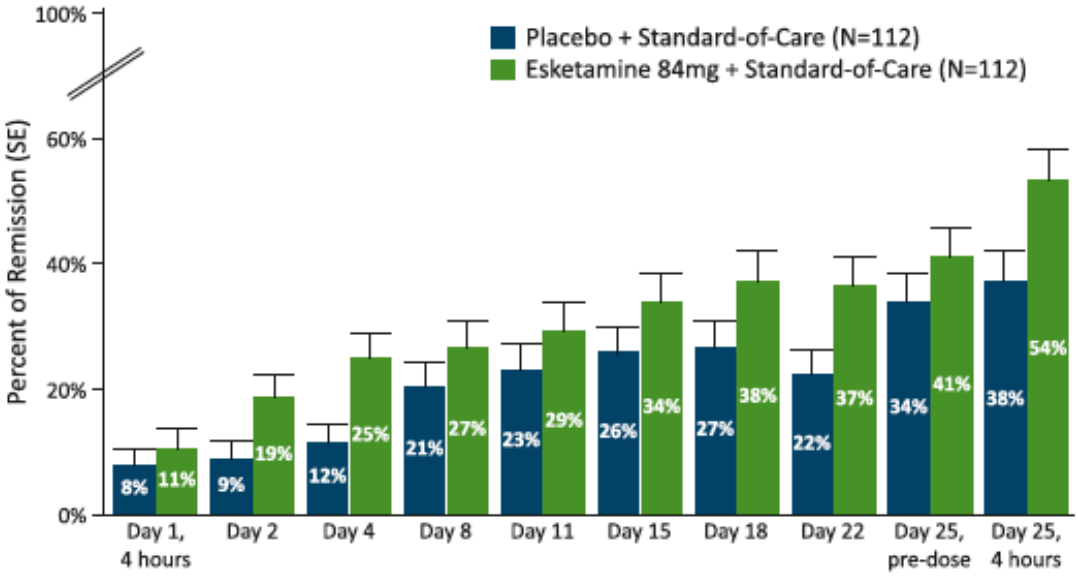
Supplementary Figure 3. Least-Square Mean Changes (±SE) from Baseline for MADRS Total Score During the Follow-up Phase (MMRM; Observed Cases)



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

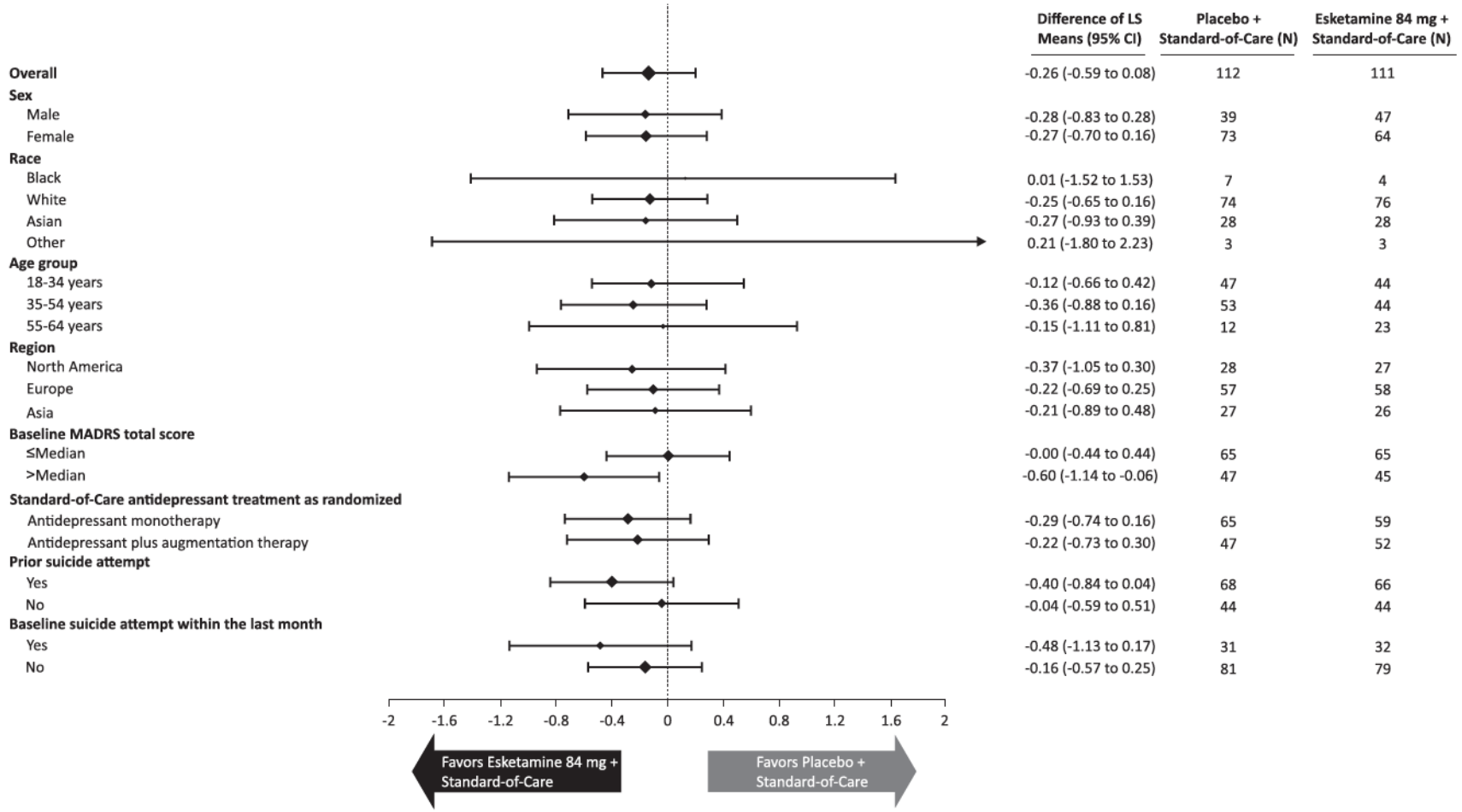
MADRS = Montgomery-Asberg Depression Rating Scale; MMRM = mixed-effects model using repeated measures; SE = standard error
Note: Negative change in score indicates improvement.

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



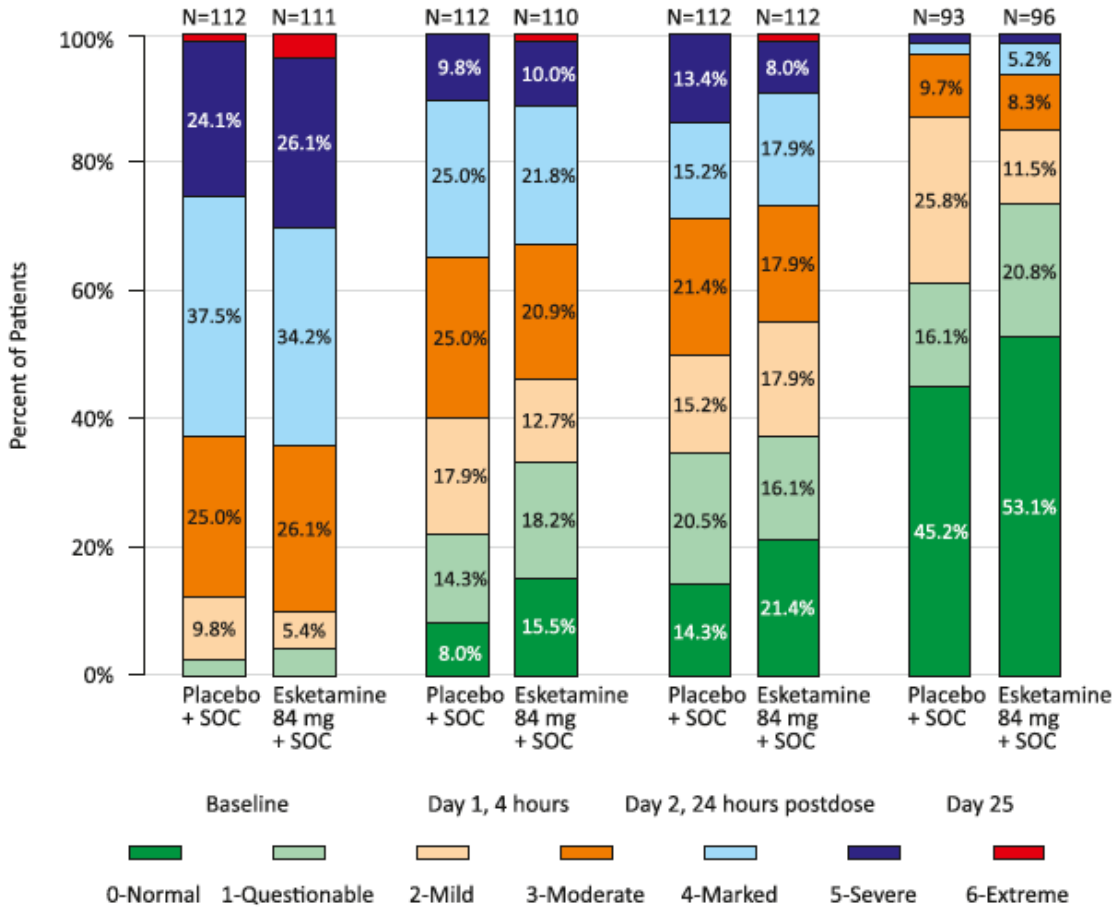
MADRS = Montgomery-Asberg Depression Rating Scale; MMRM = mixed-effects model using repeated measures
Remission defind as MADRS total score ≤12.
Notes: Negative change in score indicates improvement.
The remission rate during the follow-up phase on day 90 exceeded 45% in each treatment group.

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

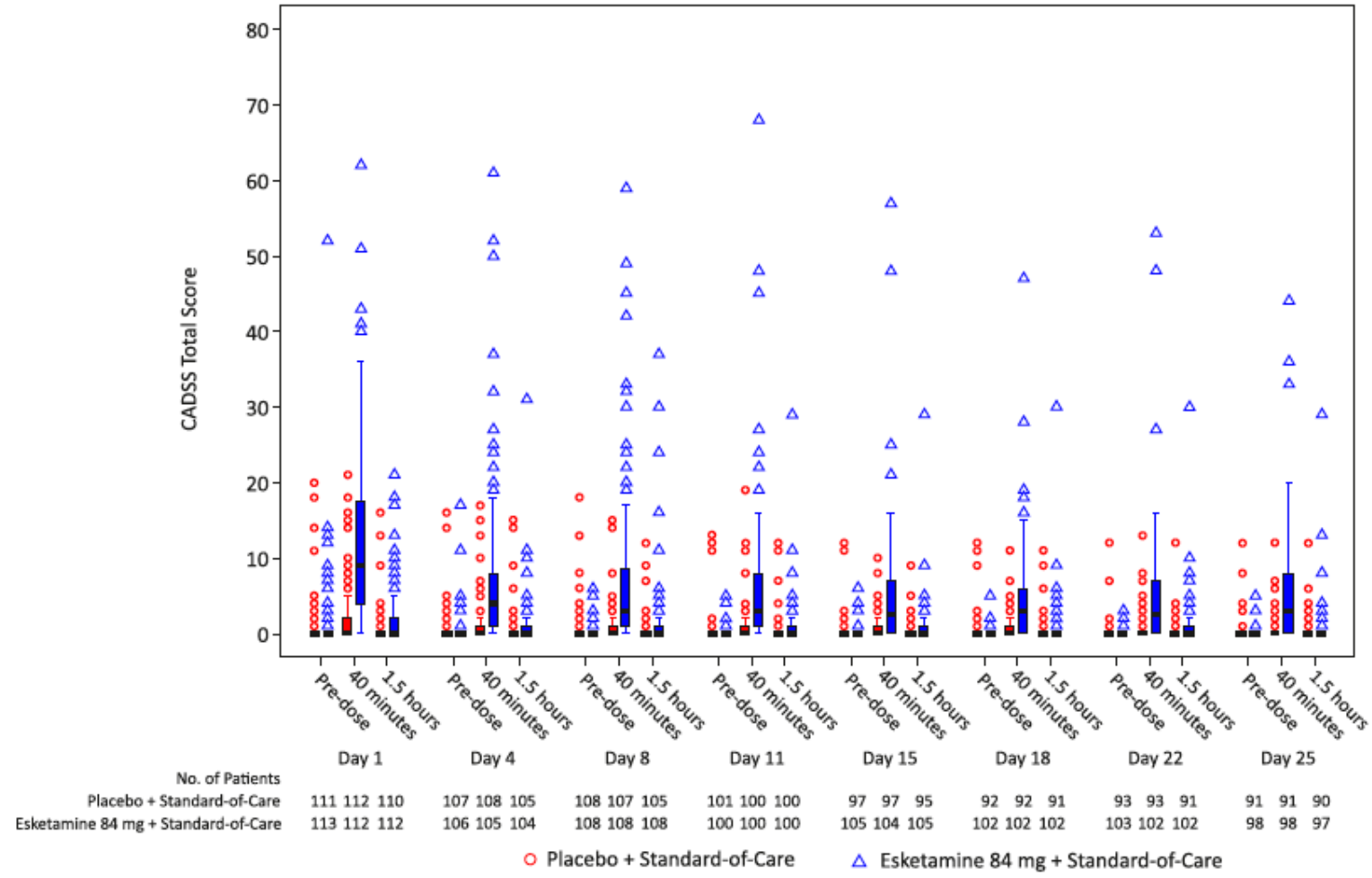
	Number (%) of Patients	
	Placebo + Standard-of-Care[b] N = 91	Esketamine 84 mg + Standard-of-Care[b] N = 101
Patients with ≥1 serious adverse events	10 (11.0)	13 (12.9)
Depression suicidal	3 (3.3)	5 (5.0)
Suicide attempt	2 (2.2)	3 (3.0)
Depression	1 (1.1)	2 (2.0)
Suicidal ideation	3 (3.3)	2 (2.0)
Completed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