

Efficacy and Safety of Intranasal Esketamine Adjunctive to Oral Antidepressant Therapy in Treatment-Resistant Depression

A Randomized Clinical Trial

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IMPORTANCE Approximately one-third of patients with major depressive disorder (MDD) do not respond to available antidepressants.

OBJECTIVE To assess the efficacy, safety, and dose-response of intranasal esketamine hydrochloride in patients with treatment-resistant depression (TRD).

DESIGN, SETTING, AND PARTICIPANTS This phase 2, double-blind, doubly randomized, delayed-start, placebo-controlled study was conducted in multiple outpatient referral centers from January 28, 2014, to September 25, 2015. The study consisted of 4 phases: (1) screening, (2) double-blind treatment (days 1-15), composed of two 1-week periods, (3) optional open-label treatment (days 15-74), and (4) posttreatment follow-up (8 weeks). One hundred twenty-six adults with a *DSM-IV-TR* diagnosis of MDD and history of inadequate response to 2 or more antidepressants (ie, TRD) were screened, 67 were randomized, and 60 completed both double-blind periods. Intent-to-treat analysis was used in evaluation of the findings.

INTERVENTIONS In period 1, participants were randomized (3:1:1) to placebo (n = 33), esketamine 28 mg (n = 11), 56 mg (n = 11), or 84 mg (n = 12) twice weekly. In period 2, 28 placebo-treated participants with moderate-to-severe symptoms were rerandomized (1:1:1) to 1 of the 4 treatment arms; those with mild symptoms continued receiving placebo. Participants continued their existing antidepressant treatment during the study. During the open-label phase, dosing frequency was reduced from twice weekly to weekly, and then to every 2 weeks.

MAIN OUTCOMES AND MEASURES The primary efficacy end point was change from baseline to day 8 (each period) in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score.

RESULTS Sixty-seven participants (38 women, mean [SD] age, 44.7 [10.0] years) were included in the efficacy and safety analyses. Change (least squares mean [SE] difference vs placebo) in MADRS total score (both periods combined) in all 3 esketamine groups was superior to placebo (esketaamine 28 mg: -4.2 [2.09], $P = .02$; 56 mg: -6.3 [2.07], $P = .001$; 84 mg: -9.0 [2.13], $P < .001$), with a significant ascending dose-response relationship ($P < .001$). Improvement in depressive symptoms appeared to be sustained (-7.2 [1.84]) despite reduced dosing frequency in the open-label phase. Three of 56 (5%) esketamine-treated participants during the double-blind phase vs none receiving placebo and 1 of 57 participants (2%) during the open-label phase had adverse events that led to study discontinuation (1 event each of syncope, headache, dissociative syndrome, and ectopic pregnancy).

CONCLUSIONS AND RELEVANCE In this first clinical study to date of intranasal esketamine for TRD, antidepressant effect was rapid in onset and dose related. Response appeared to persist for more than 2 months with a lower dosing frequency. Results support further investigation in larger trials.

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Major depressive disorder (MDD) is a common and disabling illness, with a lifetime prevalence of approximately 20% in the United States.^{1,2} Major depressive disorder impairs socio-occupational functioning³ and increases suicide risk,⁴ adverse sequelae of other common comorbid medical conditions (eg, cardiovascular disease, type 2 diabetes, and obesity), and mortality.⁵⁻⁹ Limitations of currently available antidepressant therapies include delayed onset of efficacy and low remission rates after multiple courses of pharmacotherapy.¹⁰

Research on mood disorder pathophysiology implicated abnormalities in glutamatergic transmission, along with synaptic and dendritic atrophy, in neural circuits that modulate emotional behavior.¹¹ Several studies have shown antidepressant efficacy with the *N*-methyl-D-aspartate (NMDA) receptor antagonist, ketamine.¹²⁻¹⁷ One limitation of ketamine for treating depression is that it may require intravenous administration, reducing its applicability in outpatient settings.

Esketamine, the *S*-enantiomer of ketamine, has a higher affinity for the NMDA receptor than the *R*-enantiomer¹⁸ and is being developed as an intranasal formulation for therapy in treatment-resistant depression (TRD). Rapid onset of antidepressant effects has been observed following intravenous administration of esketamine.¹⁹ We report findings from a study of intranasal esketamine, assessing its efficacy and safety compared with placebo in individuals with TRD.

Methods

Population

The study enrolled medically stable (based on physical examination, medical history, vital signs, and 12-lead electrocardiogram performed at screening) adults (aged 20-64 years) with a diagnosis of MDD, according to the *DSM-IV-TR*.²⁰

All participants had TRD, defined as inadequate response to 2 or more antidepressants (assessed by Massachusetts General Hospital Antidepressant Treatment Response Questionnaire²¹), with at least 1 inadequate response in the current depression episode. Otherwise, an antidepressant failure from a prior episode was acceptable. All participants continued the antidepressants they were receiving at study entry during the trial. At screening and before the dose on day 1, eligible participants had a score of 34 or more on the 30-item, clinician-rated Inventory of Depressive Symptomatology,^{22,23} corresponding to moderate to severe depression. Key exclusion criteria included recent or current suicidal ideation with intent to act, suicidal behavior, or homicidal ideation or intent, diagnosis of bipolar or related disorders, intellectual disability, psychotic disorder, MDD with psychosis, posttraumatic stress disorder, obsessive-compulsive disorder, substance/alcohol use disorders in the past year, and recent use of cannabis (more inclusion/exclusion criteria reported in the eAppendix in [Supplement 1](#)).

Independent review boards (United States: Sterling Institutional Review Board, University of Pennsylvania Institutional Review Board, Hartford Healthcare Institutional Review Board, and Western Institutional Review Board) and an

Key Points

Question Is intranasal esketamine hydrochloride an efficacious treatment option for patients with treatment-resistant depression?

Findings In this randomized, double-blind clinical trial of 67 adults with treatment-resistant depression, significant improvement of depressive symptoms, assessed by the Montgomery-Åsberg Depression Rating Scale total score, was observed after 1 week with intranasal esketamine, 28 to 84 mg administered twice weekly, with a significant ascending dose-response relationship. Improvement appeared to be sustained with reduced dosing frequency for up to 9 weeks.

Meaning Results of this first clinical trial of intranasal esketamine for treatment-resistant depression support study in larger trials.

independent ethics committee (Belgium: Ethisch Comité O.L. Vrouwenziekenhuis) approved the study protocol and amendments. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki,²⁴ consistent with Good Clinical Practices and applicable regulatory requirements. All individuals provided written informed consent before participating in the study. Financial compensation was provided.

Design

This phase 2, 2-panel, double-blind, doubly randomized, delayed-start,²⁵⁻²⁸ placebo-controlled study (a variant of sequential parallel comparison design²⁷⁻³⁶) was conducted from January 28, 2014, to September 25, 2015. In panel A, reported herein, 14 study sites (13 in the United States, 1 in Belgium) enrolled participants. The study protocol is available in [Supplement 2](#).

The study consisted of 4 phases: (1) screening; (2) double-blind treatment (days 1-15), composed of two 1-week periods (period 1, period 2); (3) optional open-label treatment (days 15-74) with tapering of intranasal dosing frequency; and (4) post-treatment follow-up (8 weeks). Based on prior studies of ketamine in which efficacy was reported after 1 to 2 doses, the duration of each period in the double-blind phase was 1 week, during which time it was expected that efficacy could be achieved. This design allowed evaluation of the dose(s) needed to proceed to evaluation in phase 3. The purpose of the open-label, flexible-dose phase was to evaluate the effect of less-frequent dosing on sustaining efficacy.

At the beginning of double-blind period 1, eligible participants were randomized (3:1:1:1) to intranasal placebo or esketamine 28, 56, or 84 mg, twice weekly (days 1 and 4) based on the first of 2 computer-generated randomization schedules (period 1 and period 2). Randomization was balanced by using randomly permuted blocks and stratified by study center. At the end of period 1, those randomized to placebo who had moderate to severe symptoms (assessed by the 16-item Quick Inventory of Depressive Symptomatology-Self Report^{23,37} [QIDS-SR₁₆] total score: moderate, 11-16; severe, >16) were rerandomized (1:1:1:1) to intranasal esketamine 28, 56, or 84 mg or placebo twice

weekly (days 8 and 11); those having mild or no symptoms continued placebo. To maintain the blinding, all participants completed an identical process before entry into period 2, whether or not they were rerandomized. Regardless of response in the double-blind phase, all participants were eligible to enter the optional open-label phase. Esketamine, 56 mg, was administered on the first day of the open-label phase (study day 15); subsequent doses could be adjusted (range, 28–84 mg) based on the investigator's clinical judgment, with administration twice weekly for the first 2 weeks, weekly for the next 3 weeks, then every 2 weeks thereafter.

Study Drug and Administration

Study drug was provided in a disposable nasal spray device containing 200 μ L of solution (ie, 2 sprays). Each device delivered either esketamine hydrochloride, 16.14 (14 mg of esketamine base) per 100- μ L spray or placebo. To maintain blinding, the placebo solution (intranasal solution of water for injection) had a bittering agent (denatonium benzoate) added to simulate the taste of esketamine intranasal solution. As described above, the antidepressant that participants had been receiving immediately before study entry was continued unchanged.

On each dosing day during the double-blind phase, participants self-administered 1 spray of study drug (esketamine or placebo) into each nostril at 3 points, each separated by 5 minutes. In the open-label phase, depending on the dose selected, participants self-administered 1 spray of esketamine into each nostril at 1, 2, or 3 points (corresponding to 28, 56, or 84 mg, respectively), each separated by 5 minutes.

Efficacy Assessments

Efficacy was assessed with the Montgomery-Åsberg Depression Rating Scale^{38,39} (MADRS) on days 1 (predose and 2 hours postdose), 2, 8 (predose), 9, and 15, using the MADRS structured interview guide.³⁹

Overall illness severity was assessed on the Clinical Global Impression of Severity scale.⁴⁰ Participants assessed their severity of anxiety on the Generalized Anxiety Disorder 7-item scale⁴¹ (eTables 1 and 2 in [Supplement 1](#)).

Safety Assessments

Adverse events were monitored throughout the study. Other safety assessments (ie, laboratory tests, vital signs, physical examination) were performed at prespecified time points. Vital signs, the Clinician Administered Dissociative States Scale (CADSS),⁴² and the 4-item positive symptom subscale from the Brief Psychiatric Rating Scale⁴³ were assessed predose, at 40 minutes, and 2 hours postdose.

Statistical Analysis

Efficacy data were analyzed in intent-to-treat analysis sets for each period and phase. The intent-to-treat analysis sets included all participants who received at least 1 dose of study medication during that period or phase and had baseline and at least 1 postbaseline MADRS total score within that period or phase. Safety data were analyzed in period 1, period 2,

double-blind, and open-label data sets for all participants receiving at least 1 dose of study medication.

Efficacy End Points and Analyses

The primary efficacy end point—change from baseline (predose, day 1 in each period) to end point (day 8 in each period) in MADRS total score—was analyzed using the analysis of covariance model. For period 1, the model included treatment and country as factors and baseline MADRS total score as a covariate. For period 2, the model included treatment and country as factors, period 2 baseline QIDS-SR₁₆ score (moderate or severe), and period 2 baseline MADRS total score as a continuous covariate.

Given the consistency between periods 1 and 2 results,²⁵ esketamine dose groups were compared with placebo using a combined test on the weighted test statistics for each period in the double-blind treatment phase. A dose-response analysis on the primary efficacy end point was performed using data combined from both periods. The multiple comparison procedure modeling methodology was performed.^{39,44}

Sample Size Determination

Sample size was determined based on the following differences between intranasal esketamine and placebo for mean change from baseline in MADRS total score: 9-point treatment difference was assumed for period 1 (day 8), 7-point treatment difference for period 2 (day 15) was assumed for individuals with a moderate QIDS-SR₁₆ score, and 9-point treatment difference for period 2 (day 15) was assumed for individuals with a severe QIDS-SR₁₆ score.

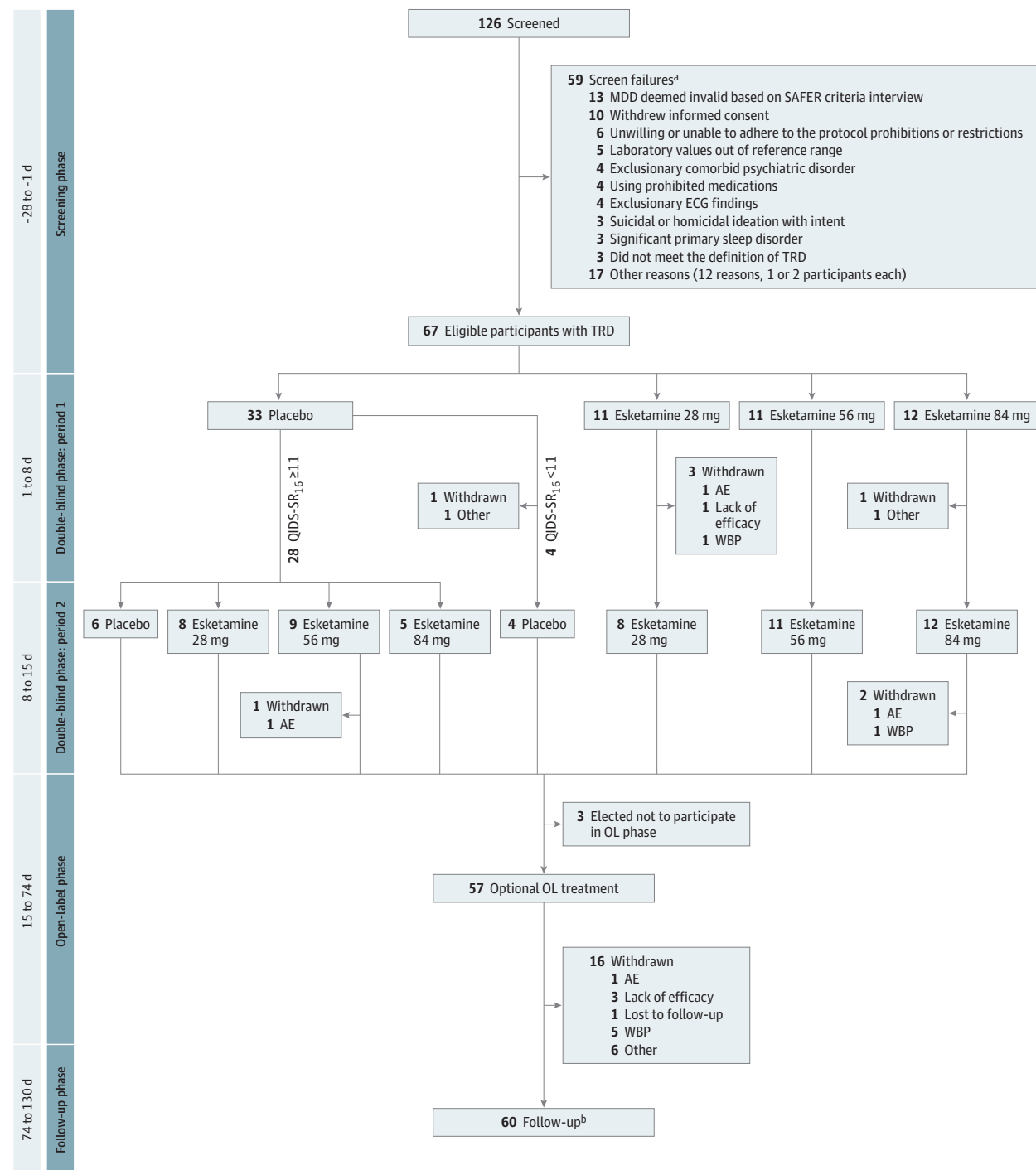
Based on the results of an intravenous esketamine study,¹⁹ it was estimated that 40% of placebo-receiving participants would have a moderate QIDS-SR₁₆ score and 55% would have a severe QIDS-SR₁₆ score at the end of period 1 (day 8 predose). Additional assumptions for the sample size calculation included SD of 10, 92.5% power for the combined data from day 8 and day 15,⁴⁵ overall 1-sided significance level of .05, and 5% dropout rate for period 1. It was calculated that this panel of the doubly randomized, outcome-based design required 60 individuals to be randomly assigned to treatment on day 1 in a 3:1:1 ratio (30 in the placebo group and 10 per intranasal esketamine dose group). Statistical analysis was performed using SAS, version 9.2 (SAS Institute Inc).

Results

Participants

A total of 126 individuals were screened, 67 of whom met the eligibility criteria and were randomized (38 women, mean [SD] age, 44.7 [10.0] years). Of 33 participants randomized to placebo in period 1, 28 (85%) had a QIDS-SR₁₆ score of 11 or higher at the end of period 1 and thus were randomly reassigned to esketamine or placebo in period 2 (**Figure 1**). Most randomized participants (63 of 67 [94%]) completed period 1 and the 2-week double-blind phase (ie, periods 1 and 2 combined, 60 of 67 [90%], hereafter termed *completers*). Of these completers, 57 entered the open-label phase, with 51 (89%) sub-

Figure 1. Disposition of Participants



Seven participants started the follow-up phase earlier than day 74, having received 2 weeks of study drug during the open-label phase of the study. AE indicates adverse event; ECG, electrocardiogram; MDD, major depressive disorder; OL, open-label; QIDS-SR₁₆, 16-item Quick Inventory of Depressive Symptoms-Self-Report; SAFER, State vs Trait, Assessability, Face Validity, Ecological Validity, Rule of Three Ps; TRD, treatment-resistant depression; WBP, withdrawal by participant.

withdrawal by participant.

^a Participants could have multiple reasons for being a screen failure.

^b Participants entered the follow-up phase if they did not choose to withdraw from the study.

sequently entering the follow-up phase, 41 (80%) of whom completed the week 8 follow-up visit.

The treatment groups were similar with respect to demographic and baseline clinical characteristics (eTable 3 in

Supplement 1). Forty-three (64%) participants reported only 1 antidepressant treatment failure in the current episode (in addition to 1 in prior episodes), 15 (22%) had 2 treatment failures, and 9 (13%) reported 3 or more antidepressant failures. Twenty-six (39%) participants reported use of atypical antipsychotics as an adjunctive treatment of MDD before study entry.

Efficacy

The mean MADRS total score decreased from baseline to day 8 in period 1 and from day 8 to day 15 in period 2 in all groups, with greater improvement in all esketamine dose groups compared with placebo (least squares mean difference ranging from -5.0 to -10.5 in period 1 and from -3.1 to -6.9 in period 2) (**Table 1**). Change from baseline in the MADRS total score was statistically significantly greater in all 3 esketamine groups than in the placebo group after 1 week of treatment; the ascending dose-response relationship also was significant. Response was rapid in onset (**Figure 2**; eFigure 1 in **Supplement 1**) and appeared to increase over time during repeated dosing, as evidenced by a decrease in the mean MADRS total score during the open-label phase (mean [SE] change from open-label baseline to day 74, -7.2 [1.84]). In addition, improvement in mean MADRS ratings persisted over the 8-week follow-up phase (without additional esketamine doses) in participants who remained in the study (**Figure 3**).

For completers who received 2 weeks of the same treatment in the double-blind phase, the mean decrease in the MADRS total score was greater in each esketamine dose group compared with placebo at day 15, with the magnitude of decrease directly related to dose (treatment differences relative to placebo of -12.5, -8.3, and -6.0 for esketamine 84 mg, 56 mg, and 28 mg, respectively). Efficacy appeared to be better sustained between drug administrations with the 2 higher doses (**Figure 1**).

Among those who received the same treatment for both periods and completed the double-blind phase, the proportion of responders (defined as $\geq 50\%$ improvement from baseline in MADRS total score) in each esketamine dose group was numerically higher than in the placebo group at the period 2 end point (28 mg: 38% [3 of 8], 56 mg: 36% [4 of 11], 84 mg: 50% [5 of 10], and placebo: 10% [1 of 10]). A similar trend for remission (defined as MADRS total score ≤ 10) was observed across groups. Among completers who received the same treatment in both periods, more participants who received the 2 higher esketamine doses compared with placebo achieved remission after 2 weeks of treatment (13% [1 of 8], 27% [3 of 11], and 40% [4 of 10] in the 28-mg, 56-mg, and 84-mg groups, respectively, and 10% [1 of 10], in the placebo group). Response and remission rates at the end of the open-label and follow-up phases are presented by type of treatment in the double-blind and open-label phases in **Table 2**.

Safety

Three of 56 (5%) esketamine-treated participants during the double-blind phase (compared with none receiving placebo) and 1 of 57 (2%) during the open-label phase had adverse events leading to discontinuation of the study drug (1 event each of

syncope, headache, dissociative syndrome, and ectopic pregnancy). During the double-blind phase, the 3 most common treatment-emergent adverse events observed among esketamine-treated participants were dizziness, headache, and dissociative symptoms; the frequency of each was more than 2-fold higher for esketamine than for placebo (eTable 4 in **Supplement 1**). A dose-response trend was noted for dizziness and nausea, but not for other adverse events. The type and frequency of adverse events reported in the open-label phase were similar to those in the double-blind phase; events reported for more than 10% of 57 open-label participants included dizziness (22 [39%]), dysgeusia (13 [23%]), nausea (9 [16%]), headache (8 [14%]), and sedation (6 [11%]). Overall, 14 of 57 (25%) participants reported transient dissociative symptoms. Most adverse events occurring on dosing days were transient and either mild or moderate in severity. No death was reported.

Most of the esketamine-treated participants manifested transient elevations in blood pressure (maximum mean change: systolic, 19.0 mm Hg; diastolic, 10.3 mm Hg) and heart rate (maximum mean change: 9.4 bpm) on dosing days. Maximum blood pressure values were observed in most cases at 10 or 40 minutes after the dose (systolic: 199 mm Hg; diastolic: 115 mm Hg); elevated values typically returned to the value observed before dosing by 2 hours after the dose (eFigures 2 and 3 in **Supplement 1**). A dose effect was not observed for heart rate, although the greatest mean increases from baseline during both periods were observed in the 84-mg esketamine group.

Perceptual changes and/or dissociative symptoms, as measured by the CADSS, began shortly after the start of intranasal dosing, peaked at approximately 30 to 40 minutes, and resolved by 2 hours (eFigure 4 in **Supplement 1**). Perceptual changes/dissociative symptoms attenuated in all dose groups with repeated dosing. No participant manifested symptoms suggestive of psychosis based on the Brief Psychiatric Rating Scale positive assessment.

Discussion

We observed a significant and clinically meaningful treatment effect (vs placebo) with 28-mg, 56-mg, and 84-mg doses of esketamine, as evidenced by change in the MADRS total score, with a significant relationship between esketamine dose and antidepressant response observed after 1 week of treatment. Duration of efficacy appeared to be shorter with the 28-mg dose administered twice weekly. Results from the open-label phase suggest that improvement in depressive symptoms can be sustained with lower frequency (weekly or every 2 weeks) of esketamine administration. The size of the medication-placebo difference was substantial from baseline to 1 week and was larger than the mean difference from placebo seen at 6 to 8 weeks in antidepressant studies in the US Food and Drug Administration database.⁴⁶ The majority of participants maintained improvement over the 2-month follow-up phase.

The 56- and 84-mg intranasal doses of esketamine produce plasma esketamine levels that are in the pharmacoki-

Table 1. MADRS Total Score: Change From Baseline to 2 Hours, 24 Hours, and Period End Point

Variable ^a	Placebo	Esketamine 28 mg	Esketamine 56 mg	Esketamine 84 mg
Period 1				
No.	33	11	11	12
MADRS total score at baseline, mean (SD)	35.0 (5.18)	31.3 (3.80)	33.2 (6.26)	35.0 (4.22)
Change at 2 h				
LS mean change (SE)	-9.7 (1.76)	-16.4 (2.76)	-14.3 (2.70)	-17.6 (2.60)
LS mean difference from placebo (SE)		-6.7 (3.03)	-4.6 (2.96)	-7.9 (2.84)
P value		.02	.06	.003
Responders, No. (%)	6 (18)	6 (55)	4 (36)	7 (58)
Remitters, No. (%)	1 (3)	3 (27)	2 (18)	3 (25)
Change at 24 h				
LS mean change (SE)	-5.7 (1.79)	-14.8 (2.80)	-15.7 (2.74)	-16.4 (2.64)
LS mean difference from placebo (SE)		-9.1 (3.08)	-10.0 (3.00)	-10.7 (2.88)
P value		.002	<.001	<.001
Responders, No. (%)	1 (3)	4 (36)	3 (27.3)	5 (42)
Remitters, No. (%)	0	4 (36)	2 (18)	3 (25)
Change at study period end point				
LS mean change (SE)	-4.9 (1.74)	-9.8 (2.72)	-12.4 (2.66)	-15.3 (2.56)
LS mean difference from placebo (SE)		-5.0 (2.99)	-7.6 (2.91)	-10.5 (2.79)
P value		.05	.006	<.001
Responders, No. (%)	2 (6)	1 (9)	2 (18)	5 (42)
Remitters, No. (%)	1 (3)	1 (9)	1 (9)	3 (25)
Period 2^b				
No.	6	8	9	5
MADRS total score at baseline, mean (SD)	29.3 (5.79)	31.3 (7.09)	34.9 (6.13)	30.4 (4.67)
Change at 2 h				
LS mean change (SE)	-6.8 (3.74)	-10.3 (3.18)	-11.7 (3.22)	-11.6 (3.44)
LS mean difference from placebo (SE)		-3.5 (3.82)	-4 (3.92)	-4.9 (4.36)
P value		.18	.11	.14
Responders, No. (%)	1 (17)	1 (13)	2 (22)	2 (40)
Remitters, No. (%)	1 (17)	1 (13)	0	2 (40)
Change at 24 h				
LS mean change (SE)	-4.1 (4.09)	-8.9 (3.48)	-10.2 (3.52)	-11.6 (3.76)
LS mean difference from placebo (SE)		-4.8 (4.18)	-6.1 (4.29)	-7.5 (4.77)
P value		.13	.09	.07
Responders, No. (%)	0	0	1 (11)	2 (40)
Remitters, No. (%)	0	0	0	1 (20)
Change at study period end point				
LS mean change (SE)	-4.5 (2.92)	-7.6 (2.49)	-8.9 (2.51)	-11.4 (2.68)
LS mean difference from placebo (SE)		-3.1 (2.99)	-4.4 (3.06)	-6.9 (3.41)
P value		.15	.08	.03
Responders, No. (%)	0	1 (13)	0	1 (20)
Remitters, No. (%)	0	1 (13)	0	1 (20)
Periods 1 and 2 Combined				
Mean difference from placebo (SE)		-4.2 (2.09)	-6.3 (2.07)	-9.0 (2.13)
90% CI for mean difference vs placebo		-7.67 to -0.79	-9.71 to -2.88	-12.53 to -5.52
Combined period test statistic		-2.02	-3.04	4.24
P value		.02	.001	<.001

Abbreviations: LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale.

^a Period 1 (days 1-8) and period 2 (days 8-15) are discussed in the Design section

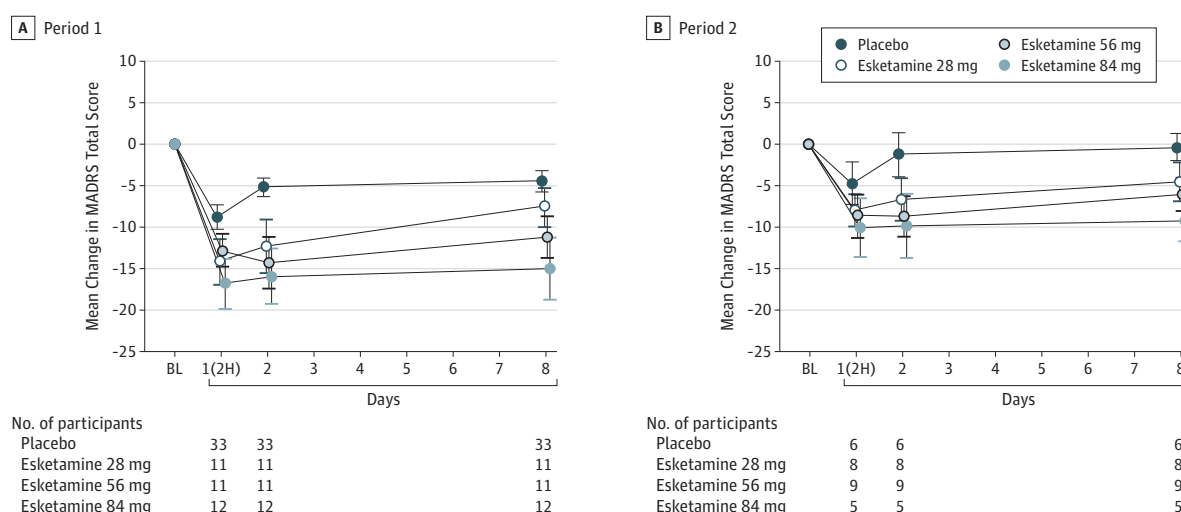
of the Methods and shown in the vertical axis of Figure 1.

^b The study samples reported for period 2 include only the placebo nonresponsive participants rerandomized following period 1.

netic range achieved by intravenous administration of esketamine, 0.2 mg/kg, which produced a similar clinical outcome as reported for intravenous ketamine, 0.5 mg/kg (consistent with higher affinity for NMDA receptors compared with arketamine⁴⁷).¹⁹

In what we believe to be the first study of intranasal esketamine for TRD, efficacy and safety were compared with placebo using a double-blind, doubly randomized, delayed-start design.²⁵ This design allowed for a smaller sample size to assess efficacy, dose-response, and safety than a standard par-

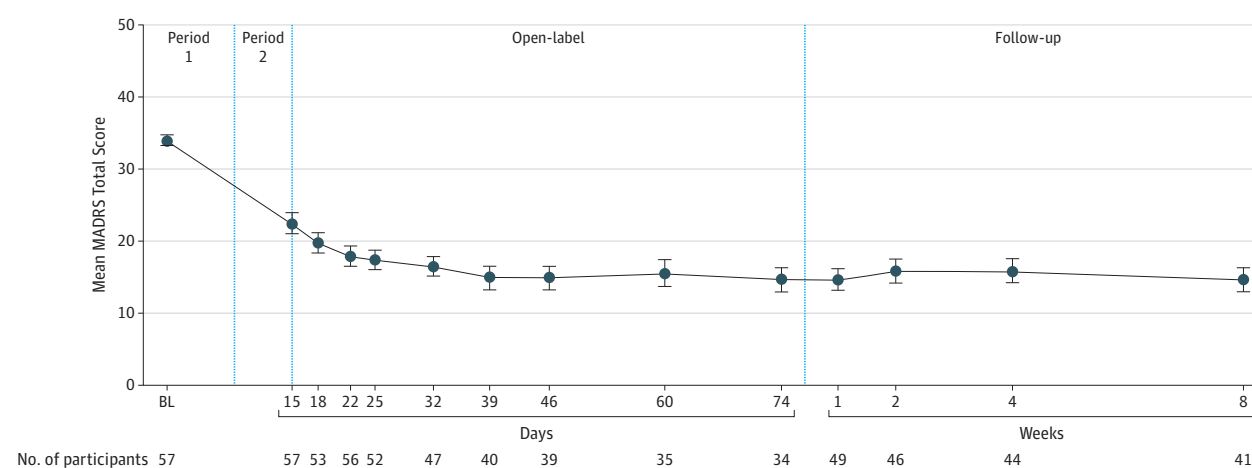
Figure 2. Mean Change in Montgomery-Åsberg Depression Rating Scale (MADRS) Total Score Over Time in Double-Blind Phase



Changes shown in periods 1 (A) and 2 (B). Period 2 consisted only of participants who had received placebo in period 1 and had moderate to severe symptoms ($n = 28$). Period 1 (days 1-8) and period 2 (days 8-15) are discussed in the Design

section of the Methods and shown in the vertical axis of Figure 1. BL indicates baseline; 2H, 2 hours post dose. Error bars indicate SE.

Figure 3. MADRS Total Score: Mean Change in Montgomery-Åsberg Depression Rating Scale (MADRS) Total Score From Baseline to Follow-up End Point for Participants Who Entered the Open-Label Phase



Period 1 (days 1-8), period 2 (days 8-15), open-label period (days 15-74), and the follow-up period (days 74-130) are discussed in the Design section of the Methods and shown in the vertical axis of Figure 1. BL indicates baseline; error bars, SE.

allel-group design, while preserving a low chance of type 2 error to avoid missing the efficacy signal. The key aim of the design was to include only placebo-receiving participants from period 1 who required treatment in period 2 and to rerandomize them to receive 1 of 3 intranasal esketamine doses or intranasal placebo. At the end of the trial, efficacy data from both randomizations (day 1 and day 8) were combined in an integrated analysis. Given the rerandomized placebo, nonresponders were expected to have a lower placebo response; this approach was used to mitigate high placebo responses observed in psychiatric clinical trials.²⁵ The consistency in results obtained from the period 1 and period 2 samples sup-

ports their combination using weights as discussed by Chi et al,²⁵ although caution is required in interpretation due to the small sample size.

In general, the esketamine doses evaluated in this study (28, 56, and 84 mg) appeared to be safe, with no new or unexpected safety concerns observed. Overall, transient increases in blood pressure after the dose, particularly increases in systolic blood pressure, support an increase in cardiac output as the underlying mechanism, consistent with previous reports for ketamine.¹⁵ Analysis of perceptual change symptoms (measured by CADSS assessment) suggests that onset begins shortly after initiation of esketamine and resolution occurs by 2 hours after administra-

Table 2. Response and Remission Rates for Participants Who Completed the OL and Follow-up Phases^a

Variable	Placebo/Placebo/OL Esketamine (n = 10) ^b	Placebo/Esketamine/OL Esketamine (n = 20)	Esketamine/ Esketamine/OL Esketamine (n = 27)	Total (n = 57)
Response Rate^c				
OL end point, day 74, No.	6	10	18	34
≥50% Improvement, No. (%)	6 (100)	5 (50)	11 (61)	22 (65)
Week 8 (follow-up), No.	7	12	22	41
≥50% Improvement, No. (%)	5 (71)	3 (25)	15 (68)	23 (56)
Remission Rate^c				
OL end point, day 74, No.	6	10	18	34
No, No. (%)	4 (67)	6 (60)	13 (72)	23 (68)
Yes, No. (%)	2 (33)	4 (40)	5 (28)	11 (32)
Week 8 (follow-up), No.	7	12	22	41
No, No. (%)	3 (43)	9 (75)	12 (55)	24 (59)
Yes, No. (%)	4 (57)	3 (25)	10 (46)	17 (42)

Abbreviation: OL, open-label.

^a The follow-up phase includes data from 7 participants enrolled under the original version of the protocol in which participants received 2 weeks of study drug during the OL phase of the study and data from 50 participants enrolled under a protocol amendment in which participants received up to 9 weeks of study drug during the OL phase of the study. Percentages calculated with the

number of participants per a visit as denominator; percentage change calculated based on period 1 baseline.

^b Esketamine was given as esketamine hydrochloride.

^c Response: Montgomery-Åsberg Depression Rating Scale (MADRS) total score ≥50%; remission: MADRS total score ≤10.

tion. These symptoms were dose dependent and attenuated with repeated administration. In contrast, antidepressant efficacy did not attenuate across administrations.

Limitations

Generalizability of the study findings is limited by the small sample size and enrollment criteria that excluded individuals with a history of psychotic symptoms, substance/alcohol use disorders, recent use of cannabis, or significant medical comorbidities. Also excluded were individuals having current suicidal ideation with intent—a group that was evaluated in a separate study.⁴⁸ Difficulty blinding esketamine, despite adding a bittering agent to placebo to mimic the taste of esketamine, is another limitation.

Conclusions

Intranasal esketamine administered at doses of 28, 56, and 84 mg appeared to be efficacious in treating TRD. There was evidence of robust and durable efficacy in the double-blind treatment phase (56 and 84 mg). Improvement in depressive symptoms persisted over the open-label phase, despite reduced dosing frequency, and for up to 2 months after cessation of esketamine dosing. Results support further investigation of intranasal efficacy of esketamine for the treatment of TRD in larger trials. A phase 3 study evaluating the necessary frequency of dosing and duration of effect is under way.⁴⁹

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