NEW RESEARCH

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Effect of Esketamine on Depressive Symptoms in Adolescents With Major Depressive Disorder at Imminent Suicide Risk: A Randomized Psychoactive-Controlled Study

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Objective: To evaluate the efficacy, safety, and tolerability of esketamine nasal spray vs psychoactive placebo (oral midazolam) in rapidly reducing depressive symptoms in adolescents with major depressive disorder at imminent risk for suicide.

Method: This double-blind, double-dummy, phase 2b study randomized (1:1:1:2) 147 adolescents (12 to <18 years old) to esketamine (28, 56, or 84 mg) or midazolam twice weekly for 4 weeks. Participants concomitantly received comprehensive standard of care, including initial hospitalization, oral antidepressant, and evidenced-based psychotherapy. The primary efficacy end point—change in Children's Depression Rating Scale–Revised (CDRS-R) total score from baseline to 24 hours post first dose—was analyzed using analysis of covariance, according to a pooled sequential multiple testing procedure.

Results: All participants were moderately to severely depressed at enrollment; approximately 95% were moderately to extremely suicidal. Pooled esketamine doses (56 and 84 mg) showed superiority over midazolam in reducing CDRS-R total score at 24 hours post first dose (between-group difference of least squares means [95% CI]: −5.8 [−11.19, −0.35], $p = .037$). The between-group differences for individual esketamine 84 mg and 56 mg doses vs midazolam were −5.7 ([−12.91, 1.55], $p = .123$) and −5.9 ([−12.25, 0.53], $p = .072$), respectively. Severity of suicidality, per Clinical Global Impression of Severity of Suicidality–revised (CGI-SS-R), improved in all 4 groups (between-group difference of least squares means [95% CI]: −0.2 [−0.90, 0.41], −0.3 [−0.93, 0.31], 0.0 [−0.69, 0.72] for esketamine 28, 56, and 84 mg, respectively, at 24 hours post first dose). Common adverse events (incidence ≥20%) reported for esketamine were dizziness, nausea, dissociation, headache, dysgeusia, somnolence, vomiting, hypoesthesia, and intentional self-injury.

Conclusion: The primary efficacy end point of the study was met for the pooled esketamine doses (56 and 84 mg). Esketamine in conjunction with comprehensive standard of care rapidly improved depressive symptoms among adolescents at imminent risk for suicide.

Plain language summary: This double-blind randomized controlled clinical trial compared the effects of esketamine nasal spray (28, 56, or 84 mg) to a psychoactive placebo (midazolam) in 147 adolescents with major depressive disorder who were at imminent risk for suicide. All participants also received standard-of-care treatment, including initial hospitalization, oral antidepressant treatment, and evidenced-based psychotherapy. Combined 56- and 84-mg doses of esketamine were superior to midazolam in reducing depressive symptoms at 24 hours following the first dose; all 4 treatment groups showed continued improvement in depressive symptoms and severity of suicidality after 4 weeks of treatment. The most common side effects reported for esketamine-treated participants were dizziness, nausea, dissociation, headache, bitter taste, and sleepiness.

Clinical trial registration information: Study to Evaluate the Efficacy and Safety of 3 Fixed Doses of Intranasal Esketamine in Addition to Comprehensive Standard of Care for the Rapid Reduction of the Symptoms of Major Depressive Disorder, Including Suicidal Ideation, in Pediatric Participants Assessed to Be at Imminent Risk for Suicide; https://clinicaltrials.gov/study/NCT03185819

Key words: esketamine; major depressive disorder; RCT; suicide

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Major depressive disorder (MDD) is one of the most prevalent psychiatric disorders in adolescents[1] and is the condition mostly commonly associated with suicide.[2,3] The presence of MDD is associated with a 5-fold higher risk for suicide attempts in adolescents.[4,5] Up to 80% of adolescents who attempt suicide meet the criteria for depression at the time of suicide attempt,[2,5,6] and up to 60% of adolescents who die by suicide have a depressive disorder at the time of death.[7,8]

Given that the time between onset of suicidal ideation and suicide attempt is often short[9] and the outcome is potentially lethal, immediate intervention and treatment options for rapid relief of depressive symptoms are needed. Nevertheless, currently there are no regulatory

authority–approved pharmacological treatments for adolescents with MDD who are at imminent risk for suicide, and few for adolescents with MDD. Additionally, patients with acute suicidal behavior or thoughts are typically excluded from antidepressant trials. The current standard of care (SOC) for this population is hospitalization, treatment with antidepressant medication, and evidenced-based psychotherapy,[10-13] each with limitations. Standard antidepressant medications require 4 to 6 weeks to have an optimal effect in improving mood,[12,14] and access to evidence-based psychotherapies can be challenging and variable. The benefits of hospitalization are temporary and not completely effective, with the risk for suicide remaining high in the weeks after discharge.[15] A recent report[16] showed that 13% of nonpsychotic adolescents (ages 12-15) hospitalized in a psychiatric facility attempted or reattempted suicide within 6 months of discharge.

Esketamine nasal spray, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, coadministered with oral antidepressant therapy has demonstrated rapid reduction of depressive symptoms 24 hours post first dose.[17,18] It is the only drug approved in the United States for the treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior.[19] In the European Union, esketamine nasal spray is the only drug approved in adults with a moderate-to-severe episode of MDD as acute short-term treatment for the rapid reduction of depressive symptoms, which according to clinical judgment constitute a psychiatric emergency.[20] Herein, we report findings from a phase 2b study that compared esketamine to psychoactive placebo (oral midazolam), each given in addition to comprehensive SOC, for rapidly reducing depressive symptoms in adolescents with MDD who were assessed to be at imminent risk for suicide.

METHOD

Ethical Practices

Ethical practices are summarized in the Supplement (available online). The study is registered at ClinicalTrials.gov (NCT03185819). Given the vulnerability of the population, the study was conducted in the context of comprehensive SOC treatment (described under "SOC Antidepressant Therapy").

Study Population

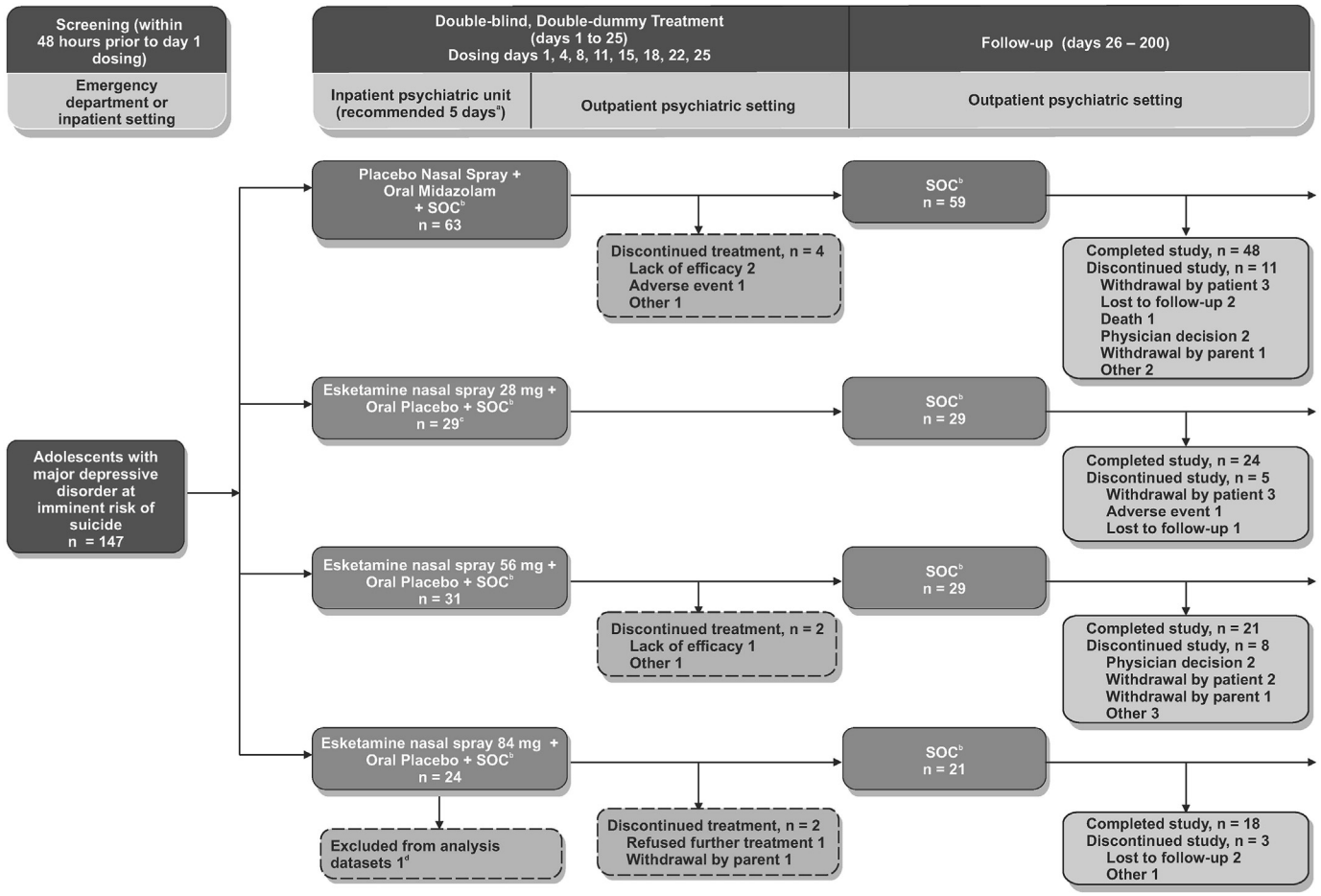
Candidates for the study were screened after presenting to an emergency department or inpatient psychiatric unit. The study enrolled adolescents (12 to <18 years of age) who met *DSM-5*[21] diagnostic criteria for MDD without psychosis, based on assessment with the Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI-KID 7.0.2).[22] Eligibility criteria also required that participants be experiencing current suicidal thinking with intent, responding affirmatively to MINI-KID questions B3 ("Think about hurting yourself with the possibility that you might die [killing yourself] in the present") and B10 ("Want to go through with a plan to kill yourself in the past 24 hours"); be in clinical need of acute psychiatric hospitalization due to imminent risk for suicide; and have moderate-to-severe depressive symptoms as evidenced by Children's Depression Rating Scale–Revised (CDRS-R) total score of ≥58 at baseline (predose, day 1). Participants were required to voluntarily agree to SOC treatment, including hospitalization (for 5 days after randomization, unless a longer or shorter period was clinically warranted per local standard practice), initiation or optimization of treatment with an oral antidepressant(s) (specified in "SOC Antidepressant Therapy") for at least the double-blind treatment phase, and evidence-based psychotherapy through at least the initial 8 weeks of the posttreatment follow-up phase (day 81). Certain psychiatric comorbidities disqualified participants (eg, current *DSM-5* diagnosis of bipolar disorder, moderate-to-severe substance or alcohol use disorder, intellectual disability, obsessive-compulsive disorder, autism spectrum disorder, conduct disorder, borderline personality disorder, current or prior diagnosis of psychotic disorder). A full list of the inclusion and exclusion criteria is presented in the Supplement (available online).

Study Design

This randomized, double-blind, double-dummy, psychoactive placebo-controlled, multicenter study was conducted from January 2018 to March 2023 at 37 sites in the United States (87 participants enrolled), Spain (17 participants enrolled), France (13 participants enrolled), Brazil (11 participants enrolled), Italy (9 participants enrolled), Hungary (8 participants enrolled), and Poland (2 participants enrolled). The study consisted of a screening evaluation performed within 48 hours of day 1 (first study drug dosing day), followed by 4 weeks of double-blind treatment (days 1-25) given in the context of comprehensive SOC including initial hospitalization, and then posttreatment follow-up (days 26-200) during which participants received SOC treatment, but no study drug (Figure 1).

Eligible participants were randomized (1:1:1:2) to esketamine nasal spray 28 mg, 56 mg, or 84 mg or to oral psychoactive placebo (ie, midazolam 0.125 mg/kg, henceforth referred to as midazolam), administered twice weekly for 4 weeks. Midazolam was chosen for its psychomimetic effects (eg, sedation, disorientation), its pharmacokinetic profile, and its use as a comparator in ketamine studies. A

FIGURE 1 Study Design and Disposition of Participants



Note: *SOC = standard of care.*

[a]*Recommended duration of at least 5 days; hospital discharge before 5 days (from randomization) must have been approved by the study sponsor.*

[b]*Given the vulnerability of the patient population, all participants were treated in the context of comprehensive SOC treatment, including initial hospitalization, initiation or optimization of an oral antidepressant, and evidence-based psychotherapy.*

[c]*One patient was excluded from the full efficacy analysis dataset.*

[d]*One patient was excluded from all analyses due to Good Clinical Practice compliance issues at the site.*

double-dummy design was used (ie, participants in an esketamine dose group received oral placebo and participants in the midazolam group received intranasal placebo). On each double-blind dosing day, participants received oral study drug first, followed closely by intranasal study drug, which was self-administered under the supervision of the investigator (or designee).

Randomization was balanced using randomly permuted blocks of 4 and stratified by study center. A computerized system was used to randomly assign participants; investigators were not provided with the randomization codes. To maintain the study blind, an unblinded pharmacist (or other qualified health care professional), who was not involved with either the study conduct or data collection, prepared study drug.

Participants were required to participate in evidence-based psychotherapy through at least day 81; frequency and type of therapy were not mandated. Criteria for permitted use of concomitant pharmacotherapy are presented in the Supplement (available online).

SOC Antidepressant Therapy

One of 3 SOC antidepressant medications (fluoxetine, escitalopram, or sertraline) was initiated or optimized for all participants, ideally at baseline on day 1, but no later than by day 7. Dose titration and adjustments of SOC antidepressants were allowed during the first 2 weeks of double-blind treatment, based on the clinical judgment of the investigators, with doses maintained thereafter to the end of the double-blind phase (day 25). Participants taking a

recently initiated (<2 weeks prior) antidepressant at screening could continue the antidepressant at the same dose during treatment with the study drug. During the follow-up phase, participants were treated with SOC antidepressant(s), managed per clinical judgment.

Efficacy and Safety Assessments

Clinicians assessed depression symptoms using the CDRS-R[23] (total score range, 17-113) and Montgomery–Åsberg Depression Rating Scale (MADRS)[24] (total score range, 0-60). The CDRS-R was modified to assess depressive symptoms at the 4-hour (day 1 and day 25) and 24-hour (post first dose) time points (see the Supplement, available online). Suicidal ideation and behavior were assessed using the Suicide Ideation and Behavior Assessment Tool (SIBAT).[25] The SIBAT contains both patient- and clinician-reported modules, which include assessments of Clinical Global Impression of Severity of Suicidality–revised (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- and patient-reported Frequency of Suicidal Thinking (FoST). Only trained and certified raters were allowed to perform the MINI-KID, CDRS-R, MADRS, and other clinician-rated scales. Study raters were responsible for both the inpatient and the outpatient phases of the trial; as much as possible, a given rater was to rate a given participant throughout the entire trial, irrespective of inpatient or outpatient settings. Rater training and certification demonstrated excellent interrater agreement.

Adverse events were solicited by site staff throughout the study. The following safety assessments were performed during the double-blind phase: effect on present-state dissociative symptoms using the Clinician-Administered Dissociative States Scale (CADSS)[26]; effect on sedation using the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale[27]; occurrence of psychosis-like side effects using a 4-item positive symptom subscale (consisting of suspiciousness, hallucinations, unusual thought content, and conceptual disorganization) of the Brief Psychiatric Rating Scale[28,29] (BPRS+); occurrence and severity of potential treatment-emergent manic episodes using the Young Mania Rating Scale (YMRS)[30]; vital signs.

In addition, effects on cognitive functioning were measured by a computerized cognitive battery during the double-blind and posttreatment follow-up phases. The Physician Withdrawal Checklist (PWC-20)[31] was used to assess potential withdrawal symptoms, and Timeline Follow-Back (TLFB)[32] was used to assess whether ketamine or phencyclidine use occurred during the posttreatment follow-up phase.

Statistical Methods

Safety data from the double-blind phase were analyzed in a safety analysis dataset, which included all randomized participants who received ≥1 dose of double-blind study drug. Efficacy data were analyzed in a full efficacy analysis dataset, which included participants in the safety analysis dataset who had baseline and ≥1 postdose CDRS-R scores. Efficacy and safety data were also analyzed in a follow-up analysis dataset, which included participants who completed the double-blind phase and either entered the posttreatment follow-up phase or provided adverse event data after the double-blind phase.

Efficacy End Points and Analyses. The primary efficacy end point—change in CDRS-R total score from the baseline assessment conducted on study day 1 (predose; recall period past 7 days) to 24 hours post first dose (day 2; recall period 24 hours) in the double-blind phase—was analyzed using an analysis of covariance (ANCOVA) model with treatment and analysis center as factors and baseline CDRS-R total score as a continuous covariate. The pooling algorithm for analysis centers is provided in the Supplement (available online).

A prespecified, pooled sequential multiple testing procedure was used to control for type I error. First, the esketamine 56 mg and 84 mg treatment groups were pooled and compared with midazolam at the 2-sided significance level of .05. Next, if this comparison achieved statistical significance favoring esketamine, the 56 mg and 84 mg doses were each simultaneously tested vs midazolam at the 2-sided significance level of .05. Finally, the 28 mg dose was tested only if both the 56 mg and the 84 mg doses were significant. Dose response for change from baseline to 24 hours post first dose in CDRS-R total score was analyzed using a multiple trend test, a best fit sigmoid E_{max} model, and multiple comparison procedures and modeling. Changes from baseline in CDRS-R total score at day 25 end point (4 hours post final dose) and all postbaseline time points during the double-blind and posttreatment follow-up phases were analyzed using the ANCOVA model described for the primary end point analysis. MADRS was also evaluated using the same methodology. Missing data were imputed using last observation carried forward.

Response of MDD (defined as ≥50% improvement in CDRS-R total score from baseline minus 17 and as ≥50% improvement in MADRS total score from baseline) and remission of MDD (defined as CDRS-R total score ≤28 and as MADRS total score ≤12) at 4 hours post first dose and at day 25 end point were summarized by treatment group. Estimates of the treatment difference in proportions and 95% CIs were reported.

Change in severity of suicidality, based on CGI-SS-R, was analyzed throughout the 25-day double-blind phase using ANCOVA (last observation carried forward data). The percentage of participants who met criteria for resolution of suicidality (defined by CGI-SS-R score of 0 [normal, not at all suicidal] or 1 [questionably suicidal]) was summarized by treatment group and visit. CGI-SR-I was analyzed similarly to CGI-SS-R. Clinician- and patient-reported FoST scores were summarized over time. Forest plots were created post hoc, showing the least squares (LS) mean (95% CI) changes in CGI-SS-R score and other suicidality indices (ie, CDRS-R suicidal ideation item, MADRS suicidal thoughts item, CGI-SR-I, clinician-reported FoST, patient-reported FoST) at 4 hours post first dose, 24 hours post first dose, and at day 25 end point, based on ANCOVA using last observation carried forward data. Frequency distributions or descriptive statistics were provided for adverse events, vital signs, and scores for clinician-reported safety outcomes (CADSS, MOAA/S, YMRS, BPRS+, PWC-20).

Sample Size Determination. The sample size for this study was calculated using an effect size of 0.65[33] between any dose of esketamine and midazolam for the primary efficacy end point and a 2-sided significance level of .05. Approximately 29 participants were to be randomized to each esketamine dose group and 58 were to be randomized to midazolam to achieve 94% power for the comparison of pooled 56 mg and 84 mg doses of esketamine vs midazolam, and 92% power for at least 1 of the 2 esketamine doses vs midazolam.

As the study was sized/powered for only the primary efficacy end point, mention of statistical significance in this article is limited to the primary efficacy end point. Point estimates of treatment differences (either difference in means or proportions) and 95% CIs are reported for the other efficacy end points. Of note, 95% CIs that do not include zero for differences in means and proportions correspond to a 2-sided p value of $< .05$.

RESULTS

Participants and Treatment

A total of 147 adolescents were randomized to study drug (n = 29, n = 31, n = 24, and n = 63 to esketamine 28 mg, esketamine 56 mg, esketamine 84 mg, and midazolam, respectively) (Figure 1). Of these, 139 (94.6%) participants completed double-blind treatment, and 138 entered the posttreatment follow-up phase, of whom 111 (80.4%) completed 6-month follow-up.

The treatment groups were generally similar with respect to demographic and baseline clinical characteristics (Table 1). Participants were moderately to severely depressed at enrollment; approximately 95% were moderately to extremely suicidal. More than half (54%) reported a suicide attempt within the past month. SOC antidepressant therapy used during the double-blind phase is summarized in Table S1 (available online).

Efficacy Results

Symptoms of Depression. Pooled esketamine 84 mg and 56 mg doses plus comprehensive SOC showed clinically meaningful and statistically significant superiority over midazolam plus comprehensive SOC in reducing depressive symptoms at 24 hours post first dose based on CDRS-R (between-group difference of LS means [95% CI]: −5.8 [−11.19, −0.35], 2-sided $p = .037$, effect size [95% CI]: 0.36 [0.00, 0.73]) (Table 2). Given the pooled findings at 24 hours post first dose, follow-up testing was conducted on the individual 56 mg and 84 mg dose groups relative to the midazolam group. The between-group difference was not statistically significant for the esketamine 84 mg and 56 mg dose groups considered separately (difference of LS means [95% CI]: −5.7 [−12.91, 1.55], 2-sided $p = .123$, effect size [95% CI]: 0.34 [−0.14, 0.82] for 84 mg; difference of LS means [95% CI]: −5.9 [−12.25, 0.53], 2-sided $p = .072$, effect size [95% CI]: 0.38 [−0.05, 0.81] for 56 mg). Due to the testing hierarchy, the 28 mg dose was not formally tested.

A significant dose response, based on change in CDRS-R total score, was observed at 24 hours post first dose (multiple trend test 1-sided $p = .030$). Results from the best fit sigmoidal E_{max} model and multiple comparison procedures and modeling provided similar estimates for the treatment differences between esketamine plus comprehensive SOC and midazolam plus comprehensive SOC as the primary analysis. The esketamine doses of 84 mg and 56 mg showed numerically greater treatment differences compared with midazolam than the esketamine 28 mg dose (see Figure S1, available online).

The LS mean change from baseline in CDRS-R total score, beginning at 4 hours post first dose to day 25 in the double-blind phase, is shown in Figure S2a (available online). At the end of the double-blind phase (day 25), all 4 treatment groups showed continued improvement on the CDRS-R total score (LS mean [95% CI] between-group difference: −7.0 [−12.85, −1.06], −1.0 [−6.72, 4.63], and −6.5 [−12.94, −0.10] for the esketamine 28 mg, 56 mg, and 84 mg groups, respectively, relative to the midazolam group), which was sustained over the posttreatment follow-up phase of the study (Figure S2b, available online).

Consistent with the results of CDRS-R analyses, improvement in depressive symptoms, as assessed by

TABLE 1 Demographics and Baseline Characteristics (Safety Analysis Dataset)

	Oral midazolam + SOC[a] (n = 63)			Esketamine 28 mg + SOC[a] (n = 29)			Esketamine 56 mg + SOC[a] (n = 31)			Esketamine 84 mg + SOC[a] (n = 23)			Total (N = 146)		
	Mean	**(SD)**		**Mean**	**(SD)**		**Mean**	**(SD)**		**Mean**	**(SD)**		**Mean**	**(SD)**	
Age, y	15.2	(1.45)		14.9	(1.33)		14.8	(1.52)		14.3	(1.43)		14.9	(1.46)	
	n	**(%)**		**n**	**(%)**		**n**	**(%)**		**n**	**(%)**		**n**	**(%)**	
12-14	19	(30.2)		14	(48.3)		14	(45.2)		13	(56.5)		60	(41.1)	
15-17	44	(69.8)		15	(51.7)		17	(54.8)		10	(43.5)		86	(58.9)	
	n	**(%)**		**n**	**(%)**		**n**	**(%)**		**n**	**(%)**		**n**	**(%)**	
Sex															
Female	48	(76.2)		24	(82.8)		25	(80.6)		17	(73.9)		114	(78.1)	
Male	15	(23.8)		5	(17.2)		6	(19.4%)		6	(26.1)		32	(21.9)	
	n	**(%)**		**n**	**(%)**		**n**	**(%)**		**n**	**(%)**		**n**	**(%)**	
Race															
American Indian or Alaska Native	2	(3.2)		0			0			0			2	(1.4)	
Asian	1	(1.6)		0			2	(6.5)		0			3	(2.1)	
Black or African American	6	(9.5)		4	(13.8)		1	(3.2)		4	(17.4)		15	(10.3)	
Multiple	0			0			2	(6.5)		0			2	(1.4)	
White	53	(84.1)		25	(86.2)		23	(74.2)		17	(73.9)		118	(80.8)	
Not reported	1	(1.6)		0			3	(9.7)		2	(8.7)		6	(4.1)	
	n	**(%)**		**n**	**(%)**		**n**	**(%)**		**n**	**(%)**		**n**	**(%)**	
Ethnicity															
Hispanic or Latino	16	(25.4)		7	(24.1)		8	(25.8)		3	(13.0)		34	(23.3)	
Not Hispanic or Latino	46	(73.0)		19	(65.5)		20	(64.5)		19	(82.6)		104	(71.2)	
Not reported	1	(1.6)		3	(10.3)		3	(9.7)		1	(4.3)		8	(5.5)	
	Mean	**(SD)**	**[Range]**	**Mean**	**(SD)**	**[Range]**	**Mean**	**(SD)**	**[Range]**	**Mean**	**(SD)**	**[Range]**	**Mean**	**(SD)**	**[Range]**
CDRS-R total score	76.1	(10.65)	[58-101]	77.6	(8.08)	[60-93]	76.4	(9.08)	[60-95]	75.3	(11.78)	[58-98]	76.3	(10.00)	[58-101]
MADRS total score	38.8	(6.19)	[26-51]	38.7	(7.04)	[21-49]	38.4	(5.88)	[27-51]	39.4	(5.95)	[29-49]	38.8	(6.21)	[21-51]
	n	**(%)**		**n**	**(%)**		**n**	**(%)**		**n**	**(%)**		**n**	**(%)**	
CGI-SS-R															
Normal, not at all suicidal	0			0			0			0			0		
Questionably suicidal	1	(1.6)		0			0			1	(4.3)		2	(1.4)	
Mildly suicidal	3	(4.8)		1	(3.4)		2	(6.5)		0			6	(4.1)	
Moderately suicidal	7	(11.1)		11	(37.9)		5	(16.1)		5	(21.7)		28	(19.2)	
Markedly suicidal	21	(33.3)		8	(27.6)		10	(32.3)		10	(43.5)		49	(33.6)	
Severely suicidal	25	(39.7)		9	(31.0)		10	(32.3)		6	(26.1)		50	(34.2)	
Among most extremely suicidal patients	6	(9.5)		0			4	(12.9)		1	(4.3)		11	(7.5)	

(*continued*)

TABLE 1 Continued

	Oral midazolam + SOC[a] (n = 63)		Esketamine 28 mg + SOC[a] (n = 29)		Esketamine 56 mg + SOC[a] (n = 31)		Esketamine 84 mg + SOC[a] (n = 23)		Total (N = 146)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patient-reported frequency of suicidal thinking[b]										
Never	0		0		1	(3.2)	0		1	(0.7)
Rarely	3	(4.8)	0		0		1	(4.3)	4	(2.7)
Sometimes	6	(9.5)	4	(13.8)	2	(6.5)	1	(4.3)	13	(8.9)
Often	17	(27.0)	12	(41.4)	7	(22.6)	8	(34.8)	44	(30.1)
Most of the time	29	(46.0)	10	(34.5)	19	(61.3)	12	(52.2)	70	(47.9)
All of the time	8	(12.7)	3	(10.3)	2	(6.5)	1	(4.3)	14	(9.6)
Suicide attempt										
Lifetime	51	(81.0)	26	(89.7)	24	(77.4)	16	(69.6)	117	(80.1)
Within last 30 days	31	(49.2)	14	(48.3)	18	(58.1)	16	(69.6)	79	(54.1)

Note: *CDRS-R = Children's Depression Rating Scale–Revised; CGI-SS-R = Clinical Global Impression of Severity of Suicidality–Revised; MADRS = Montgomery–Åsberg Depression Rating Scale; SOC = standard of care.*

[a]*Comprehensive SOC included initial hospitalization, initiation or optimization of an oral antidepressant, and evidenced-based psychotherapy.*

[b]*From Suicide Ideation and Behavior Assessment Tool (SIBAT), Module 7 Assessment of Frequency of Suicidal Thinking (FoST).*

MADRS total score, was also observed in each of the 3 esketamine dose groups compared with midazolam at 24 hours post first dose (see Table S2, available online). The LS mean [95% CI] between-group differences were −1.4 [−5.97, 3.24], −3.5 [−7.97, 0.92], and −3.3 [−8.32, 1.72] for the esketamine 28 mg, 56 mg, and 84 mg groups, respectively.

In analyses defined by CDRS-R total score, response (53.6%-61.3%) and remission (16.1%-21.7%) were achieved by participants in all esketamine dose groups at 24 hours post first dose (see Table S3, available online). The differences vs midazolam for response were 4.4%, 12.1%, and 7.3% for the esketamine 28 mg, 56 mg, and 84 mg dose groups, respectively, and for remission were 9.9%, 8.2%, and 13.8% for the respective dose groups. At the day 25 end point, a majority of participants in all treatment groups had achieved response (esketamine 28 mg, 56 mg, and 84 mg, each plus comprehensive SOC: 96.4%, 71.0%, and 73.9%, respectively; midazolam plus comprehensive SOC: 77.8%), and the percentage of participants who achieved remission had increased in all treatment groups (esketamine 28 mg, 56 mg, and 84 mg, each plus comprehensive SOC: 60.7%, 35.5%, 56.5%; midazolam plus comprehensive SOC: 41.3%). Response and remission rates assessed by MADRS are presented in Table S3 (available online).

Severity of Suicidality. At 24 hours post first dose, participants in all 4 treatment groups experienced improvement in the severity of suicidality, as measured by CGI-SS-R (Figure 2). The LS mean change from baseline was −1.6, −1.6, and −1.3 points for the esketamine 28 mg, 56 mg, and 84 mg plus comprehensive SOC groups, respectively, and −1.3 points for the midazolam plus comprehensive SOC group (LS mean differences [95% CI] vs midazolam were −0.2 [−0.90, 0.41], −0.3 [−0.93, 0.31], and 0.0 [−0.69, 0.72] for the respective esketamine dose groups. Further improvement was observed in all 4 treatment groups at the day 25 end point.

At 4 hours post first dose, the LS mean change from baseline was −1.3, −1.7, and −1.3 points for the esketamine 28 mg, 56 mg, and 84 mg plus comprehensive SOC groups, respectively, and −0.9 points for the midazolam plus comprehensive SOC group (LS mean differences [95% CI] vs midazolam were −0.5 [−1.06, 0.08], −0.8 [−1.36, −0.28], and −0.5 [−1.10, 0.15] for the respective esketamine dose groups.

The percentage of participants who met criteria for resolution of suicidality directionally favored the esketamine dose groups, each plus comprehensive SOC, over the midazolam group plus comprehensive SOC at most time

TABLE 2 Primary End Point: Children's Depression Rating Scale–Revised (CDRS-R) Total Score Changes From Baseline to 24 Hours Post First Dose

	Oral midazolam + SOC[a] (n = 63)		Pooled esketamine 56 mg + esketamine 84 mg (n = 54)		Esketamine 28 mg + SOC[a] (n = 28)		Esketamine 56 mg + SOC[a] (n = 31)		Esketamine 84 mg + SOC[a] (n = 23)	
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Baseline	76.1	(10.65)	75.9	(10.23)	77.6	(8.08)	76.4	(9.08)	75.3	(11.78)
Change from baseline to 24 h post first dose	−26.2	(16.72)	−31.2	(14.90)	−29.6	(18.15)	−31.8	(12.92)	−30.3	(17.48)
ANCOVA analysis[b]										
Difference of LS means[c] (SE)	—		−5.8 (2.74)		−2.4 (3.35)		−5.9 (3.23)		−5.7 (3.65)	
95% CI on difference	—		−11.19, −0.35		−9.08, 4.19		−12.25, 0.53		−12.91, 1.55	
2-sided *p* value	—		.037		—		.072		.123	

Note: *CDRS-R total score ranges from 17 to 113; a higher score indicates a more severe condition. Negative change in score indicates improvement. Negative difference favors esketamine. ANCOVA = analysis of covariance; LS = least squares; SOC = standard of care.*
[a]*Comprehensive SOC included initial hospitalization, initiation or optimization of an oral antidepressant, and evidenced-based psychotherapy.*
[b]*Based on ANCOVA model with treatment (oral midazolam, esketamine 28 mg, 56 mg, and 84 mg) and analysis center as factors and baseline value as a covariate.*
[c]*Esketamine + SOC minus oral midazolam + SOC.*

points during the double-blind phase, beginning at 4 hours post first dose and at day 25 (see Figure S3; available online). Results for other indices of suicidality are presented in Figure S4 (available online).

Safety Results

The most common treatment-emergent adverse events reported for esketamine-treated adolescents (incidence ≥20% all dose groups combined) during the double-blind phase were dizziness, nausea, dissociation, headache, dysgeusia, somnolence, vomiting, hypoesthesia, and intentional self-injury (Table 3). Of note, the rates of treatment-emergent intentional self-injury were similar between the treatment groups (20.5% for esketamine and 19.0% for midazolam). Across the esketamine dose groups, a majority of known common events with esketamine occurred on a dosing day and resolved the same day (eg, 93.0% of dizziness events, 95.3% of nausea events, 94.8% of dissociation events, 100% of dysgeusia events, 98.9% of somnolence events). Most adverse events were mild or moderate in severity.

The most frequently reported adverse events during the posttreatment follow-up phase are summarized in Table S4 (available online). One participant treated with midazolam (adverse event of blood pressure increase) and no participants treated with esketamine discontinued study drugs during the double-blind phase due to an adverse event.

Serious adverse events were reported for 12 participants during the double-blind phase (esketamine 28 mg, 56 mg, 84 mg: 4 [13.8%], 7 [22.6%], 1 [4.3%], respectively; midazolam: 9 [14.3%]), none of which were considered related to study drug by the investigator. Suicide attempt (7 [8.4%] esketamine-treated participants and 5 [7.9%] midazolam-treated participants) and suicidal ideation (5 [6.0%] and 3 [4.8%] participants, respectively) were the only serious events reported by >1 participant. During the 6-month posttreatment follow-up phase, serious adverse events were reported for 25 (31.6%) participants who had been randomized to and treated with esketamine during the double-blind phase and 19 (32.2%) participants who had been randomized to midazolam; the most common (incidence >5%) events were suicide attempt (12 [15.2%] and 9 [15.3%] participants, respectively), suicidal ideation (11 [13.9%] and 4 [6.8%] participants, respectively), and depression (worsening) with suicidal ideation (4 [5.1%] and 3 [5.1%] participants, respectively).

There were no deaths during the double-blind phase. One participant died by suicide on day 193 in the follow-up phase, over 5 months after their last dose of study drug on day 29. This participant, who was randomized to midazolam plus SOC during the double-blind phase, had 4 known prior attempts and 2 additional attempts during the study.

Dissociative symptoms, as measured by the CADSS total score, were noted at the 40-minute postdose assessment across the esketamine dose groups and to a lesser extent in the midazolam group (see Figure S5, available online). Mean increases in CADSS total score from predose

FIGURE 2 Clinical Global Impression of Severity of Suicidality–Revised (CGI-SS-R) Score: Frequency Distribution at Baseline, 4 Hours Post First Dose, 24 Hours Post First Dose, and Day 25

Note: *At 24 hours post first dose, the least squares mean difference [95% CI] vs midazolam was −0.2 [−0.90, 0.41], −0.3 [−0.93, 0.31], and 0.0 [−0.69, 0.72] for the esketamine 28 mg, 56 mg, and 84 mg plus comprehensive standard of care (SOC) groups. Comprehensive SOC included initial hospitalization, initiation or optimization of an oral antidepressant, and evidenced-based psychotherapy. Please note color figures are available online.*

were generally dose related, typically resolved by 1.5 hours post dose, and attenuated with repeated dosing during the double-blind phase.

Sedation was measured by MOAA/S. During the double-blind phase, fewer participants in an esketamine plus comprehensive SOC group (28 mg: 5/29 [17.2%], 56 mg: 6/31 [19.4%], 84 mg: 6/23 [26.1%]) had an MOAA/S score ≤3 (corresponding to moderate or greater sedation) vs participants in the midazolam plus comprehensive SOC group (37/63 [58.7%]). An MOAA/S score ≤2 was recorded for 2 of 83 (2.4%) esketamine-treated participants and 23 of 63 (36.5%) midazolam-treated participants. No participant in either treatment group required medical intervention or experienced respiratory depression.

Symptoms of mania and psychosis-like adverse effects were measured by YMRS and BPRS+, respectively, the results of which are presented in the Supplement (available online). Analyses of the cognitive data identified no systematic effects

TABLE 3 Treatment-Emergent Adverse Events During the Double-Blind Treatment Phase

	Oral midazolam + SOC[a] (n = 63)		Total esketamine + SOC[a] (n = 83)		Esketamine 28 mg + SOC[a] (n = 29)		Esketamine 56 mg + SOC[a] (n = 31)		Esketamine 84 mg + SOC[a] (n = 23)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants with ≥1 adverse event	58	(92.1)	80	(96.4)	27	(93.1)	30	(96.8)	23	(100)
Most frequently reported adverse events[b]										
Dizziness	27	(42.9)	48	(57.8)	16	(55.2)	16	(51.6)	16	(69.6)
Nausea	11	(17.5)	36	(43.4)	8	(27.6)	15	(48.4)	13	(56.5)
Dissociation	11	(17.5)	35	(42.2)	12	(41.4)	12	(38.7)	11	(47.8)
Headache	18	(28.6)	30	(36.1)	10	(34.5)	13	(41.9)	7	(30.4)
Dysgeusia	15	(23.8)	27	(32.5)	10	(34.5)	8	(25.8)	9	(39.1)
Somnolence	24	(38.1)	27	(32.5)	10	(34.5)	9	(29.0)	8	(34.8)
Vomiting	4	(6.3)	18	(21.7)	5	(17.2)	7	(22.6)	6	(26.1)
Hypoesthesia[c]	2	(3.2)	23	(27.7)	8	(27.6)	9	(29.0)	6	(26.1)
Intentional self-injury	12	(19.0)	17	(20.5)	6	(20.7)	6	(19.4)	5	(21.7)
Euphoric mood	6	(9.5)	16	(19.3)	6	(20.7)	5	(16.1)	5	(21.7)
Anxiety	10	(15.9)	9	(10.8)	3	(10.3)	4	(12.9)	2	(8.7)
Vision blurred	1	(1.6)	9	(10.8)	2	(6.9)	4	(12.9)	3	(13.0)
Abdominal pain upper	4	(6.3)	8	(9.6)	3	(10.3)	2	(6.5)	3	(13.0)
Insomnia	8	(12.7)	8	(9.6)	4	(13.8)	2	(6.5)	2	(8.7)
Nasal discomfort	2	(3.2)	8	(9.6)	2	(6.9)	3	(9.7)	3	(13.0)
Sedation	9	(14.3)	8	(9.6)	2	(6.9)	4	(12.9)	2	(8.7)
Decreased appetite	0		7	(8.4)	3	(10.3)	4	(12.9)	0	
Suicide attempt	5	(7.9)	7	(8.4)	1	(3.4)	5	(16.1)	1	(4.3)
Tremor	1	(1.6)	7	(8.4)	3	(10.3)	2	(6.5)	2	(8.7)
Abdominal pain	1	(1.6)	5	(6.0)	3	(10.3)	0		2	(8.7)
Suicide ideation	5	(7.9)	5	(6.0)	3	(10.3)	2	(6.5)	0	

Note: Adverse events listed in decreasing order based on incidence across the esketamine dose groups and in alphabetical order for events with the same incidence. Investigators classified adverse events as mild (ie, awareness of symptoms that are easily tolerated, caused minimal discomfort, and did not interfere with everyday activities), moderate (sufficient discomfort to cause interference with normal activity), or severe (ie, extreme distress, causing significant impairment of functioning or incapacitation, and prevented normal everyday activities). SOC = standard of care.

[a]*Comprehensive SOC included initial hospitalization, initiation or optimization of an oral antidepressant, and evidenced-based psychotherapy.*

[b]*Incidence ≥10% in any esketamine dose group.*

[c]*Includes participants who had adverse event(s) of hypoesthesia, oral hypoesthesia, or both.*

of any dose of esketamine on attention/processing speed, executive function, working memory, or visual or verbal learning and memory (see Table S5, available online).

Findings from the PWC-20 during the 2 weeks after cessation of treatment with esketamine are presented in the Supplement (available online). No participant reported ketamine or phencyclidine use during the posttreatment follow-up phase (TLFB).

Transient elevations in blood pressure were observed with esketamine across all dosing days (mean [SD] maximum increases from predose: systolic, 9.4 [10.46], 10.7 [10.43], and 14.8 [13.24] mm Hg in the 28 mg, 56 mg, and 84 mg dose groups, respectively, and 5.0 [13.32] mm Hg for midazolam; diastolic, 9.1 [7.38], 10.7 [11.15], 15.0 [8.63], and 2.8 [9.30] mm Hg for the respective treatment groups). Few participants (1 [1.2%] esketamine-treated participant and 2 [3.2%] midazolam-treated participants) had elevated blood pressure reported as a treatment-emergent adverse event during the double-blind phase.

DISCUSSION

This novel phase 2b, dose-ranging study of esketamine enrolled vulnerable adolescents with MDD, the majority of whom were severely depressed and moderately to extremely

suicidal, a population typically excluded from antidepressant trials. More than half of the participants attempted suicide within 30 days before enrollment, and 80% had made a lifetime attempt. Following the design of phase 2 and 3 studies of esketamine in adults with MDD and acute suicidal ideation or behavior,[17,18,33] this study included a 4-week double-blind treatment period to rapidly control depressive symptoms and to bridge the gap of the delayed onset of the newly initiated or optimized oral antidepressant therapy, which often requires 4 to 6 weeks to exert their full effect.[12,14] Remarkably, 95% of the participants completed the treatment phase, and 80% completed the 6-month posttreatment follow-up phase.

Esketamine-treated study participants experienced rapid reduction of depressive symptoms. Results on the primary efficacy end point revealed statistically significant and clinically meaningful improvement of depressive symptoms at 24 hours post first dose with the pooled esketamine 56 mg and 84 mg doses compared with psychoactive placebo (midazolam), each in conjunction with comprehensive SOC. For context to these findings, albeit limited by differences in assessment time points, the between-group difference of −5.8 vs midazolam on the primary end point (post first dose on day 2) exceeds that for fluoxetine (−2.8), sertraline (−3.5), and escitalopram (−2.6) at study end point (week 6 to week 12) in randomized placebo-controlled registration trials.[34] Although the treatment differences vs midazolam in the individual esketamine 56 mg and 84 mg dose groups with relatively small sample sizes did not achieve statistical significance, the magnitude of the mean differences was consistent with that observed in the pooled dose analysis. A significant dose-response relationship for change in CDRS-R total score was observed at 24 hours post first dose.

The rapid reduction in depressive symptoms seen in this study of adolescents is consistent with that demonstrated in the phase 2 and 3 studies of esketamine in adults with MDD who had acute suicidal ideation or behavior.[17,18,33] Effect size relative to midazolam at 24 hours post first dose for the pooled 56 mg and 84 mg doses (0.36) and the individual 56 mg (0.38) and 84 mg (0.34) doses is similar to that observed in the phase 2/3 studies of esketamine[17,18,33] as well as in contemporary antidepressant trials.[35] A large majority of participants in all treatment groups had responded by day 25, when full oral antidepressant effects can be expected. Interestingly, the response and remission rates in the 28 mg dose at day 25 were the highest among all the treatment groups. However, this dose was less effective for rapid reduction of depressive symptoms. There was no rebound of depressive symptoms, as evidenced by CDRS-R and MADRS scores during the posttreatment follow-up phase.

The severity of suicidality improved in all treatment groups at 24 hours post first dose; the 95% CI for differences between each esketamine plus comprehensive SOC group and the midazolam plus comprehensive SOC group included zero, indicating no treatment differences for the esketamine dose groups compared with midazolam. Several factors, including the nonspecific benefits of study participation, may have led to mitigation of the suicidal crisis. Indeed, the comprehensive nature of the care provided, including initial hospitalization, supportive psychosocial intervention, initiation or optimization of oral antidepressant, and evidenced-based psychotherapy, likely had a significant therapeutic effect.

Additionally, this study used midazolam, a short-acting benzodiazepine, as a psychoactive placebo, potentially dampening signal detection on some measures of depressive symptoms, as has been observed by others.[36] Nonetheless, there appeared to be some improvement in severity of suicidality in the esketamine plus comprehensive SOC groups over the midazolam plus SOC group at 4 hours post first dose (Figure 2), as was the case for esketamine plus comprehensive SOC in the ASPIRE trials of adults, compared with placebo plus SOC.[17,18]

No new or unexpected safety concerns in adolescents were observed in this study compared with previous studies of adults with MDD at imminent risk for suicide.[17,18] The most common treatment-emergent adverse events (eg, dissociation, dizziness, dysgeusia, somnolence) reported for esketamine-treated adolescents were similar to those reported in adults, albeit with higher incidence rates. The onset of dissociative symptoms occurred shortly after the initiation of esketamine dosing, generally resolved by 1.5 hours after administration, and attenuated with repeated dose administration, consistent with the findings in the aforementioned phase 3 studies of adults.[17,18] The percentage of participants with moderate or greater sedation (MOAA/S score $\leq$3) at any time during the study was nearly 3-fold higher in the midazolam plus SOC group compared with the esketamine plus SOC groups, making midazolam an imperfect control for prevention of functional unblinding.

Of the participants treated with esketamine or midazolam, approximately 20% reported treatment-emergent self-injurious behavior during the 4-week double-blind phase and 24% and 37%, respectively, during the 6-month follow-up phase of the study. This is not unexpected given that the study enrolled adolescents with MDD at imminent risk of suicide, the majority (80%) of whom

reported a lifetime history of suicide attempt(s) at study entry.

All serious adverse events reported during the double-blind phase were related to underlying disease and deemed not related to study drugs according to the investigators. The occurrence of suicide attempts in the posttreatment follow-up phase was dispersed over the 6-month period, with no discernible pattern. There was a 15% incidence of suicide attempts during the 6-month posttreatment follow-up phase among participants randomized to esketamine or to midazolam. This is similar to the previously reported 13% incidence for hospitalized adolescents who attempted or reattempted suicide within 6 months of discharge from a psychiatric facility.[16]

Elevations in blood pressure among participants treated with esketamine were transient, with only 1 participant in the esketamine group (compared with 2 participants in the midazolam group) having an adverse event of increased blood pressure reported, reflecting the fact that investigators did not consider most blood pressure findings clinically significant. The magnitude of changes from predose in systolic and diastolic blood pressures in this study of adolescents is consistent with those observed in the ASPIRE studies of adults.[17,18]

The literature on ketamine or esketamine use in adolescents for depression or suicidality is scant. A few case reports and small studies of intravenous ketamine showed promising results in reduction of depressive symptoms in adolescents.[37] In a randomized, double-blind, single-dose crossover study of 17 adolescents with MDD (none imminently suicidal), a single ketamine infusion reduced depressive symptoms 24 hours post infusion compared with a midazolam infusion.[38] Participants were significantly more likely to respond to ketamine than to midazolam (76% and 35%, respectively). In a double-blind study, Zhou *et al.*[39] randomized 54 adolescent inpatients with moderate-to-severe MDD and suicidal ideation ($\geq$3 months) to receive 3 intravenous infusions of esketamine or midazolam administered over 5 days combined with routine inpatient care and antidepressants. A significantly greater reduction in suicidal ideation was seen with esketamine vs midazolam, beginning at 24 hours post first dose and remaining though day 6 (24 hours post last dose). Improvement of depression symptoms was numerically greater with esketamine vs midazolam from days 2 to 6, with a significant between-group difference observed only at day 6.[39]

The current phase 2b dose-ranging study is limited by the relatively small sample size, which was based on treatment differences for the primary efficacy end point; the study was not powered for other efficacy end points. Therefore, treatment differences should be interpreted with caution. We also acknowledge that modifications to the CDRS-R, to adapt this scale for the 24-hour time point, may need additional assessment of its psychometric properties. Conducting research in a population of adolescents with MDD and active suicidal ideation/intent presents several methodological challenges, including the aforementioned nonspecific treatment effect of hospitalization and study care. Another limitation is the transient side effects associated with esketamine. These well-characterized effects have the potential to lead to functional unblinding. To address this point, midazolam (which is known to produce psychoactive effects) was used as the active comparator. Despite differences in side-effect profiles, midazolam has been considered useful in maintaining the integrity of blinding for clinical trials assessing the antidepressant efficacy of ketamine.[36] However, no perfectly matched control for esketamine currently exists, and the potential for functional unblinding in this study thus remains a methodological limitation that requires consideration in the interpretation of the results.

This unprecedented study reveals important new information regarding the rapid reduction of depressive symptoms with esketamine nasal spray in adolescents with MDD and imminent suicidality. The results support further investigation of esketamine nasal spray for the rapid reduction of depressive symptoms in larger trials of adolescents.

CRediT authorship contribution statement

Colette Kosik-Gonzalez: Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis (supporting), Data curation, Conceptualization. **Dong-Jing Fu:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis (supporting), Data curation, Conceptualization. **Li Nancy Chen:** Writing – review & editing, Formal analysis. **Rosanne Lane:** Writing – review & editing, Validation, Methodology, Formal analysis. **Michael H. Bloch:** Writing – review & editing. **Melissa DelBello:** Writing – review & editing. **Carmen Moreno:** Writing – review & editing. **Wayne C. Drevets:** Writing – review & editing, Conceptualization. **Carla M. Canuso:** Writing – review & editing, Conceptualization.

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

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