Effect of Esketamine Nasal Spray Monotherapy on Emotional Blunting in Adult Patients With Treatment-Resistant Depression: A Post Hoc Analysis

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Introduction

- Emotional blunting is described as emotional numbness with an inability to feel negative or positive emotions, reduced emotional responsiveness, and feelings of detachment from others[1,2]
- Among patients with major depressive disorder (MDD) in the acute phase of depression, 72% reported severe emotional blunting[3]
- A common reason for treatment discontinuation, emotional blunting may be a residual symptom of depression or a side effect of antidepressant medication.[1,3] Approximately half of patients (46%) on selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, or tricyclic antidepressants reported experiencing emotional blunting[3]
- Esketamine nasal spray (ESK), the S-enantiomer of racemic ketamine, is a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist. The mechanism by which esketamine exerts its antidepressant effect is unknown[4]
- ESK is approved by the US Food and Drug Administration for treatment-resistant depression (TRD) in adults, as monotherapy or in conjunction with an oral antidepressant, and for depressive symptoms in adults with MDD with acute suicidal ideation or behavior, in conjunction with an oral antidepressant[5]
- A phase 4, multicenter, double-blind, randomized, placebo-controlled study (NCT04599855) showed that ESK monotherapy resulted in rapid and superior improvement in Montgomery-Åsberg Depression Rating Scale (MADRS) total score and numerical improvement in all 10 MADRS item scores at day 28[6,7]

Objective

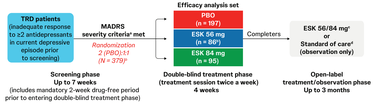
- This post hoc analysis examined the effect of ESK monotherapy on emotional blunting in patients with TRD by using MADRS items 7 and 8

Methods

Study design

- This was a multicenter, double-blind, randomized, placebo-controlled study (NCT04599855) conducted in the United States (**Figure 1**)

Figure 1: Study design



ESK, esketamine nasal spray; MADRS, Montgomery-Åsberg Depression Rating Scale; PBO, placebo; TRD, treatment-resistant depression. Current antidepressant medications (including adjunctive treatments) were tapered during the screening phase, resulting in a ≥2-week antidepressant- (and antipsychotic-) free observation period immediately prior to randomization.
[a]MADRS total score ≥28 at screening week 1, week 2, and day 1 (pre-randomization) and ≤25% improvement in the MADRS total score from screening week 1 to day 1 (pre-randomization); referred to as "nonresponse criteria" in the protocol.
[b]Of the 87 patients randomly assigned to receive ESK 56 mg, 1 did not receive a dose of study drug and was not included in the efficacy analysis set. [c]With or without standard of care. [d]Only 1 patient received standard of care without ESK.

- In the screening phase, patients were required to have taken no antidepressant medications for a minimum of 2 weeks prior to randomization
- In the double-blind treatment phase, patients were randomly assigned 2:1:1 to receive placebo, ESK 56 mg, or ESK 84 mg, twice weekly for 4 weeks

Assessments

- MADRS composite score of items 7 and 8 (emotional blunting composite score, range of scores 0-12), individual MADRS items 7 and 8, and Patient Health Questionnaire-9 (PHQ-9) item 1 were used as proxies for emotional blunting
  - MADRS item 7 is lassitude (range of scores 0-6), and is defined as "Representing difficulty getting started or slowness initiating and performing everyday activities"
  - MADRS item 8 is inability to feel (range of scores 0-6), and is defined as "Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced "
  - PHQ-9 item 1 is defined as "Little interest or pleasure in doing things," with score ranging from not experiencing it at all (0) to experiencing it every day (3) over the last 2 weeks
- Least squares (LS) mean change from baseline was assessed on days 2 (approximately 24 hours after first dose), 8, 15, 22, and 28 for MADRS scores; and days 15 and 28 for PHQ-9 item 1 score
  - The difference in LS mean changes from baseline among patients treated with ESK (56 mg or 84 mg) versus placebo were evaluated using analysis of covariance (ANCOVA) models, including treatment group, screening antidepressant status, and the baseline score as covariates
- The percentage of patients and the odds ratio (95% CI) of attaining a 1- or 2-point improvement from baseline in MADRS emotional blunting composite score (days 2 and 28) and PHQ-9 item 1 (days 15 and 28) were also measured
  - The percentage of patients achieving 1- or 2-point improvements was compared between treatment groups using the Cochran-Mantel-Haenszel test, adjusting for screening antidepressant status
- Treatment-emergent adverse events (TEAEs) were monitored throughout

Results

Demographic and baseline characteristics

- This analysis included 378 patients, of which 86 received ESK 56 mg, 95 received ESK 84 mg, and 197 received placebo
- At baseline, patient demographic and diseases characteristics (**Table 1**) and mean (SD) MADRS and PHQ-9 scores were similar between treatment groups (**Table 2**)

Table 1: Patient demographics and baseline clinical characteristics

	ESK 56 mg n = 86	ESK 84 mg n = 95	PBO n = 197	Total N = 378
Mean age (SD), years	46.5 (14.18)	44.8 (14.65)	45.2 (13.77)	45.4 (14.06)
Female, n (%)	51 (59.3)	61 (64.2)	119 (60.4)	231 (61.1)
Race, n (%)				
White	76 (88.4)	81 (85.3)	171 (86.8)	328 (86.8)
Black or African American	4 (4.7)	8 (8.4)	13 (6.6)	25 (6.6)
Other[a]	5 (5.8)	6 (6.3)	9 (4.6)	20 (5.3)
Mean duration of current episode (range), weeks	419.8 (12-2555)	406.4 (10-2236)	289.0 (10-1872)	348.3 (10-2555)
Number of episodes since diagnosis, n (%)				
≥3	54 (62.8)	55 (57.9)	127 (64.5)	236 (62.4)
Number of prior unsuccessful antidepressant trials, n (%)				
2	49 (57.0)	58 (61.1)	117 (59.4)	224 (59.3)
≥3	37 (43.0)	37 (38.9)	80 (40.6)	154 (40.7)
History of suicidal ideation in the past 6 months, n (%)	38 (44.2)	52 (54.7)	105 (53.3)	195 (51.6)

ESK, esketamine nasal spray; PBO, placebo.
[a]Includes American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, and Multiple. Does not include patients who were Not Reported (n = 4) or Unknown (n = 1).

Table 2: Mean baseline MADRS and PHQ-9 scores

	ESK 56 mg n = 86	ESK 84 mg n = 95	PBO n = 197
Mean baseline MADRS score (SD)			
Total score	37.5 (5.23)	36.6 (4.48)	37.5 (4.90)
Item 7	4.2 (0.97)	4.3 (0.78)	4.2 (1.00)
Item 8	4.1 (0.82)	4.2 (0.83)	4.2 (0.72)
Composite score (items 7+8)	8.3 (1.37)	8.5 (1.21)	8.5 (1.40)
Mean baseline PHQ-9 score, (SD)			
Total score	20.7 (3.43)	19.9 (3.79)	19.8 (4.07)
Item 1	2.7 (0.54)	2.6 (0.64)	2.5 (0.70)

ESK, esketamine nasal spray; MADRS, Montgomery-Åsberg Depression Rating Scale; PBO, placebo; PHQ-9, Patient Health Questionnaire-9.

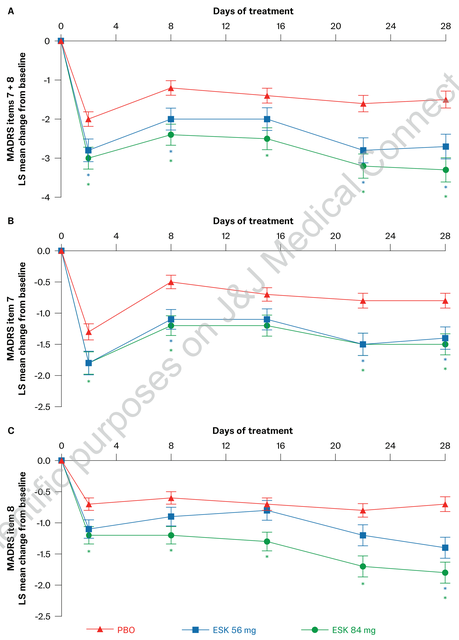
Change from baseline in emotional blunting composite score (MADRS items 7 + 8)

- On day 28, LS mean change in the emotional blunting composite score was −2.7 for ESK 56 mg, −3.3 for ESK 84 mg, and −1.5 for placebo ($P < 0.01$) (**Figure 2A**)
- As early as day 2, improvements in the emotional blunting composite score were significantly greater with ESK, with LS mean change from baseline of −2.8 for ESK 56 mg and −3.0 for ESK 84 mg, compared with −2.0 for placebo ($P < 0.05$) (**Figure 2A**)
- On day 28, LS mean change in MADRS item 7 score was −1.4 for ESK 56 mg, −1.5 for ESK 84 mg, and −0.8 for placebo ($P < 0.01$) (**Figure 2B**) and LS mean change in MADRS item 8 score was −1.4 for ESK 56 mg, −1.8 for ESK 84 mg, and −0.7 for placebo ($P < 0.01$) (**Figure 2C**)

Change from baseline in PHQ-9 item 1 score

- PHQ-9 item 1 scores also showed significant improvement with ESK at day 28, with LS mean change from baseline of −0.7 for ESK 56 mg, −1.0 for ESK 84 mg, and −0.3 for placebo ($P \leq 0.001$)

Figure 2: LS mean change from baseline in (A) emotional blunting composite score (MADRS items 7 + 8), (B) MADRS item 7 and (C) MADRS item 8

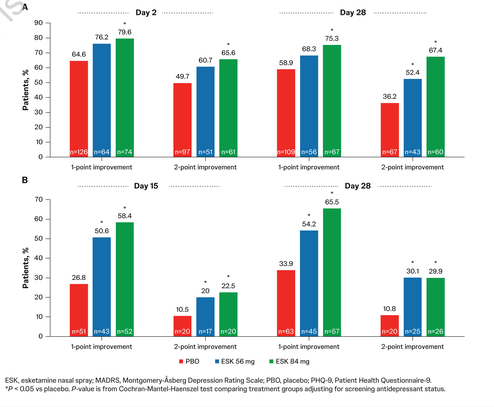


ESK, esketamine nasal spray; LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale; PBO, placebo.
*$P < 0.05$ vs placebo. P-value is from test for significant difference from ANCOVA model with change from baseline as the dependent variable, treatment as factor, and screening antidepressant status, and baseline value as covariates.

Proportion and odds ratio of patients attaining a 1- or 2- point improvement

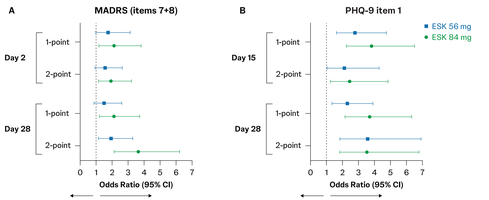
- In the ESK 84-mg group, significantly more patients attained a 1- or 2-point improvement in emotional blunting composite score versus placebo on day 28 and as early as day 2 ($P < 0.05$; **Figure 3A**)
- In the ESK 56-mg group, significantly more patients attained a 2-point improvement in emotional blunting composite score versus placebo on day 28 ($P < 0.05$; **Figure 3A**)
- In both ESK 56-mg and ESK 84-mg groups, significantly more patients attained a 1- or 2-point improvement in PHQ-9 item 1 score versus placebo on days 15 and 28 ($P < 0.05$; **Figure 3B**)
- The odds ratio (95% CI) for patients achieving a 1- or 2-point improvement in emotional blunting composite score (days 2 and 28) and PHQ-9 item 1 score (days 15 and 28) are shown in **Figure 4**

Figure 3: Percentage of patients with 1- or 2-point improvement from baseline in (A) emotional blunting composite score (MADRS items 7 + 8) and (B) PHQ-9 item 1



ESK, esketamine nasal spray; MADRS, Montgomery-Åsberg Depression Rating Scale; PBO, placebo; PHQ-9, Patient Health Questionnaire-9.
*$P < 0.05$ vs placebo. P-value is from Cochran-Mantel-Haenszel test comparing treatment groups adjusting for screening antidepressant status.

Figure 4: Odds ratio of patients achieving a 1- or 2-point improvement from baseline in (A) emotional blunting composite score (MADRS items 7 + 8) and (B) PHQ-9 item 1



ESK, esketamine nasal spray; MADRS, Montgomery-Åsberg Depression Rating Scale; PBO, placebo; PHQ-9, Patient Health Questionnaire-9.

Safety

- The most commonly reported TEAEs were nausea (24.8%), dissociation (24.3%), dizziness (21.7%), and headache (19.0%)
- Most TEAEs occurred on dosing days, were mild or moderate in severity, and resolved on the same day
- Serious adverse events were reported in 6 patients: ESK 56 mg: ankle fracture (n = 1); ESK 84 mg: ophthalmic migraine (n = 1) and suicide attempt (n = 1); placebo: self-injurious ideation (n = 1), suicidal ideation (n = 1), and acute myocardial infarction (n = 1). No serious adverse events were considered related to study medication
- No deaths were reported

Key Takeaway

Using MADRS items 7 and 8 and PHQ-9 item 1 as proxies for emotional blunting, results of this post hoc analysis show that ESK monotherapy significantly reduced emotional blunting versus placebo through day 28 and as early as day 2

Conclusion

Esketamine nasal spray monotherapy significantly reduced emotional blunting versus placebo through day 28 and as early as day 2 as measured by MADRS items 7 and 8 and PHQ-9 item 1. No new safety signals were identified

Limitations

The MADRS was developed specifically to detect change in depressive symptoms when measuring the effect of antidepressants on depression. It was not developed to measure emotional blunting as a stand-alone scale

Additionally, MADRS items 7 and 8 and PHQ-9 item 1 are not validated to assess emotional blunting

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Disclosures

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