Efficacy and Safety of Esketamine Nasal Spray as Monotherapy in Adults With Treatment-Resistant Depression Based on Oral Antidepressant Status at Study Entry: A Post Hoc Analysis

Andrew J Cutler[1], Dong-Jing Fu[2], Ibrahim Turkoz[2], **Patricia Cabrera**[2], Oliver Lopena[2], Lisa Lim[2], Muhammad Ahmed[2], Dillon McGovern[2]

[1]SUNY Upstate Medical University, Syracuse, NY; [2]Johnson & Johnson, Titusville, NJ

Introduction

- Major depressive disorder (MDD) is a chronic and potentially life-threatening psychiatric disorder that affects ~280 million people worldwide.[1] A proportion of patients with MDD (30%-55%) do not have an adequate response to ≥2 antidepressant regimens and are considered to have treatment-resistant depression (TRD)[2]
- Some patients stop their oral antidepressants (OADs) due to tolerability issues or lack of efficacy[3]
- Esketamine nasal spray (ESK) was initially approved by the US Food and Drug Administration in 2019, in conjunction with an OAD, for the treatment of TRD in adults and in 2020 for depressive symptoms in adults with MDD with acute suicidal ideation or behavior[4]
- Primary findings from a phase 4, randomized, double-blind, placebo-controlled, multicenter study showed that ESK as monotherapy led to a superior improvement in Montgomery-Åsberg Depression Rating Scale (MADRS) total score compared with placebo at day 28, with improvements seen as early as day 2[5]
  - Based on these results, ESK was approved by the US Food and Drug Administration as the first and only monotherapy for adults with TRD[4]

Objective

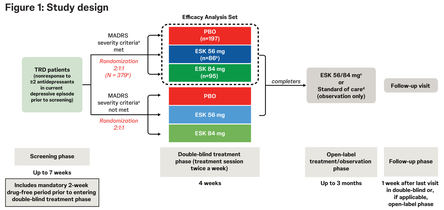
- To evaluate the efficacy and safety of ESK monotherapy in adults with TRD based on their OAD treatment status at study entry

Methods

Study design

- This is a subgroup analysis of a randomized, double-blind, multicenter, placebo-controlled study (NCT04599855) conducted in the United States (**Figure 1**)
- Patients entered the screening phase either taking OADs or not taking OADs
- Prior to randomization, patients were required to discontinue OADs for ≥2 weeks in the screening phase
- Patients were randomly assigned 2:1:1 to receive fixed doses of placebo, ESK 56 mg, or ESK 84 mg twice weekly for 4 weeks

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 (prerandomization) and ≤25% improvement in the MADRS total score from screening week 1 to day 1 (prerandomization); referred to as "nonresponse criteria" in the protocol.
[b]One of 57 patients randomly assigned to ESK 56 mg 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.

Data analyses

- Efficacy was assessed in all randomly assigned patients who received ≥1 dose of study intervention in the double-blind treatment phase and who met the predefined severity criteria based on MADRS assessments during the screening phase (efficacy analysis set) (**Figure 1**)
- Within the on- and off-OAD treatment subgroups, changes from baseline in MADRS total score at days 2, 8, 15, 22, and 28 during the double-blind treatment phase were assessed using a mixed-effect model for repeated measures and included fixed-effect model terms for intervention group, study center, day, day-by-treatment interaction, and baseline MADRS total score as a covariate. The difference of least squares means was used to assess differences between placebo and ESK (56 mg, 84 mg, or both doses) intervention groups
- In this short-term study, a change in MADRS total score from baseline was considered clinically meaningful if it was, on average, 2 points different in patients treated with ESK compared with placebo[6,7]
- Response was defined as a ≥50% improvement in MADRS total score compared with baseline
- Remission was defined as having a MADRS total score of ≤12
- Safety was assessed in all patients who received ≥1 dose of study intervention in the double-blind treatment phase (safety analysis set)
- Treatment-emergent adverse events (TEAEs) were summarized descriptively

Results

Demographics and baseline characteristics

- A total of 378 patients were in the efficacy analysis set; 248 patients (65.6%) were on OAD treatment at study entry, and 130 patients (34.4%) were off OAD treatment at study entry (**Table 1**)
- Patient demographics and baseline characteristics, including psychiatric history, were generally similar between the on- and off-OAD treatment subgroups
  - In both on- and off-OAD treatment subgroups, patients were primarily White (87.1% and 86.2%, respectively) and female (60.5% and 62.3%, respectively)
  - The mean MADRS total score was 37.2 and 37.5 for the on- and off-OAD treatment subgroups, respectively
- For patients who were on OAD treatment at study entry, the most common OADs were bupropion (35.9%), duloxetine (15.9%), trazodone (14.6%), sertraline (13.6%), fluoxetine (11.7%), and escitalopram (10.0%); the proportion of patients taking these medications were similar between placebo and ESK treatment groups (**Table 2**)

Table 1: Patient demographics and baseline characteristics

	On OAD treatment at study entry[a]			Off OAD treatment at study entry[a]		
	PBO n = 124	ESK n = 124	Total n = 248	PBO n = 73	ESK n = 57	Total n = 130
Mean age (SD), years	46.9 (13.1)	46.2 (13.9)	46.5 (13.5)	42.5 (14.4)	44.2 (15.4)	43.2 (14.9)
Female, n (%)	78 (62.9)	72 (58.1)	150 (60.5)	41 (56.2)	40 (70.2)	81 (62.3)
Race, n (%)						
American Indian or Alaska Native	0	0	0	0	1 (1.8)	1 (0.8)
Asian	3 (2.4)	4 (3.2)	7 (2.8)	2 (2.7)	2 (3.5)	4 (3.1)
Black or African American	12 (9.7)	7 (5.6)	19 (7.7)	1 (1.4)	5 (8.8)	6 (4.6)
White	107 (86.3)	109 (87.9)	216 (87.1)	64 (87.7)	48 (84.2)	112 (86.2)
Not reported	1 (0.8)	0	1 (0.4)	2 (2.7)	1 (1.8)	3 (2.3)
Duration of current episode, mean (SD), weeks	244.7 (286.9)	395.9 (492.0)	320.3 (409.0)	364.4 (373.0)	449.4 (409.7)	401.6 (390.3)
Baseline MADRS total score, mean (SD)	37.5 (5.0)	36.9 (4.9)	37.2 (4.9)	37.7 (4.8)	37.2 (4.8)	37.5 (4.8)
Baseline PHQ-9 total score, mean (SD)	19.5 (4.2)	20.3 (3.6)	19.9 (3.9)	20.3 (3.9)	20.3 (3.7)	20.3 (3.8)
Baseline CGI-S score, mean (SD)	4.9 (0.6)	4.9 (0.6)	4.9 (0.6)	4.9 (0.6)	5.0 (0.7)	5.0 (0.7)
Number of prior OADs with nonresponse, n (%)						
2	76 (61.3)	76 (61.3)	152 (61.3)	41 (56.2)	31 (54.4)	72 (55.4)
≥3	48 (38.7)	48 (38.7)	96 (38.7)	32 (43.8)	26 (45.6)	58 (44.6)

CGI-S, Clinical Global Impression-Severity; ESK, esketamine nasal spray; MADRS, Montgomery-Åsberg Depression Rating Scale; OAD, oral antidepressant; PBO, placebo; PHQ-9, 9-item Patient Health Questionnaire.
[a]Assessment of the efficacy analysis set, N = 378.

Table 2: Most common oral antidepressants taken within 7 days of study entry

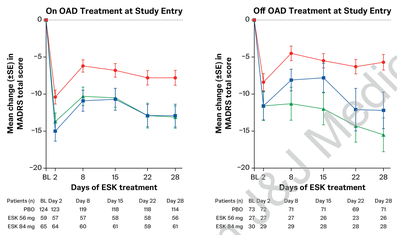
	On OAD treatment at study entry		
	PBO n = 151	ESK n = 142	Total[a,b] n = 293
Bupropion, n (%)	63 (39.9)	48 (31.6)	111 (35.9)
Duloxetine, n (%)	25 (15.8)	24 (15.8)	49 (15.9)
Trazodone, n (%)	22 (13.9)	23 (15.1)	45 (14.6)
Sertraline, n (%)	20 (12.7)	22 (14.5)	42 (13.6)
Fluoxetine, n (%)	15 (9.5)	21 (13.8)	36 (11.7)
Escitalopram, n (%)	19 (12.0)	12 (7.9)	31 (10.0)

ESK, esketamine nasal spray; OAD, oral antidepressant, PBO, placebo.
[a]Patients who were on OAD treatment at study entry and had the name of a prior OAD medication, taken within 7 days of study entry, recorded.
[b]Assessment of the safety analysis set, N = 476 total patients.

Change from baseline in MADRS total score

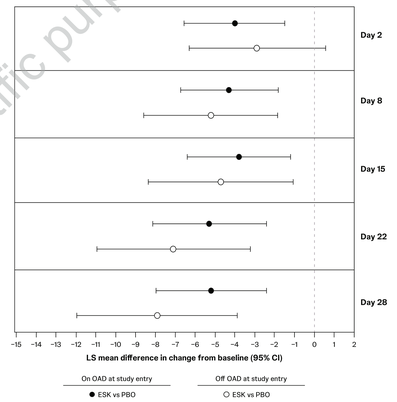
- ESK demonstrated improvements in mean MADRS total score change over time compared with placebo, regardless of OAD treatment status at study entry (**Figure 2**)
- Regardless of OAD treatment status at study entry, a clinically meaningful decrease in MADRS total score occurred at day 28, and starting as early as day 2, in patients treated with ESK compared with placebo (**Figure 3**)
- Similarly, an improvement in MADRS total score in patients treated with ESK compared with placebo was seen at both ESK doses (56 mg and 84 mg) and at all time points (**Figure 4**)

Figure 2: Mean change from baseline in MADRS total score over time



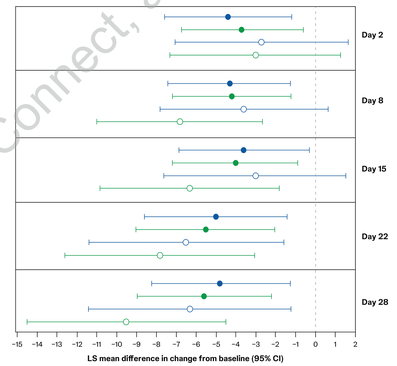
BL, baseline; ESK, esketamine nasal spray; MADRS, Montgomery-Åsberg Depression Rating Scale; OAD, oral antidepressant; PBO, placebo.
MADRS total score ranges from 0 to 60; a higher score indicates a more severe condition. Negative change in score indicates improvement.

Figure 3: Least squares mean difference in change from baseline in MADRS total score in patients treated with ESK compared with placebo



ESK, esketamine nasal spray; LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale; OAD, oral antidepressant; PBO, placebo.
Assessment of full efficacy analysis set, N = 378.
LS mean differences and 95% CIs are based on a mixed model for repeated measures with change from baseline as the response variable and the fixed-effect model terms for intervention group, analysis center, day, and day-by-intervention interaction, and the baseline MADRS total score as covariates. A negative difference favors ESK.

Figure 4: Least squares mean difference in change from baseline in MADRS total score in patients treated with ESK (54 mg or 84 mg) compared with placebo



ESK, esketamine nasal spray; LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale; OAD, oral antidepressant; PBO, placebo.
Assessment of the efficacy analysis set, N = 378.
LS mean differences and 95% CIs are based on a mixed model for repeated measures with change from baseline as the response variable and the fixed-effect model terms for intervention group, analysis center, day, and day-by-intervention interaction, and the baseline MADRS total score as covariates. A negative difference favors ESK.

Response and remission rates

- Numerically higher response rates (≥50% improvement in MADRS total score compared with baseline) and remission rates (MADRS total score of ≤12) were observed with ESK treatment, regardless of OAD status, compared with placebo at all time points of the double-blind treatment phase (days 2, 8, 15, 22, and 28)
- At day 28, response rates for on- and off-OAD treatment ESK subgroups (56-mg and 84-mg groups combined) were 29.9% and 29.6%, respectively, compared with placebo at 19.3% and 8.5%, respectively
- At day 28, remission rates for on- and off-OAD ESK treatment subgroups (56-mg and 84-mg groups combined) were 19.7% and 22.2%, respectively, compared with placebo at 9.6% and 4.2%, respectively

Safety

- The most common TEAEs (≥5% of patients) were nausea, headache, dizziness, dissociation, and fatigue (**Table 3**)
- Common TEAEs were experienced in similar proportions between on- and off-OAD treatment subgroups
- Most TEAEs were mild and resolved within the same day as dosing

Table 3: Most common treatment-emergent adverse events (in ≥5% of total patients)

	On OAD treatment at study entry[a]		Off OAD treatment at study entry[a]	
	PBO n = 161	ESK n = 158	PBO n = 89	ESK n = 68
Nausea, n (%)	16 (9.9)	34 (21.5)	5 (5.6)	22 (32.4)
Headache, n (%)	18 (11.2)	31 (19.6)	4 (4.5)	12 (17.6)
Dizziness, n (%)	12 (7.5)	32 (20.3)	6 (6.7)	17 (25.0)
Dissociation, n (%)	2 (1.2)	39 (24.7)	5 (5.6)	16 (23.5)
Fatigue, n (%)	6 (3.7)	12 (7.6)	5 (5.6)	3 (4.4)

ESK, esketamine nasal spray; OAD, oral antidepressant; PBO, placebo.
[a]Assessment of the safety analysis set, N = 476 total patients.

Key Takeaway

Regardless of OAD status at study entry, treatment with esketamine nasal spray as monotherapy in adults with treatment-resistant depression is associated with clinically meaningful improvements in MADRS total score versus placebo at day 28, and as early as day 2

- In this analysis of patients with treatment-resistant depression, approximately 1/3 of patients were not receiving an OAD upon study entry

Esketamine nasal spray monotherapy can be an important new treatment option for patients with treatment-resistant depression

Limitations

This is a post hoc subgroup analysis, and the small number of patients and the difference in sample size between subgroups may limit the interpretation of the results

Conclusions

Patients treated with twice-weekly esketamine nasal spray monotherapy have clinically meaningful improvements in MADRS total score compared with placebo and have a higher rate of remission and response over 28 days of treatment, regardless of whether they were being treated with OADs at the time of study entry

The incidence of TEAEs was similar between on- and off-OAD treatment subgroups, and TEAEs were mild and transient in nature

Acknowledgments

The authors thank Emily Spaulding, PhD (ApotheCom, Yardley, PA), for editorial and writing assistance, which was funded by Janssen Scientific Affairs, LLC, a Johnson & Johnson company.

Disclosures

AJC has served as a consultant or on advisory boards for AbbVie, Acadia, Alfasigma, Alkermes, Anavex Life Sciences, Arrivo BioVentures, Autobahn Therapeutics, Axsome, Biogen, Biohaven, Boehringer Ingelheim, Brii Biosciences, Bristol Myers Squibb, Cerevel, Cognitive Research Corporation, Corium, Delpor, Evolution Research Group, 4M Therapeutics, Intra-Cellular Therapies, J&J Innovative Medicine, Jazz Pharma, Karuna, LivaNova, Lundbeck, Luye Pharma, MapLight Therapeutics, MedAvante-ProPhase, Mertavi, Neumora, Neurocrine, Neuroscience Education Institute, NeuroSigma, Noven, Otsuka, PaxMedica, Relmada, Sage Therapeutics, Sirtsei Pharmaceuticals, Supernus, Teva, Thynk, Tris Pharma, Vanda Pharmaceuticals, and VistaGen; has served on speaker bureaus for AbbVie, Alfasigma, Alkermes, Axsome, Boehringer Ingelheim, Bristol Myers Squibb, Corium, Intra-Cellular Therapies, J&J, Lundbeck, Neurocrine, Noven, Otsuka, Supernus, Teva, Tris Pharma, and Vanda Pharmaceuticals; has served on data safety monitoring boards for Alar Pharma, COMPASS Pathways, Freedom Biosciences, and Pain Therapeutics; and holds has stock options/equity in 4M Therapeutics.

D-JF, IT, PC, OL, LL, MA, and DM are employees of Johnson & Johnson and may hold stock or restricted stock units in Johnson & Johnson.

Presented at the American Society of Clinical Psychopharmacology (ASCP) Annual Meeting; May 27-30, 2025; Scottsdale, Arizona, USA

References

1. World Health Organization. Depressive disorder (depression). https://www.who.int/news-room/fact-sheets/detail/depression. Accessed March 17, 2025. 2. McIntyre RS et al. *World Psychiatry*. 2023;22(3):394-412. 3. Warden D et al. *Psychother Psychosom*. 2009;78(6):372-379. 4. SPRAVATO® (esketamine) nasal spray, CIII. Prescribing information. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2025. 5. Janik A et al. Presented at: Psych Congress; October 29-November 2, 2024; Boston, MA, USA. Poster #112. 6. Melander H et al. *Eur Neuropsychopharmacol*. 2008;18(9):623-627. 7. Montgomery SA, Moller HJ. *Int Clin Psychopharmacol*. 2009;24(3):111-118.

Novel Pathways in Depression

Scan the QR code

This study was funded by Janssen Scientific Affairs, LLC, a Johnson & Johnson company.