Efficacy and Safety of Esketamine Nasal Spray as Monotherapy in Adult Patients With Treatment-Resistant Depression for up to 4 Months of Treatment: A Post Hoc Analysis

Andrew J Cutler[1], Dong-Jing Fu[2], Ibrahim Turkoz[2], Mai Himedan[2], Oliver Lopena[2], Lisa Lim[2], John S Verbanac[2]

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

Introduction

- Treatment-resistant depression (TRD) is a chronic condition and is associated with higher rates of relapse, increased mortality, and a greater risk for suicide compared with non–treatment-resistant depression[1,2]
  - TRD is most frequently defined as an inadequate response to at least 2 oral antidepressants of adequate dose and duration during the current episode
- Esketamine nasal spray (ESK) was initially approved in the US for the treatment of TRD in adults, in conjunction with an oral antidepressant[3]
- Findings from a phase 4, randomized, double-blind, placebo-controlled, multicenter study (NCT04599855) demonstrated that ESK as monotherapy led to a rapid and superior improvement in Montgomery-Åsberg Depression Rating Scale (MADRS) total score compared with placebo at day 28[4]
  - Based on these findings, ESK was approved in the US as the first and only monotherapy for adults with TRD[3,5]
- The objective of this post hoc analysis was to evaluate the efficacy and safety of ESK used as monotherapy in adult patients with TRD for a duration of up to 4 months, including double-blind and open-label treatment phases

Methods

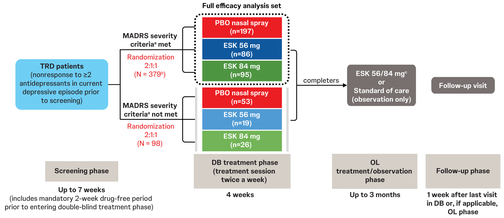
Study design

- The multicenter ESK phase 4 study included adults (≥18 years) with major depressive disorder and a history of nonresponse (≤25% improvement) to ≥2 different oral antidepressants
  - Nonresponse to oral antidepressants was assessed using the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire
- The study had 4 phases: screening, double-blind (DB) treatment, open-label (OL) treatment/observation, and follow-up (**Figure 1**)
- During the 4-week DB phase, patients were randomly assigned to receive monotherapy with fixed doses of ESK 56 mg, ESK 84 mg, or placebo (PBO) twice weekly
- During the 12-week OL phase, all patients who received ESK treatment followed US prescribing information dosing recommendations, with flexible ESK dosing (56 or 84 mg) based on clinical judgement
  - All patients received OL ESK 56 mg on Day 28, regardless of their assignment in the DB phase; subsequent doses were flexible (56 or 84 mg) based on efficacy and tolerability
  - The recommended dosing frequency was twice weekly for Weeks 5 to 8, followed by once weekly dosing from Weeks 9 to 12. From Week 13 to Week 16, the dosing frequency (weekly or every other week) was based on clinical judgment
- If clinically indicated, patients could receive an oral antidepressant during the OL phase in addition to ESK
- This post hoc analysis included patients from 3 cohorts from the study
  - Received PBO during the DB phase and subsequently switched to flexibly dosed ESK during the OL phase (PBO/ESK)
  - Received ESK 56 mg during the DB phase and continued with flexibly dosed ESK during the OL phase (ESK 56 mg/ESK)
  - Received ESK 84 mg during the DB phase and continued with flexibly dosed ESK during the OL phase (ESK 84 mg/ESK)
- Only patients from the full efficacy analysis set (**Figure 1**) who received ESK as monotherapy (without add-on oral antidepressants) during the OL phase were included in this analysis; randomized patients who were not part of the full efficacy analysis set were not included

Assessments

- Efficacy was measured using the change in MADRS total score over time
- Additional assessments included the proportion of patients who achieved the following at end of the DB (day 28) and OL (day 105)
  - Clinically substantial improvement (≥12-point reduction in MADRS total score from DB baseline)
  - Response (≥50% reduction in MADRS total score from DB baseline)
  - Remission (MADRS total score ≤12)
- Treatment-emergent adverse events (TEAEs) were monitored for the duration of the study

Figure 1: Study design



DB, double-blind; ESK, esketamine nasal spray; MADRS, Montgomery-Åsberg Depression Rating Scale; OL, open-label; PBO, placebo; TRD, treatment-resistant depression.
[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 "non-response criteria") in the protocol.
[b]There was 1 patient who was not treated.
[c]If clinically indicated, patients could receive an oral antidepressant in addition to ESK. However, this analysis only included patients who received ESK monotherapy without add-on oral antidepressants.

Results

Baseline characteristics

- Of a total 227 patients included in this analysis, 121 received placebo, 48 received ESK 56 mg, and 58 received ESK 84 mg during the DB phase
- Demographic and baseline characteristics were comparable among the treatment arms (**Table 1**)
  - At DB baseline, mean age was 44.8 years, most patients (60.4%) were female, and mean (SD) MADRS total score was 37.3 (4.74)

Table 1: Demographics and baseline characteristics

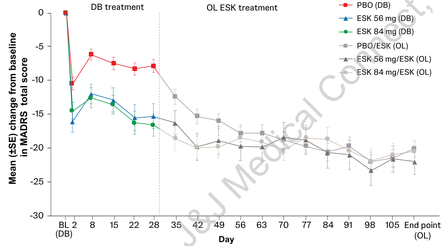
	PBO/ESK N = 121	ESK 56 mg/ESK N = 48	ESK 84 mg/ESK N = 58	Total N = 227
Mean age (SD), years	44.2 (13.49)	45.5 (15.42)	45.4 (15.15)	44.8 (14.29)
Sex, n (%)				
Female	73 (60.3)	27 (56.3)	37 (63.8)	137 (60.4)
Male	48 (39.7)	21 (43.8)	21 (36.2)	90 (39.6)
Race, n (%)				
American Indian or Alaska Native	0	1 (2.1)	0	1 (0.4)
Asian	2 (1.7)	0	2 (3.4)	4 (1.8)
Black or African American	9 (7.4)	3 (6.3)	3 (5.2)	15 (6.6)
Native Hawaiian or Other Pacific Islander	0	0	1 (1.7)	1 (0.4)
White	105 (86.8)	43 (89.6)	51 (87.9)	199 (87.7)
Multiple[a]	3 (2.5)	0	1 (1.7)	4 (1.8)
Not Reported	1 (0.8)	1 (2.1)	0	2 (0.9)
Unknown	1 (0.8)	0	0	1 (0.4)
Antidepressant status at screening/entry, n (%)				
On-treatment	66 (54.5)	30 (62.5)	38 (65.5)	134 (59.0)
Off-treatment	55 (45.5)	18 (37.5)	20 (34.5)	93 (41.0)
Mean duration of current depressive episode (SD), weeks	305.1 (338.89)	294.1 (294.83)	379.9 (454.55)	321.9 (363.80)
Mean baseline MADRS score (SD)	37.5 (4.95)	37.5 (4.82)	36.6 (4.23)	37.3 (4.74)
Failed antidepressant intervention history, n (%)[b]				
2	71 (58.7)	29 (60.4)	36 (62.1)	136 (59.9)
≥3	50 (41.3)	19 (39.6)	22 (37.9)	91 (40.1)

ESK, esketamine nasal spray; MADRS, Montgomery-Åsberg Depression Rating Scale; PBO, placebo.
[a]If multiple race categories were selected, the race was recorded as "Multiple."
[b]Failed antidepressant medications taken for at least 6 weeks during the current episode as obtained from the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire.

Efficacy

- Improvements in depressive symptoms during the DB phase continued in the OL phase across the ESK treatment groups (**Figure 2**)
  - Mean (SE) changes in MADRS total score from DB baseline to the end of the OL phase were −20.1 (1.25), −22.0 (1.93) and −20.5 (1.62), in the PBO/ESK, ESK 56 mg/ESK, and ESK 84 mg/ESK groups, respectively
  - For patients who received PBO during the DB phase and subsequently switched to flexibly dosed ESK (PBO/ESK), mean (SE) change in MADRS total score from day 28 to day 105 was −12.2 (1.18)
- At the end of the OL phase, the proportion of patients achieving clinically substantial improvement, response, and remission was similar among the 3 treatment arms (**Figure 3**)
  - At the end of the OL phase, clinically substantial improvement in MADRS total score was attained in 68.9%, 70.8%, and 77.6% of patients in the PBO/ESK, ESK 56 mg/ESK, and ESK 84 mg/ESK groups, respectively
  - Response was attained in 58.0%, 60.4%, and 65.5% of patients, and remission was attained in 41.2%, 47.9%, and 39.7% of patients, respectively, at day 105

Figure 2: Mean (±SE) change from baseline in MADRS total score over time



PBO/ESK	121	119	120	119	121	115	112	107	101	105	106	100	96	93	93	97	119
ESK 56 mg/ESK	48	47	47	46	48	47	43	45	43	44	43	43	39	43	36	45	48
ESK 84 mg/ESK	58	57	58	58	58	54	54	51	50	53	53	51	52	51	43	52	58

BL, baseline; DB, double-blind; ESK, esketamine nasal spray; MADRS, Montgomery-Åsberg Depression Rating Scale; OL, open-label; PBO, placebo.

Safety

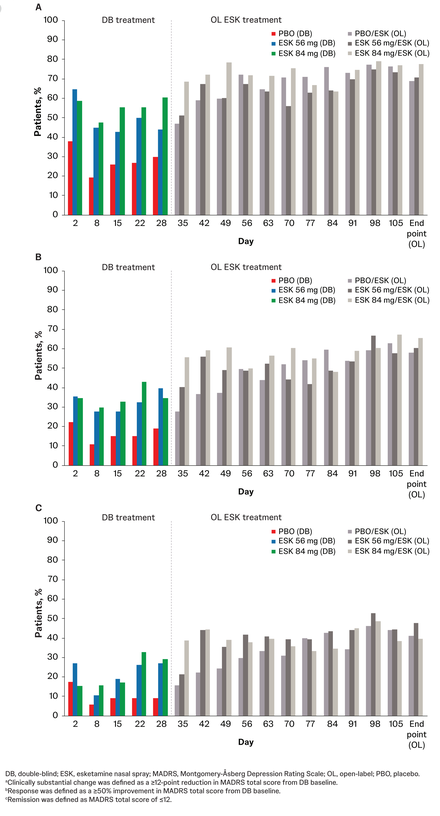
- The most commonly reported TEAEs were nausea, dissociation, dizziness, and headache (**Table 2**)
- Results from this analysis were consistent with the established safety and tolerability profile of ESK, with no new safety signals identified[6]

Table 2: Most frequently reported (≥5%) TEAEs during the DB and OL phases

TEAE, n (%)	PBO/ESK N = 121	ESK 56 mg/ESK N = 48	ESK 84 mg/ESK N = 58
Anxiety	2 (1.7)	0	4 (6.9)
Blood pressure increased	1 (0.8)	3 (6.3)	3 (5.2)
Dissociation	4 (3.3)	9 (18.8)	11 (19.0)
Dizziness	6 (5.0)	13 (27.1)	10 (17.2)
Fatigue	5 (4.1)	3 (6.3)	2 (3.4)
Feeling drunk	0	5 (10.4)	4 (6.9)
Headache	11 (9.1)	5 (10.4)	12 (20.7)
Nausea	10 (8.3)	12 (25.0)	12 (20.7)
Vomiting	1 (0.8)	2 (4.2)	5 (8.6)

DB, double-blind; ESK, esketamine nasal spray; OL, open-label; PBO, placebo; TEAE, treatment-emergent adverse event.
Patients were counted only once for any given event, regardless of the number of times they experienced the event.

Figure 3: Proportion of patients achieving (A) clinically substantial change,[a] (B) response,[b] and (C) remission[c]



DB, double-blind; ESK, esketamine nasal spray; MADRS, Montgomery-Åsberg Depression Rating Scale; OL, open-label; PBO, placebo.
[a]Clinically substantial change was defined as a ≥12-point reduction in MADRS total score from DB baseline.
[b]Response was defined as a ≥50% improvement in MADRS total score from DB baseline.
[c]Remission was defined as MADRS total score of ≤12.

Key Takeaway

ESK monotherapy demonstrated efficacy up to 4 months in adult patients with TRD, with a well established safety profile

Conclusions

This analysis showed that treatment with esketamine nasal spray monotherapy alone for up to 4 months in adult patients with TRD was associated with clinically substantial and sustained improvements in depression symptoms

TEAEs were consistent with the established safety and tolerability profile of esketamine nasal spray, with no new safety signals identified

Limitations

This is a post hoc analysis with small numbers of patients in each subgroup

Acknowledgments

The authors thank Laura van Laeren, PhD (ApotheCom, Yardley, PA), for editorial and writing assistance, which was funded by Johnson & Johnson.

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, Bril 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, LivoNova, Lundbeck, Luye Pharma, MapLight Therapeutics, MedAvante-ProPhase, Mentavi, Neumora, Neurocrine, Neuroscience Education Institute, NeuroSigma, Noven, Otsuka, PsyMedica, 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; owns stock options or equity in 4M Therapeutics; and is on data safety monitoring boards for Alar Pharma, COMPASS Pathways, Freedom Biosciences, and Pain Therapeutics. DJF, IT, MH, OL, LL, and JSV are employees of Janssen Scientific Affairs, LLC, a Johnson & Johnson company, and stockholders of Johnson & Johnson.

Previous presentation

Presented at the 2025 Anxiety and Depression Association of America (ADAA) Annual Conference; April 3-5, 2025; Las Vegas, Nevada, USA; the 28th Annual Meeting of the American Association of Psychiatric Pharmacists (AAPP); April 27-30, 2025; Salt Lake City, Utah, USA; and the Psych Congress Elevate; May 28-31, 2025; Las Vegas, Nevada, USA

Novel Pathways in Depression

Scan the QR code

The QR code is intended to provide scientific information for individual reference, and the information should not be altered or reproduced in any way.

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

Presented at Psych Congress; September 17 - 21, 2025, San Diego, California, USA

References

1. Gaynes BN et al. Definition of treatment-resistant depression in the Medicare population. Rockville (MD): Agency for Healthcare Research and Quality; 2018. 2. McIntyre RS et al. *World Psychiatry*. 2023;22(3):394-412. 3. SPRAVATO® (esketamine) nasal spray, CIII. Prescribing information. Janssen Pharmaceuticals, Inc; 2025. Accessed August 20, 2025. https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/SPRAVATO-pipdf
4. Janik A et al. *JAMA Psychiatry*. Published online July 02, 2025. doi:10.1001/jamapsychiatry.2025.1317. 5. SPRAVATO® (esketamine) approved in the U.S. as the first and only monotherapy for adults with treatment-resistant depression. News release. Johnson & Johnson; 2025. Accessed August 20, 2025. https://www.jnj.com/media-center/press-releases/spravato-esketamine-approved-in-the-u-s-as-the-first-and-only-monotherapy-for-adults-with-treatment-resistant-depression
6. Reif A et al. *N Engl J Med*. 2023;389(14):1298-1309.