

Plain Language Summary

Montgomery-Åsberg Depression Rating Scale Anhedonia Factor Score Following Esketamine Nasal Spray Monotherapy in Adult Patients With Treatment-Resistant Depression: A Post Hoc Analysis

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Purpose of the analysis

To evaluate whether esketamine nasal spray (SPRAVATO®) monotherapy improves symptoms of anhedonia (reduced ability to experience pleasure) versus placebo in adults with treatment-resistant depression (TRD) over 4 weeks of treatment.



- **Anhedonia:** Reduced ability to experience pleasure, interest, or enjoyment from activities that are normally rewarding.
- **Esketamine:** A nasal spray formulation approved for treatment-resistant depression in adults.
- **Montgomery-Åsberg Depression Rating Scale (MADRS):** 10-item clinician-rated scale measuring depression severity.
- **5-item MADRS Anhedonia Factor Score:** A subset of five items from the MADRS (apparent sadness, reported sadness, concentration difficulties, lassitude, and inability to feel) used to assess anhedonia-related symptoms.
- **Treatment-resistant depression:** Major depressive disorder that has not adequately responded to at least two antidepressants.

How was the analysis conducted and what was the design?

This was a post hoc analysis of a multicenter, double-blind, randomized, placebo-controlled phase 4 clinical trial (NCT04599855) conducted in the United States. Adults with TRD who had inadequate response to at least two antidepressants stopped antidepressant treatment during screening and then underwent a drug-free period before randomization. Participants were assigned in a 1:1:2 ratio to receive esketamine nasal spray 56 mg, esketamine nasal spray 84 mg, or placebo twice weekly for 4 weeks. Anhedonia was evaluated using a 5-item factor derived from the Montgomery-Åsberg Depression Rating Scale (MADRS),

with outcomes assessed on Day 1, Day 2 (about 24 hours after the first dose), and through Day 28. A total of 378 patients were included in the efficacy analysis.



- The **5-item MADRS anhedonia factor score** was used to measure anhedonia symptoms; scores range in severity from 0 (no symptoms) to 30 (most severe).
- In this analysis, a **decrease of ≥ 3 points** in the 5-item MADRS Anhedonia Factor Score was considered **clinically meaningful improvement** and a **decrease of ≥ 6 points** was considered **clinically substantial improvement**.

What were the results of the study?

Esketamine monotherapy produced significantly greater improvements in anhedonia symptoms than placebo at Day 28 and as early as 24 hours after the first dose.

LS Mean Difference in 5-item MADRS Anhedonia Factor Score at Day 28

-3.4

LS mean difference for ESK 56 mg
vs placebo at Day 28
(95% CI: -5.38 to -1.44)

-4.8

LS mean difference for ESK 84 mg
vs placebo at Day 28
(95% CI: -6.72 to -2.89)

LS, least squares; CI, confidence interval

More esketamine-treated patients achieved clinically meaningful, clinically substantial, and $\geq 50\%$ improvement in the 5-item MADRS Anhedonia Factor Score at Day 28 and as early as Day 2.

What were the most common adverse events in patients treated with ESK?



The most common treatment-emergent adverse events (TEAEs) were:

- Nausea
- Dissociation – a mental state in which a person feels temporarily detached from their thoughts, feelings, body, or surroundings
- Dizziness
- Headache

What do these results mean for individuals with treatment-resistant depression?

These findings suggest that esketamine monotherapy may rapidly and meaningfully reduce anhedonia, a common and burdensome symptom of TRD. Improvements were observed within 24 hours and were

maintained through 4 weeks, supporting the potential benefit of esketamine for patients experiencing diminished interest or pleasure.

What were the limitations of the study?

The study used a 5-item MADRS anhedonia factor score that was derived from a broader depression rating scale and was not specifically developed to measure anhedonia. These results suggest that esketamine may provide improvement in anhedonia symptoms, but findings are from a post hoc analysis and should be confirmed in trials specifically powered for anhedonia outcomes.