Long-Term Efficacy and Safety of Esketamine Nasal Spray as Monotherapy: A Post Hoc Analysis of the SUSTAIN-3 Study

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24

Introduction

- Prior to January 2025, esketamine nasal spray (ESK) was approved for treatment-resistant depression (TRD) in adults and for depressive symptoms in adults with major depressive disorder with acute suicidal ideation or behavior, both in conjunction with an oral antidepressant (OAD)[1]
- Primary findings from a phase 4, multicenter, double-blind, randomized, placebo-controlled trial (TRD4005, 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, and as early as 24 hours after the first dose[2]
 - Based on these results, ESK was approved in the United States as the first and only monotherapy for adults with TRD[1,3]
- Some patients enrolled in SUSTAIN-3, a long-term open-label ESK efficacy and safety study, received ESK treatment without a concurrent OAD for a prolonged period (≥12 consecutive months) at the investigators' discretion[4,5]
 - Data from these patients can provide additional evidence to inform the long-term efficacy and safety of ESK monotherapy

Objective

- To describe the long-term efficacy and safety of ESK in adults with TRD who received ESK as monotherapy for ≥12 consecutive months in a long-term open-label study

Methods

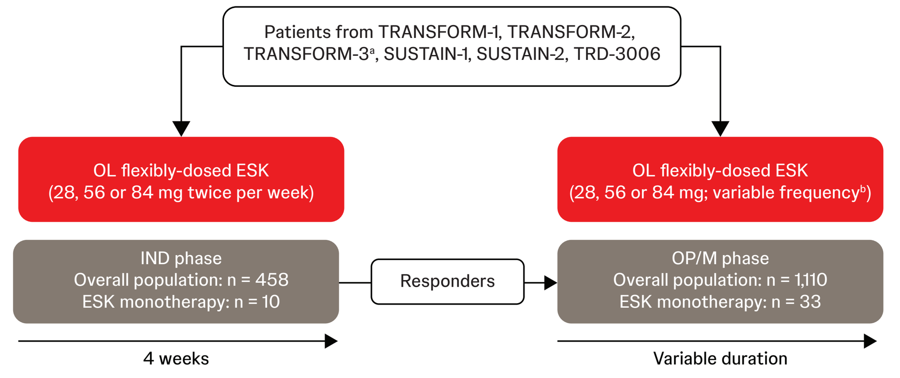
Study design

- SUSTAIN-3 was a phase 3, open-label, long-term extension study comprised of 2 phases: a 4-week induction phase (IND) and a variable duration optimization/maintenance phase (OP/M) (**Figure 1**)
 - SUSTAIN-3 enrolled patients with TRD (≥2 prior OAD treatment failures) from 1 of 6 parent studies
 - Patients entered either the IND or OP/M phase, based on their status at the end of the parent study
- Patients in SUSTAIN-3 received open-label, flexibly-dosed ESK, with a concurrent OAD; however, this post hoc subgroup analysis included patients who either never received an OAD or stopped OAD treatment but continued with ESK for variable durations
 - Patients who discontinued OAD treatment may have reinitiated OAD treatment at a later point, but received ESK monotherapy for ≥12 consecutive months during the study period
- During the IND phase, ESK was flexibly-dosed twice weekly for 4 weeks; for patients who proceeded to the OP/M phase, ESK dosing frequency was individualized based on depression severity and tolerability to weekly, every other week, or every 4 weeks[1]

Assessments

- Efficacy outcomes included changes in disease severity, evaluated per the MADRS and the 9-item Patient Health Questionnaire (PHQ-9)
- The proportions of patients who attained remission status were determined
 - For MADRS, remission was defined as a total score ≤12
 - For PHQ-9, remission was defined as a total score <5
- Treatment-emergent adverse events (TEAEs) were monitored throughout the duration of the study

Figure 1: Study design


Patients from TRANSFORM-1, TRANSFORM-2, TRANSFORM-3[a], SUSTAIN-1, SUSTAIN-2, TRD-3006
OL flexibly-dosed ESK (28, 56 or 84 mg twice per week)
OL flexibly-dosed ESK (28, 56 or 84 mg; variable frequency[b])
IND phase
Overall population: n = 458
ESK monotherapy: n = 10
Responders
OP/M phase
Overall population: n = 1,110
ESK monotherapy: n = 33
4 weeks
Variable duration

ESK, esketamine nasal spray; IND, induction; OAD, oral antidepressant; OL, open-label; OP/M, optimization/maintenance.
ESK monotherapy patients were defined as patients who did not receive OADs for ≥12 consecutive months at any point during ESK treatment.
[a]Results from the TRANSFORM-3 study (patients aged ≥65 years) were not included in this subgroup analysis.
[b]Dosing frequency adjusted based on Clinical Global Impression-Severity scale score and tolerability. Dosing frequency during OP/M could be weekly, every other week, or every 4 weeks.

Table 1: Baseline characteristics

	ESK monotherapy patients N = 33	Overall SUSTAIN-3 patients N = 1,148
Mean age (SD), years	44.5 (11.27)	49.6 (12.28)
Sex, n (%)		
Female	18 (54.5)	764 (66.6)
Male	15 (45.5)	384 (33.4)
Race, n (%)		
American Indian or Alaskan Native	0	1 (0.1)
Asian	4 (12.1)	45 (3.9)
Black or African American	2 (6.1)	45 (3.9)
White	25 (75.8)	996 (86.8)
Other	1 (3.0)	29 (2.5)
Multiple	0	10 (0.9)
Not reported	1 (3.0)	22 (1.9)
Mean duration of current MDD episode (SD), weeks	197.9 (229.95)	162.8 (257.21)
Mean (SD) baseline MADRS total score[a]		
IND baseline	33.8 (3.82)[b]	29.1 (7.96)[d]
OP/M baseline	11.2 (9.51)[c]	13.1 (8.79)[e]
Mean (SD) baseline PHQ-9 total score[a]		
IND baseline	17.2 (4.39)[b]	15.4 (5.59)[d]
OP/M baseline	6.0 (4.82)[c]	7.6 (5.60)[e]

ESK, esketamine nasal spray; IND, induction phase; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; OAD, oral antidepressant; OP/M, optimization/maintenance phase; PHQ-9, 9-item Patient Health Questionnaire.
ESK monotherapy patients were defined as patients who did not receive OADs for ≥12 consecutive months at any point during ESK treatment.
[a]Patients could enter SUSTAIN-3 at either the IND phase or OP/M phase, based on their status at the end of the parent study. [b]N = 10. [c]N = 33. [d]N = 458. [e]N = 1,110.

Table 2: Most common TEAEs

TEAE, n (%)	ESK monotherapy patients N = 33
Dizziness	18 (54.6)
Headache	17 (51.5)
Nausea	13 (39.4)
Upper respiratory tract infection	12 (36.4)
Back pain	9 (27.3)
Diarrhea	9 (27.3)
Anxiety	8 (24.2)
Dissociation	8 (24.2)
Arthralgia	7 (21.2)
Dysgeusia	7 (21.2)
Fatigue	7 (21.2)
Insomnia	7 (21.2)

ESK, esketamine nasal spray; OAD, oral antidepressant; TEAE, treatment-emergent adverse event.
ESK monotherapy patients were defined as patients who did not receive OADs for ≥12 consecutive months at any point during ESK treatment.

Results

Baseline characteristics

- A total of 1,148 patients were enrolled in SUSTAIN-3; this subgroup analysis included 33 patients who received ESK monotherapy for ≥12 consecutive months
 - Of these, 21 patients never received OAD treatment, and 12 patients discontinued OAD treatment for ≥12 consecutive months during SUSTAIN-3 (**Figure 2**)
 - Mean (SD) and median duration from study start to the start of the ESK monotherapy period was 242.9 (329.14) days and 84.0 days, respectively (range: 0-1,167 days)
- For the monotherapy group, the mean (SD) and median duration of exposure to ESK was 1,241 (550) days and 1,221 days, respectively, with a maximum duration of ESK exposure of 2,149 days (almost 6 years)
 - Mean (SD) and median duration of ESK monotherapy treatment was 926.2 (434.45) days and 875.0 days, respectively (range: 366-1,924 days)
- Baseline characteristics are shown in **Table 1**

Clinician- and patient-reported disease severity

- Changes in MADRS and PHQ-9 scores throughout the study period are shown in **Figure 3** and demonstrate that measures of depression severity remained stable throughout OP/M for patients receiving ESK monotherapy
- Mean changes in MADRS and PHQ-9 total scores from OP/M baseline to study end were similar between patients receiving ESK monotherapy and the overall population,[4] with mean (SD) changes in MADRS and PHQ-9 scores from OP/M baseline to endpoint of 0.5 (5.88) and 1.5 (4.72), respectively, in patients receiving ESK monotherapy, comparable to 0.2 (9.93) and 0.6 (6.22) in the overall SUSTAIN-3 population

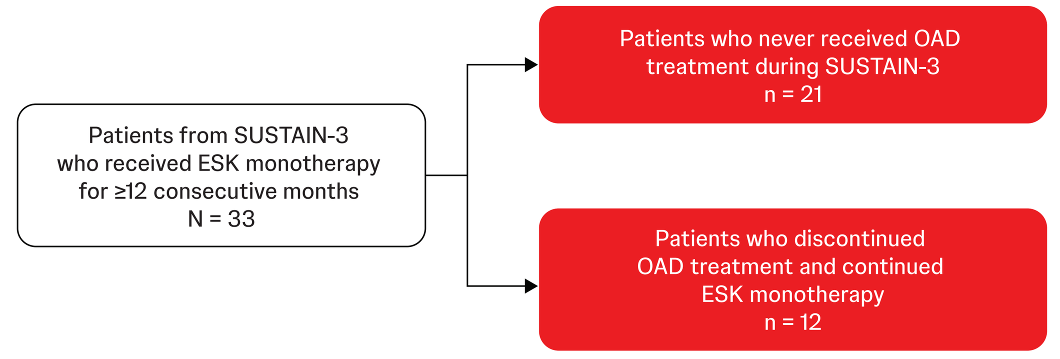
Remission

- The proportion of patients who had received ESK monotherapy who achieved remission remained stable throughout the OP/M phase (**Figure 4**)
- By study end, 57.6% of patients who had received ESK monotherapy were in remission based on MADRS total score, compared with 49.6% of the overall SUSTAIN-3 population
- For remission based on PHQ-9, 42.4% of patients who had received ESK monotherapy were in remission by study end, compared with 33.9% of the overall SUSTAIN-3 population

Safety

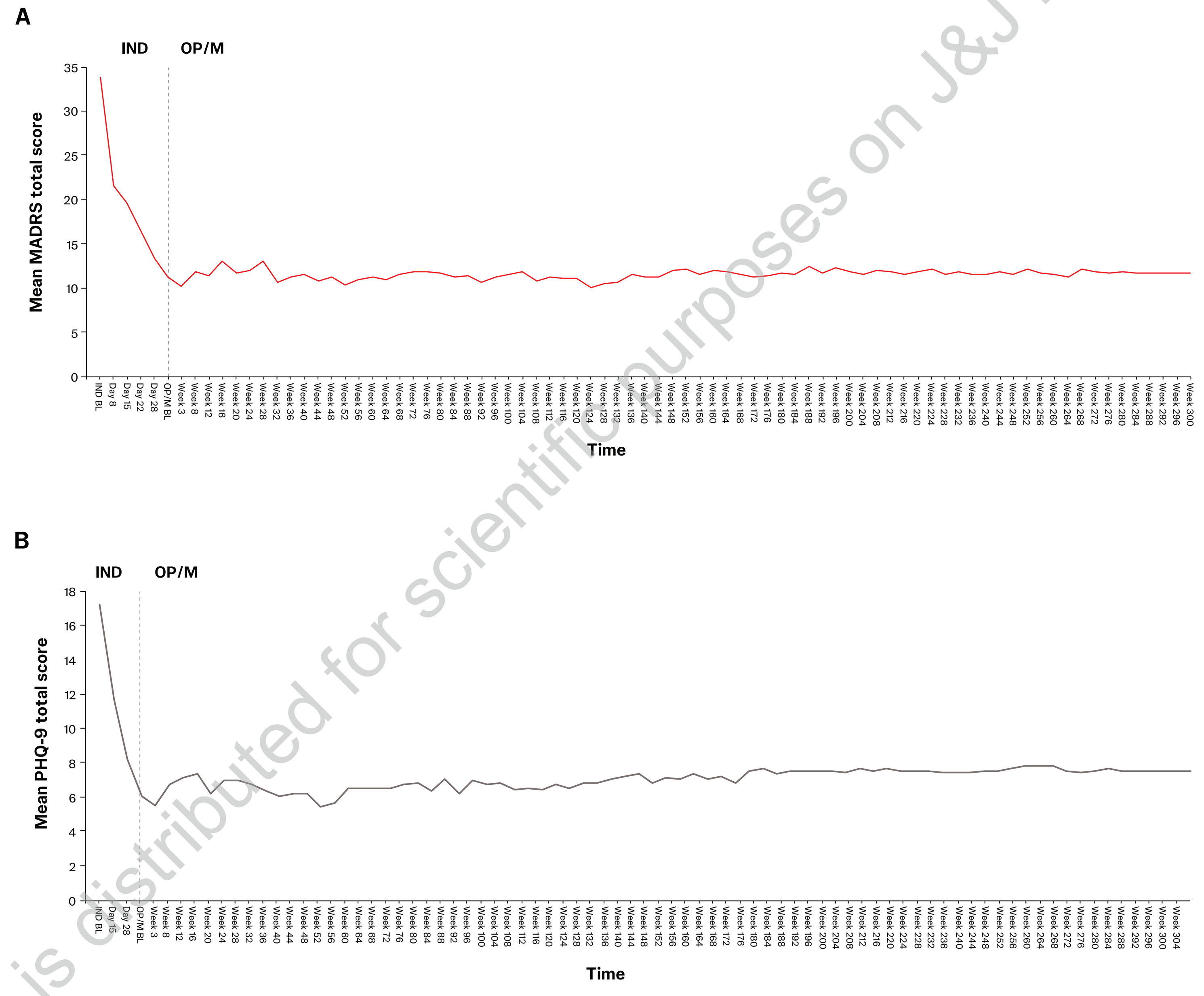
- Overall, 72.7% (n = 24) of patients who had received ESK monotherapy experienced TEAEs possibly related to study drug, and 15.2% (n = 5) experienced ≥1 serious TEAE
- The most common TEAEs (≥20% of patients) are shown in **Table 2**
- Results from this subgroup analysis were consistent with the established safety and tolerability profile of ESK, with no new safety signals identified[6]

Figure 2: Flow chart of ESK monotherapy patients


Patients from SUSTAIN-3 who received ESK monotherapy for ≥12 consecutive months N = 33
Patients who never received OAD treatment during SUSTAIN-3 n = 21
Patients who discontinued OAD treatment and continued ESK monotherapy n = 12

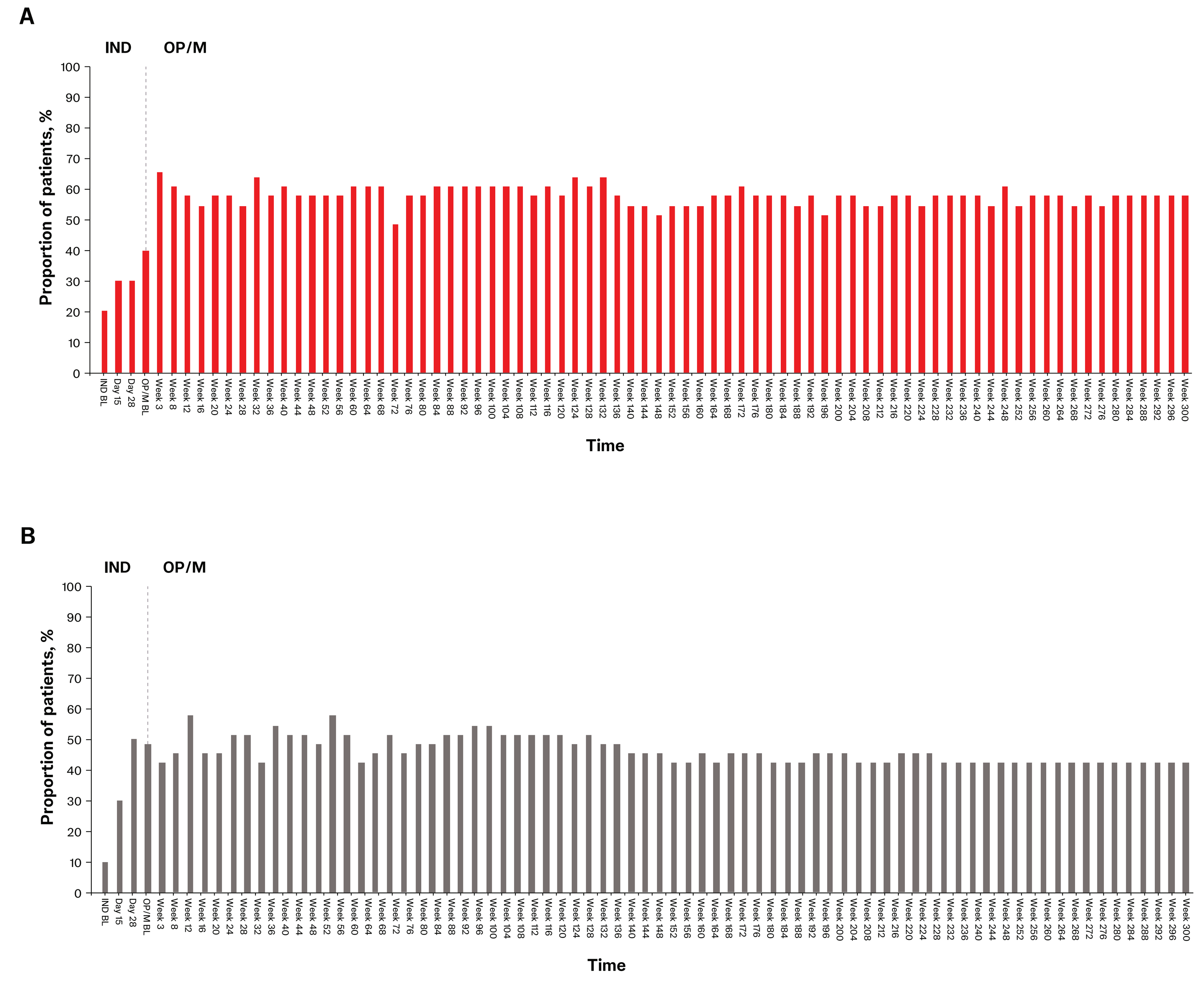
ESK, esketamine nasal spray; OAD, oral antidepressant.

Figure 3: Change in (A) MADRS and (B) PHQ-9 total scores over time for patients receiving ESK monotherapy (LOCF)


A
IND
OP/M
Mean MADRS total score
Time
B
IND
OP/M
Mean PHQ-9 total score
Time

BL, baseline; ESK, esketamine nasal spray; IND, induction phase; LOCF, last observation carried forward; MADRS, Montgomery-Åsberg Depression Rating Scale; OP/M, optimization/maintenance phase; PHQ-9, 9-item Patient Health Questionnaire.
Patients could enter SUSTAIN-3 at either the IND phase or OP/M phase, based on their status at the end of the parent study.

Figure 4: Proportion of patients receiving ESK monotherapy in remission based on (A) MADRS and (B) PHQ-9 total scores (LOCF)


A
IND
OP/M
Proportion of patients, %
Time
B
IND
OP/M
Proportion of patients, %
Time

BL, baseline; ESK, esketamine nasal spray; IND, induction phase; LOCF, last observation carried forward; MADRS, Montgomery-Åsberg Depression Rating Scale; OP/M, optimization/maintenance phase; PHQ-9, 9-item Patient Health Questionnaire.
Patients could enter SUSTAIN-3 at either the IND phase or OP/M phase, based on their status at the end of the parent study.

Key Takeaway

Patients who received ESK as monotherapy without a concurrent OAD for ≥12 months had long-term stable depressive symptoms with no new safety signals identified

Conclusions

- Patients who received esketamine nasal spray monotherapy for ≥12 consecutive months at any point during the study remained stable during the optimization/maintenance phase
- Improvements in depressive symptoms were similarly maintained in patients receiving esketamine nasal spray monotherapy and the overall SUSTAIN-3 study population
- Esketamine nasal spray monotherapy had a tolerable safety profile, and no new safety signals were identified
- Esketamine nasal spray monotherapy may be a viable treatment option for those who receive little or no benefit from OADs, or who experience treatment-limiting TEAEs from OADs

Limitations

- SUSTAIN-3 is an open-label study with no control group for comparison
- This is a subgroup analysis with a small sample size, which may limit the interpretation of the results
- Patients' ESK treatment history differed depending on which parent study they participated in prior to SUSTAIN-3
- ESK monotherapy for a continuous time period was started at different stages of the study and was of variable duration (although ≥12 consecutive months)
- Patients had different reasons for initiating and continuing monotherapy treatment

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