Long-Term Safety of Esketamine Nasal Spray Dosed in Accordance With US Prescribing Information in Adults With Treatment-Resistant Depression: a Subgroup Analysis of the SUSTAIN-3 Study

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Introduction

- Esketamine nasal spray (ESK), a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, is indicated in the United States, in conjunction with an oral antidepressant (OAD), for the treatment of treatment-resistant depression (TRD) in adults and for the treatment of depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior[1]
  - Although there is no standardized definition for TRD, it is typically defined as an inadequate response to ≥2 OAD trials of adequate dose and duration in the current depressive episode[2]
- The safety and efficacy of ESK in adults with TRD was assessed in 6 phase 3 "parent" studies, with the majority ranging in duration from 4 weeks up to 1 year[3-8]
  - Eligible patients from these studies could subsequently enroll into SUSTAIN-3 (NCT02782104), an open-label, long-term, phase 3 ESK extension study
- Analyses of interim data from the SUSTAIN-3 study have reinforced the established efficacy, safety, and tolerability of long-term flexible ESK dosing, given in conjunction with an OAD, in patients 18-64 years of age with TRD[9]
- Here we present results from analyses of the final long-term data from SUSTAIN-3 to provide additional insight to inform treatment decisions in real-world clinical practice

Objective

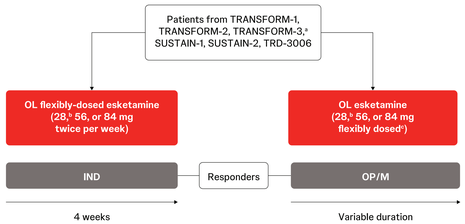
- To describe long-term safety of ESK in adults with TRD dosed according to US prescribing information

Methods

Study design

- SUSTAIN-3 was an open-label, long-term, phase 3 extension study composed of 2 phases: a 4-week induction phase (IND) and a variable-duration optimization/maintenance phase (OP/M) (**Figure 1**)
- Patients entered SUSTAIN-3 at either IND or OP/M from 1 of 6 parent studies of ESK
  - This subgroup analysis included patients aged 18-64 years who received ESK dosing consistent with US prescribing information. TRANSFORM-3 (which included patients aged ≥65 years) was not included in this subgroup analysis
- In addition to an OAD, patients received ESK 56 or 84 mg twice weekly during IND and flexible dosing during OP/M
- Safety parameters were assessed during the entire study, including assessments on dosing days
- Long-term effects, including changes from baseline over time for the computerized cognitive battery (CogState Battery) and Hopkins Verbal Learning Test-Revised, were assessed for potential effects on cognitive function
- Patients were considered to have completed the study if they were actively participating in IND or OP/M when intranasal ESK was commercially available, a pre-approval access program was available to the patient in their country or at the end of December 2022, whichever occurred first

FIGURE 1. SUSTAIN-3 study design



IND, induction phase; OL, open-label; OP/M, optimization/maintenance phase.
[a]Data from TRANSFORM-3 (patients aged ≥65 years) were not included in this subgroup analysis.
[b]A 28-mg dose was only an option for patients aged ≥65 years, who were excluded from this subgroup analysis.
[c]Based on the Clinical Global Impression-Severity Scale and tolerability.

Results

Baseline characteristics

- Overall, a total of 1148 patients were enrolled in SUSTAIN-3
  - A total of 1021 patients were included in this analysis, of which 440 patients (43.1%) entered the study at IND and 581 patients (56.9%) entered directly at the OP/M phase
- Baseline characteristics are shown in **Table 1**
  - At the beginning of IND, mean baseline Montgomery-Åsberg Depression Rating Scale and 9-item Patient Health Questionnaire scores were 29.1 and 15.4, respectively (consistent with moderate to moderately severe disease). At the beginning of OP/M, these mean scores were 13.2 and 7.7, respectively
  - At baseline, mean age was 47.3 years, 66.4% of patients were female, and 85.6% of patients were White

TABLE 1. Baseline characteristics

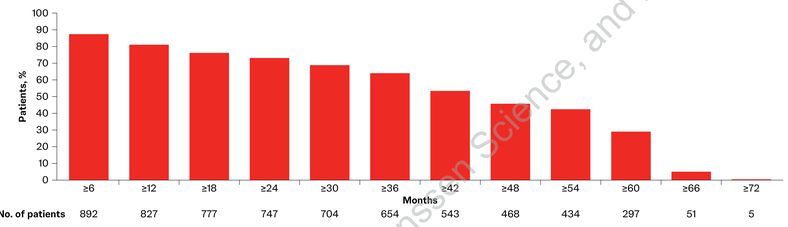
	ESK (N = 1021)
Mean age (SD), years	47.3 (10.71)
Female, n (%)	678 (66.4)
Race, n (%)	
White	874 (85.6)
Black or African American	44 (4.3)
Asian	42 (4.1)
Other/multiple races	38 (3.7)
American Indian or Alaskan Native	1 (0.1)
Ethnicity, n (%)	
Not Hispanic/Latino	814 (79.7)
Hispanic/Latino	182 (17.8)
Not reported/unknown	25 (2.4)
Mean baseline body mass index (SD), kg/m^2	28.8 (6.26)
Mean age when diagnosed with MDD (SD), years	32.8 (11.86)
Mean duration of current episode (SD), weeks	153.3 (231.46)
Mean IND baseline MADRS total score (SD)[a]	29.1 (7.94)
Mean IND baseline PHQ-9 total score (SD)[a]	15.4 (5.56)

ESK, esketamine nasal spray; IND, induction phase; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; PHQ-9, 9-item Patient Health Questionnaire.
[a]N = 439 at baseline IND.

Exposure to ESK treatment

- Median duration of exposure to ESK treatment was 46.9 months (range, 0-79) (**Figure 2**)
- During OP/M, the mean (SD) and median final daily dose of ESK was 74.8 mg (13.2) and 84.0 mg, respectively

FIGURE 2. Exposure to ESK treatment



ESK, esketamine nasal spray.

Safety

- During the combined IND and OP/M, 967 (94.7%) patients experienced a treatment-emergent adverse event (TEAE) (**Table 2**)
- Most TEAEs were mild or moderate in severity
- The most common TEAEs occurring in at least 10% of patients are shown in **Table 3**
- A total of 270 patients (26.4%), 84 patients (8.2%), and 148 patients (14.5%) experienced ≥1 event of dissociation, sedation, or elevated blood pressure, respectively
- Of all TEAEs occuring on day of dosing, 70,634/72,735 (97.1%) resolved on the same day. AEs of nausea, increase in blood pressure, sedation, and dissociation were consistent with all TEAEs
  - Most events of nausea (1606/1691; 95.0%), dissociation (7128/7138; 99.9%), sedation (1174/1180; 99.5%), or elevated blood pressure (1026/1064; 96.4%) occurred and resolved on the same day of dosing
  - A total of 78 patients (7.6%) used concomitant medications for treatment-emergent nausea; the most frequently used medications were ondansetron (n = 43) and metoclopramide (n = 20)
  - A total of 34 patients (3.3%) used concomitant medications for treatment-emergent increase in blood pressure, the most frequent being captopril (n = 15)
  - A total of 7 patients (0.7%) used concomitant medications for treatment-emergent dissociation, the most frequent being alprazolam (n = 2)

TABLE 2. Overall summary of TEAEs

	ESK (N = 1021)
TEAE	967 (94.7%)
TEAE possibly related to intranasal drug[a]	772 (75.6%)
TEAE leading to death[b]	6 (0.6%)
≥1 serious TEAE	184 (18.0%)
TEAE leading to intranasal drug withdrawn[c]	61 (6.0%)

ESK, esketamine nasal spray; IND, induction phase; OP/M, optimization/maintenance phase; TEAE, treatment-emergent adverse event.
[a]Study drug relationships of possible, probable, and very likely are included in this category.
[b]Based on investigator assessment, TEAEs leading to death were considered "not related" to study medication.
[c]An adverse event that started in the IND or OP/M and resulted in study discontinuation is counted as treatment-emergent in this table.

TABLE 3. Most common TEAEs[a] (≥10% of patients)

	ESK (N = 1021)
Headache	382 (37.4%)
Dizziness	354 (34.7%)
Nausea	351 (34.4%)
Dissociation	270 (26.4%)
Somnolence	241 (23.6%)
Nasopharyngitis	235 (23.0%)
Dysgeusia	221 (21.6%)
Back pain	199 (19.5%)
Vertigo	195 (19.1%)
Anxiety	194 (19.0%)
Vomiting	166 (16.3%)
Arthralgia	164 (16.1%)
Diarrhea	162 (15.9%)
Urinary tract infection	152 (14.9%)
Blood pressure increased	148 (14.5%)
Insomnia	147 (14.4%)
Fatigue	138 (13.5%)
Upper respiratory tract infection	133 (13.0%)
COVID-19	132 (12.9%)
Influenza	126 (12.3%)
Vision blurred	109 (10.7%)
Hypoesthesia	106 (10.4%)

ESK, esketamine nasal spray; TEAE, treatment-emergent adverse event.
[a]Incidence is based on the number of subjects experiencing ≥1 adverse event, not the number of events.

- TEAEs potentially related to suicidality occurred in 74 patients (7.2%), including suicidal ideation (n = 55), suicide attempt (n = 16), suicidal behavior (n = 4), and depression suicidal (n = 1), and completed suicide (n = 1)
- 61 patients (6.0%) discontinued treatment due to TEAEs; TEAEs that led to discontinuation are shown in **Table 4**
- Serious TEAEs occurred in 184 patients (18.0%); serious TEAEs occurring in ≥5 patients included depression (n = 16), suicide attempt (n = 15), suicidal ideation (n = 9), cholelithiasis (n = 9), COVID-19 (n =7), pneumonia (n = 5), and atrial fibrillation (n = 5)

TABLE 4. TEAEs leading to discontinuation (≥2 patients)

	ESK (N = 1021)
TEAE leading to discontinuation[a]	61 (6.0%)
Dissociation	5 (0.5%)
Blood pressure increased	4 (0.4%)
Anxiety	3 (0.3%)
Depression	3 (0.3%)
Major depression	3 (0.3%)
Mania	3 (0.3%)
Myocardial infarction	2 (0.2%)
Vertigo	2 (0.2%)

ESK, esketamine nasal spray; IND, induction phase; OP/M, optimization/maintenance phase; TEAE, treatment-emergent adverse event.
[a]An adverse event that started in IND or OP/M and resulted in study discontinuation is counted as treatment-emergent in this table.

Cognition results

- No evidence of any negative effect on cognition, as assessed using the CogState Battery and Hopkins Verbal Learning Test-Revised, was observed
- Overall, 5 patients (0.5%) experienced ≥1 TEAE related to impaired cognition during the combined IND and OP/M phases

Key takeaway

This analysis shows that the long-term safety (up to 6.5 years) of flexibly-dosed ESK in adults with TRD is consistent with its established safety and tolerability profile, with no new safety signals identified

Limitations

- SUSTAIN-3 is an open-label study with no control group for comparison
- This is a subgroup analysis of the study population, which may limit the interpretation of the results
- The generalizability of these findings may be limited by the exclusion of patients with significant psychiatric or medical comorbidities or substance dependence and potential bias related to which patients chose to continue (or not to continue) from the parent study into this study

Conclusions

Results from this subgroup analysis were consistent with the established safety and tolerability profile, with no new safety signals identified, for long-term treatment (up to 6.5 years) with flexibly-dosed ESK in adults with TRD

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Disclosures

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Previous Presentation

The data in this poster were previously presented at Psych Congress 2023; September 6-10, 2023; Nashville, Tennessee

Presented at NEI Congress; November 7-10, 2024; Colorado Springs, Colorado

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