Long-Term Efficacy 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 inadequate response to ≥2 OAD trials of adequate dose and duration in the current depressive episode[2]
- The efficacy and safety of ESK in adults with TRD was assessed in 6 phase 3 "parent" studies, with the majority ranging in duration from 4 weeks 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 the 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 participants 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

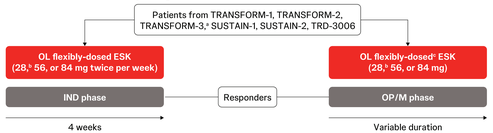
- To describe the long-term efficacy of ESK in adults with TRD dosed according to US prescribing information

Methods

Study design

- SUSTAIN-3 (NCT02782104) was a phase 3, open-label extension study composed of 2 phases: a 4-week induction (IND) phase and a variable-duration optimization/maintenance (OP/M) phase (**Figure 1**)
- Patients entered SUSTAIN-3 at either the IND or the OP/M phase from 1 of 6 parent studies of ESK
  - This subgroup analysis included adults 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 the IND phase and flexible dosing during the OP/M phase
- Patients were considered to have completed the study if they were actively participating in the IND or the OP/M phase when intranasal ESK was commercially available, a preapproval 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



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

Assessments

- Clinician- and patient-reported disease severity were evaluated by the Montgomery–Åsberg Depression Rating Scale (MADRS) and 9-item Patient Health Questionnaire (PHQ-9)
  - Changes in efficacy outcomes are summarized descriptively
- The proportion of patients who achieved response per MADRS or PHQ-9 was determined at the IND phase end point; rates of remission per MADRS or PHQ-9 at the IND and OP/M phase end points were also reported
  - For MADRS, response was defined as a ≥50% improvement from IND phase baseline, and remission was defined as a score ≤12
  - For PHQ-9, a ≥50% improvement from IND phase baseline and a score <5 (normal) were used as clinical definitions for response and remission, respectively[10-12]

Results

Baseline characteristics

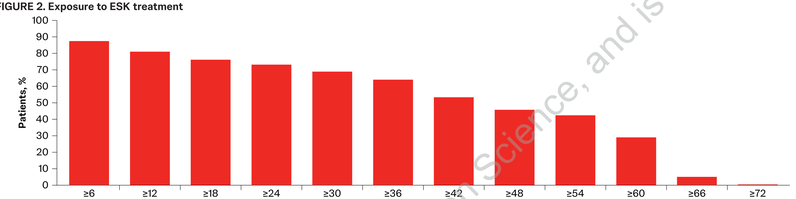
- Overall, a total of 1148 patients were enrolled in SUSTAIN-3
  - A total of 1021 patients were included in this analysis, of which 440 (43.1%) entered the study at the IND phase and 581 (56.9%) entered directly at the OP/M phase
- Baseline characteristics are shown in **Table 1**
  - At the beginning of the IND phase, mean baseline MADRS and PHQ-9 scores were 29.1 and 15.4, respectively (consistent with moderate to severe disease). At the beginning of OP/M, these mean scores were 13.2 and 7.7, respectively
  - Mean age at baseline 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)
Male, n (%)	343 (33.6)
Race, n (%)	
White	874 (85.6)
Black or African American	44 (4.3)
Asian	42 (4.1)
Other/multiple	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)
Baseline BMI, kg/m^2	
Mean (SD)	28.8 (6.26)
Range	(15; 57)
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)

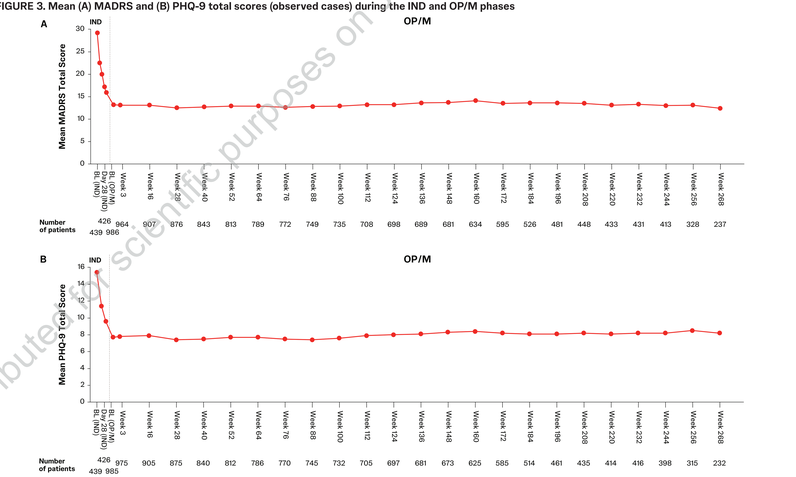
BMI, body mass index; ESK, esketamine nasal spray; IND, induction; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, major depressive disorder; PHQ-9, 9-item Patient Health Questionnaire.
[a]N = 439 at IND baseline.

FIGURE 2. Exposure to ESK treatment



ESK, esketamine nasal spray.

FIGURE 3. Mean (A) MADRS and (B) PHQ-9 total scores (observed cases) during the IND and OP/M phases



Data are presented to Week 268 of OP/M when ≥ 200 participants were present in the study.
BL, baseline; ESK, esketamine nasal spray; IND, induction phase; MADRS, Montgomery–Åsberg Depression Rating Scale; OP/M, optimum/maintenance phase; PHQ-9, 9-item Patient Health Questionnaire.

Exposure to ESK treatment

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

Efficacy

- At the beginning of the IND phase, mean baseline MADRS and PHQ-9 scores were 29.1 and 15.4, respectively (consistent with moderate to severe disease)
- During the 4-week IND phase, mean (SD) changes from baseline in MADRS and PHQ-9 total scores were −12.9 (9.67) and −5.9 (5.77), respectively (Figure 3)
  - These improvements were maintained over the OP/M phase, with mean (SD) changes from baseline in MADRS and PHQ-9 total scores during the OP/M phase of 0.1 (10.21) and 0.6 (6.33), respectively
- The proportion of patients who achieved remission per MADRS and PHQ-9 (defined as scores of ≤12 and <5, respectively) at their last assessment in the OP/M phase was 49.6% and 33.6%, respectively (**Table 2**)

TABLE 2. Response and remission rates per MADRS and PHQ-9 scores

	MADRS n/N (%)	PHQ-9 n/N (%)
IND phase end point		
≥50% improvement from baseline	218/437 (49.9)	167/435 (38.4)
Remission[a]	159/438 (36.3)	88/437 (20.1)
Last OP/M phase assessment		
Remission[a]	489/986 (49.6)	331/986 (33.6)

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

Safety

- Results from this subgroup analysis were consistent with the established safety and tolerability profile of ESK, with no new safety signals identified

Key takeaway

Improvements in severity of depressive symptoms from both clinicians' assessment and patients' perspective observed during OL treatment with esketamine nasal spray plus OAD were maintained with long-term flexible esketamine nasal spray dosing

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

This analysis demonstrates that in adults with TRD, improvements in depressive symptoms were maintained with long-term, flexibly-dosed ESK

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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.

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

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