Long-Term Efficacy of Esketamine Nasal Spray Among Early and Delayed Responders: A Subgroup Analysis of the SUSTAIN-3 Study

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Introduction

- Esketamine nasal spray (ESK) is indicated in the US, 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 OADs 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, which ranged in duration from 4 weeks to 1 year[3-8]
- Eligible patients from these studies could continue to receive treatment with ESK by subsequently enrolling in the SUSTAIN-3 study (NCT02782104), an open-label long-term extension study[9]
  - The primary objective of SUSTAIN-3 was to assess the safety and tolerability of ESK
  - The secondary objective was to assess long-term efficacy, including clinician- and patient-rated disease severity
- Analyses of data from the SUSTAIN-3 study to date have reinforced the established efficacy, safety, and tolerability of long-term flexible ESK dosing, given in conjunction with an OAD, in adults with TRD[10,11]
- Here we present results from analyses of patients treated with ESK according to US prescribing information (USPI)

Objective

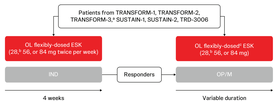
- To describe the long-term efficacy of ESK in patients with TRD dosed according to USPI, including an evaluation of early (day 8) and delayed (week 8) response

Methods

Study Design

- SUSTAIN-3 (NCT02782104) was an open-label, phase 3, long-term extension study composed of 2 phases: depending on their status at the end of the parent study, patients entered either a 4-week induction phase (IND) followed by a variable-duration optimization/maintenance phase (OP/M) or directly into OP/M (**Figure 1**)
- This subgroup analysis included adults (aged 18-64 years) treated with ESK plus an OAD who entered SUSTAIN-3 during IND

FIGURE 1: SUSTAIN-3 study design



ESK, esketamine nasal spray; IND, induction phase; OL, open-label; OP/M, optimization/maintenance phase.
This subgroup analysis only included patients who participated in IND and continued into OP/M.
*Results from the TRANSFORM-3 study were not included in this subgroup analysis.
†The 28-mg dose was only an option for patients in TRANSFORM-3 (aged ≥65 years), who were excluded from this subgroup analysis.

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
- For MADRS, response was defined as a ≥50% improvement from IND baseline and remission was defined as having a total score ≤12
- For PHQ-9, response was defined as a ≥50% improvement from IND baseline and remission was defined as having a total score <5 (normal)
- Early response was defined as achieving MADRS response by day 8; delayed response was defined as achieving MADRS response by week 8
- Safety parameters were assessed throughout the study, including assessments on dosing days

Results

Baseline characteristics

- Overall, a total of 1148 patients were enrolled in SUSTAIN-3
  - This subgroup analysis included 441 patients who entered during IND: of these, 405 (91.8%) continued from IND to OP/M and 258 (63.7%) completed OP/M
- Baseline characteristics are shown in **Table 1**
  - At baseline, mean age was 46.6 years, 68.5% of patients were female, and 84.6% were White

TABLE 1: Baseline characteristics

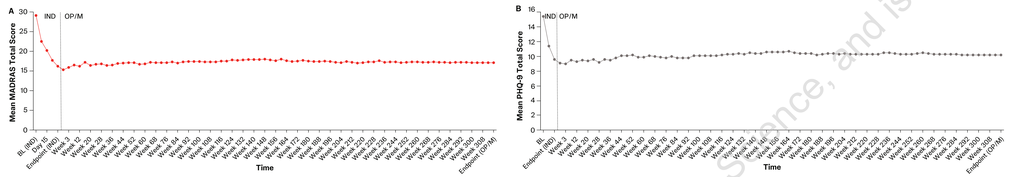
	ESK N = 441
Mean age (SD), years	46.6 (10.74)
Female, n (%)	302 (68.5)
Race, n (%)	
White	373 (84.6)
Black or African American	23 (5.2)
Asian	5 (1.1)
Other	18 (4.1)
Multiple	5 (1.1)
American Indian or Alaskan Native	1 (0.2)
Ethnicity, n (%)	
Not Hispanic/Latino	363 (82.3)
Hispanic/Latino	63 (14.3)
Not reported/unknown	15 (3.4)
Mean age when diagnosed with MDD (SD), years	31.8 (12.41)
Mean duration of current episode (SD), weeks	179.5 (268.15)
Mean baseline MADRS total score (SD)	29.1 (7.94)
Mean baseline PHQ-9 total score (SD)	15.4 (5.56)
Mean baseline CGI-S score (SD)	4.5 (0.87)

CGI-S, Clinical Global Impressions-Severity Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, major depressive disorder; PHQ-9, 9-item Patient Health Questionnaire.

Efficacy

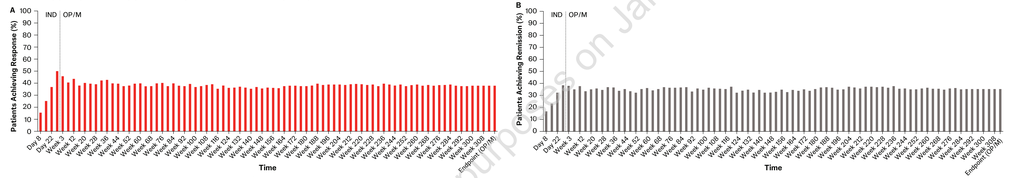
- At the beginning of IND, mean baseline MADRS total score was 29.1 (consistent with moderate-severe disease)
- Median duration of exposure to ESK treatment was approximately 3.5 years (range, 1 day to 6 years)
- During the 4-week IND, mean (SD) change from baseline in MADRS total score was −12.9 (9.67), and the mean (SD) change from baseline in PHQ-9 total score was −5.9 (5.77). These improvements were maintained over OP/M (**Figure 2**)
- At the IND endpoint, 219 patients (50.0%) had achieved response and 159 (36.3%) had achieved remission based on MADRS. Rates of response and remission appeared to remain stable over time (**Figure 3**)
- The proportion of patients achieving response or remission was similar among early (n = 65) or delayed (n = 156) responders (**Figure 4**)
  - At the OP/M endpoint, 58.5% and 53.2% of early and delayed responders, respectively, continued to meet response criteria and 52.3% and 47.4%, respectively, continued to meet remission criteria (MADRS total score ≤12) (**Table 2**)

FIGURE 2: Mean (A) MADRS and (B) PHQ-9 total score during IND and OP/M (LOCF)



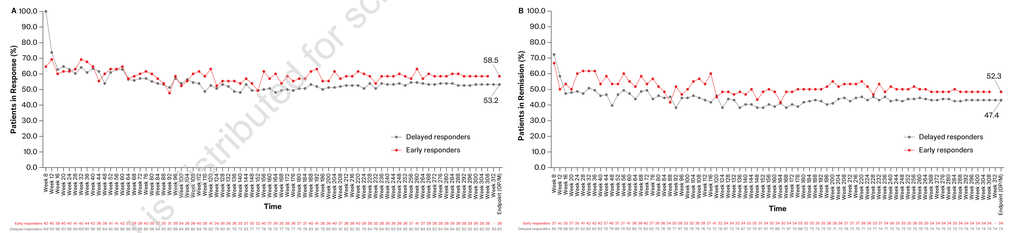
BL, baseline; IND, induction phase; LOCF, last observation carried forward; MADRS, Montgomery–Åsberg Depression Rating Scale; OP/M, optimization/maintenance phase; PHQ-9, 9-item Patient Health Questionnaire.

FIGURE 3: (A) Response[a] and (B) remission[b] per MADRS total score (LOCF)



IND, induction phase; LOCF, last observation carried forward; MADRS, Montgomery–Åsberg Depression Rating Scale; OP/M, optimization/maintenance phase.
[a]Response defined as a ≥50% improvement from baseline in MADRS total score.
[b]Remission defined as MADRS total score ≤12.

FIGURE 4: (A) Response[a] and (B) remission[b] per MADRS total score during OP/M among early (day 8) and delayed (week 8) responders (LOCF)



LOCF, last observation carried forward; MADRS, Montgomery–Åsberg Depression Rating Scale; OP/M, optimization/maintenance phase.
The analysis set for early responders includes all patients achieving MADRS response by day 8. The analysis set for delayed responders includes all patients who achieved MADRS response by week 8.
[a]Response was defined as a ≥50% improvement from baseline in MADRS total score.
[b]Remission was defined as MADRS total score ≤12.

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

	MADRS		PHQ-9	
n/N (%)	Early (day 8) responders[a]	Delayed (week 8) responders[a]	Early (day 8) responders[a]	Delayed (week 8) responders[a]
	Response[a]			
OP/M endpoint	38/65 (58.5%)	83/156 (53.2%)	31/64 (48.4%)	67/155 (43.2%)
	Remission[b]			
OP/M endpoint	34/65 (52.3%)	74/156 (47.4%)	22/65 (33.8%)	50/156 (32.1%)

IND, induction phase; MADRS, Montgomery–Åsberg Depression Rating Scale; OP/M, optimization/maintenance phase; PHQ-9, 9-item Patient Health Questionnaire.
[a]Response was defined as a ≥50% improvement from baseline in MADRS or PHQ-9 total score.
[b]Remission was defined as MADRS total score ≤12 or PHQ-9 total score <5.
[c]Response based on MADRS total score at day 8 (IND).
[d]Response based on MADRS total score at week 8 (OP/M).

Safety

- Results from this subgroup analysis were consistent with the established safety and tolerability profile of ESK, with no new safety signals identified
- During the combined IND and OP/M, 417 (94.6%) patients experienced a treatment-emergent adverse event (TEAE) and 74 (16.8%) patients experienced ≥1 serious adverse event
- The most common TEAEs (occurring in ≥10% of patients) are shown in **Table 3**

TABLE 3: Most common TEAEs

TEAE, n (%)	ESK (N = 441)
Headache	183 (41.5)
Nausea	175 (39.7)
Dizziness	150 (34.0)
Dissociation	143 (32.4)
Dysgeusia	120 (27.2)
Vertigo	111 (25.2)
Anxiety	106 (24.0)
Nasopharyngitis	104 (23.6)
Somnolence	99 (22.5)
Back Pain	84 (19.1)
Fatigue	78 (17.7)
Blood pressure increased	75 (17.0)
Vomiting	73 (16.6)
Arthralgia	73 (16.6)
Diarrhea	69 (15.7)
Insomnia	67 (15.2)
Hypoesthesia	64 (14.5)
Urinary tract infection	60 (13.6)
Hypoesthesia oral	58 (13.2)
Nasal discomfort	58 (13.2)
Vision blurred	58 (13.2)
Cough	56 (12.7)
Oropharyngeal pain	55 (12.5)
Influenza	48 (10.9)
COVID-19	46 (10.4)
Upper respiratory tract infection	45 (10.2)

ESK, esketamine nasal spray; TEAE, treatment-emergent adverse event.

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 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 subgroup analysis demonstrated the long-term efficacy (up to 6 years) of esketamine nasal spray in adults with TRD treated according to USPI
- Early and delayed responders showed similar rates of response and remission throughout OP/M, with the proportion of patients achieving response and remission remaining stable over time

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