Trajectory of Response and Remission in Induction Nonresponders to Esketamine Nasal Spray: A Subgroup Analysis of the SUSTAIN-3 Study

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Introduction

- The efficacy and safety of esketamine nasal spray (ESK) in adults with treatment-resistant depression was assessed in six phase 3 parent studies, with the majority ranging in duration from 4 weeks up to 1 year[1-6]
- 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[7]
- Analyses of long-term data from SUSTAIN-3 may inform treatment decisions in real-world clinical practice
  - A prior analysis found that patients who had achieved response by day 8 or week 8 showed similar rates of response and remission through the optimization/maintenance phase (OP/M), with the proportion of patients achieving response and remission remaining stable over time[8]

Objective

- To describe the trajectory of first response and remission in patients who were nonresponders or partial responders to ESK during the 4-week induction (IND) phase of SUSTAIN-3

Methods

Study design

- SUSTAIN-3 was a phase 3, open-label, long-term extension study comprised of 2 phases: a 4-week IND and a variable duration OP/M (**Figure 1**)
- This posthoc subgroup analysis included adults (18-64 years of age) treated with ESK, together with an oral antidepressant (OAD), according to US prescribing information, who entered SUSTAIN-3 IND and continued to OP/M
- Eligibility to participate in SUSTAIN-3 was based on the clinical judgment of the investigator: patients entering IND had completed the induction phase of their parent study but either (a) had not participated in a maintenance phase (TRANSFORM-1, TRANSFORM-2), (b) had relapsed in the maintenance phase (SUSTAIN-1), or (c) were nonresponders or otherwise not eligible for the maintenance phase (TRD-3006, SUSTAIN-1, SUSTAIN-2)
  - The majority of patients included in this analysis were enrolled from TRANSFORM-1 (28.6%), TRANSFORM-2 (9.9%), and SUSTAIN-1 (57.5%)
- In addition to an OAD, patients received ESK 56 or 84 mg twice weekly during IND and flexible ESK dosing during OP/M

FIGURE 1. Sample selection

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.
[a]Results from the TRANSFORM-3 study (patients aged ≥65 years) were not included in this subgroup analysis.
[b]Based on Clinical Global Impression-Severity scale score and tolerability.
[c]Dosing frequency during OP/M could be weekly, every other week, or every 4 weeks.

Assessments

- Clinician-reported disease severity was evaluated by the Montgomery-Åsberg Depression Rating Scale (MADRS)
- Response was defined as ≥50% improvement from baseline in MADRS total score and remission was defined as achieving MADRS total score ≤12
- Clinically meaningful and clinically substantial change was defined as a 6-point improvement and 12-point improvement in MADRS total score relative to baseline, respectively
- Cohorts were defined by their response status at end of IND, determined by improvement in MADRS total score from baseline to end of IND (day 28 of ESK treatment) as follows:
  - IND full responders had ≥50% improvement
  - IND partial responders had ≥25% to <50% improvement
  - IND nonresponders had <25% improvement

Statistics

- Time to first response, first remission, and clinically meaningful and clinically substantial change were based on Kaplan-Meier product limit estimates

Results

Baseline characteristics

- This subgroup analysis included 405 patients: of these, 94 were IND nonresponders, 93 were IND partial responders, and 218 were IND full responders
- Baseline characteristics are shown in **Table 1**
- Median duration of exposure to ESK was 43.8 months (range, 0-72) for IND nonresponders, 41.8 months (0-72) for IND partial responders and 48.1 months (0-78) for IND full responders

TABLE 1. Baseline characteristics

	IND nonresponders (n = 94)	IND partial responders (n = 93)	IND full responders (n = 218)
Mean age (SD), years	49.0 (10.7)	45.0 (11.2)	46.3 (10.5)
Female, n (%)	57 (60.6)	63 (67.7)	163 (74.8)
Race, n (%)			
Asian	1 (1.1)	1 (1.1)	3 (1.4)
Black or African American	6 (6.4)	6 (6.5)	9 (4.1)
White	76 (80.9)	81 (87.1)	184 (84.4)
Other	4 (4.3)	1 (1.1)	12 (5.5)
Multiple	1 (1.1)	1 (1.1)	2 (0.9)
Not reported	6 (6.4)	3 (3.2)	7 (3.2)
Ethnicity, n (%)			
Hispanic/Latino	12 (12.8)	15 (16.1)	33 (15.1)
Not Hispanic/Latino	78 (83.0)	75 (80.6)	177 (81.2)
Not reported	4 (4.3)	3 (3.2)	7 (3.2)
Age when diagnosed with MDD, mean (SD), years[a]	34.9 (12.8)	30.1 (12.8)	31.9 (12.1)
Duration of current episode, mean (SD), weeks[a]	180.0 (219.6)	164.6 (198.9)	181.8 (302.6)
Baseline MADRS total score, mean (SD)[b]	26.1 (8.9)	30.2 (7.3)	30.0 (7.5)
Baseline PHQ-9 total score, mean (SD)[b]	14.3 (5.8)	16.6 (5.3)	15.2 (5.4)
Baseline CGI-S, mean (SD)[b]	4.3 (1.0)	4.6 (0.8)	4.6 (0.8)
Parent study, n (%)			
TRANSFORM-1	41 (43.6)	29 (31.2)	46 (21.1)
TRANSFORM-2	6 (6.4)	9 (9.7)	25 (11.5)
SUSTAIN-1	44 (46.8)	48 (51.6)	141 (64.7)
SUSTAIN-2	0	2 (2.2)	2 (0.9)
TRD-3006	3 (3.2)	5 (5.4)	4 (1.8)

CGI-S, Clinical Global Impressions Scale-Severity; IND, induction phase; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; PHQ-9, 9-item Patient Health Questionnaire.
IND nonresponders, <25% improvement in MADRS total score from baseline to day 28 of induction phase; IND partial responders, ≥25% to <50% improvement in MADRS total score from baseline to day 28 of induction phase; IND full responders, ≥50% improvement in MADRS total score from baseline to day 28 of induction phase.
[a]Data from parent study.
[b]Data from SUSTAIN-3. If the baseline was missing from SUSTAIN-3, the last record from the parent study was used as baseline.

Efficacy

- At week 52 of OP/M (week 60 of ESK treatment), mean (SD) change in MADRS total score from IND baseline in IND nonresponders, IND partial responders, and IND full responders was −6.5 (10.95), −11.4 (8.37), and −14.7 (10.36), respectively

Time to first clinically meaningful and clinically substantial change in MADRS total score

- Median time to first clinically meaningful and clinically substantial change in MADRS total score for IND nonresponders was 50 (95% CI: 15.0, 51.0) days and 134.0 (81.0, not estimatable [NE]) days into OP/M, respectively (**Table 2**)
- Median time to first clinically meaningful and clinically substantial change for IND partial responders was 1.0 (95% CI: NE, NE) days and 11.0 (1.0, 16.0) days into OP/M, respectively (**Table 2**)
- Kaplan-Meier plots of time to first clinically meaningful and clinically substantial change are shown in **Figure 2**

Time to first response and remission

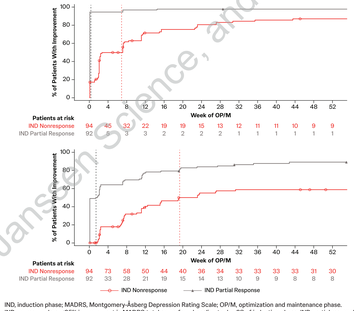
- Median time to first response and remission for IND nonresponders was 190.0 (95% CI: 135.0, NE) days and 192.0 (135.0, NE) days into OP/M, respectively (**Table 2**)
- Median time to first response and remission for IND partial responders was 78.0 (95% CI: 50.0, 106.0) days and 163.0 (78.0, 275.0) days into OP/M, respectively (**Table 2**)
- Kaplan-Meier plots of time to first response and remission are shown in **Figure 3**

TABLE 2. Time to first achievement of various efficacy outcomes up to week 52 of OP/M[a]

	IND nonresponders (n = 94)	IND partial responders (n = 93)
Time to first clinically meaningful change[b]		
Number with improvement (%)	76 (80.9)	91 (97.8)
Number censored (%)	18 (19.1)	2 (2.2)
25% quartile, days (95% CI)	14.0 (1.0, 15.0)	1.0 (NE, NE)
Median, days (95% CI)	50 (15.0, 51.0)	1.0 (NE, NE)
Time to first clinically substantial change[c]		
Number with improvement (%)	50 (53.2)	82 (88.2)
Number censored (%)	44 (46.8)	11 (11.8)
25% quartile, days (95% CI)	51.0 (17.0, 78.0)	1.0 (NE, NE)
Median, days (95% CI)	134.0 (81.0, NE)	11.0 (1.0, 16.0)
Time to first response[d]		
Number with response (%)	47 (50.0)	73 (78.5)
Number censored (%)	47 (50.0)	20 (21.5)
25% quartile, days (95% CI)	55.0 (48.0, 108.0)	17.0 (15.0, 49.0)
Median, days (95% CI)	190.0 (135.0, NE)	78.0 (50.0, 106.0)
Time to first remission[e]		
Number with remission (%)	50 (53.2)	56 (60.2)
Number censored (%)	44 (46.8)	37 (39.8)
25% quartile, days (95% CI)	50.0 (16.0, 106.0)	47.0 (15.0, 52.0)
Median, days (95% CI)	192.0 (135.0, NE)	163.0 (78.0, 275.0)

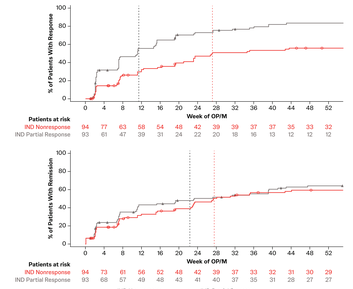
IND, induction phase; MADRS, Montgomery-Åsberg Depression Rating Scale; NE, not estimatable; OP/M, optimization and maintenance phase.
[a]Based on Kaplan-Meier product limit estimates.
[b]Clinically meaningful change was defined as a 6-point improvement in MADRS total score from IND baseline.
[c]Clinically substantial change was defined as a 12-point improvement in MADRS total score from IND baseline.
[d]Response is defined as ≥50% improvement from baseline in MADRS total score.
[e]Remission is defined as MADRS total score ≤12.

FIGURE 2. Kaplan-Meier plot of time to first (A) clinically meaningful change[a] and (B) clinically substantial change[b] in MADRS total score up to week 52 of OP/M



IND, induction phase; MADRS, Montgomery-Åsberg Depression Rating Scale; OP/M, optimization and maintenance phase.
IND nonresponders, <25% improvement in MADRS total score from baseline to day 28 of induction phase; IND partial responders, ≥25% to <50% improvement in MADRS total score from baseline to day 28 of induction phase.
[a]Clinically meaningful change was defined as a 6-point improvement in MADRS total score from IND baseline.
[b]Clinically substantial change was defined as a 12-point improvement in MADRS total score from IND baseline.
Vertical dotted lines highlight the median time to clinically meaningful change or clinically substantial change for each patient group.

FIGURE 3. Kaplan-Meier plot of time to first (A) response[a] and (B) remission[b] up to week 52 of OP/M



IND, induction phase; MADRS, Montgomery-Åsberg Depression Rating Scale; OP/M, optimization and maintenance phase.
IND nonresponders, <25% improvement in MADRS total score from baseline to day 28 of induction phase; IND partial responders, ≥25% to <50% improvement in MADRS total score from baseline to day 28 of induction phase.
[a]Response is defined as ≥50% improvement from baseline in MADRS total score.
[b]Remission is defined as MADRS total score ≤12.
Vertical dotted lines highlight the median time to response or remission for each patient group.

Safety

- Results from this subgroup analysis were consistent with the established safety and tolerability profile of ESK, with no new safety signals identified[7]
- The most common treatment-emergent adverse events (TEAEs) (>10% of total population) are shown in **Table 3**

TABLE 3. Most common TEAEs

n (%)	IND nonresponders (n = 94)	IND partial responders (n = 93)	IND full responders (n = 218)
Anxiety	22 (23.4)	15 (16.1)	55 (25.2)
Arthralgia	18 (19.1)	14 (15.1)	35 (16.1)
Back pain	23 (24.5)	21 (22.6)	36 (16.5)
Blood pressure increased	25 (26.6)	12 (12.9)	30 (13.8)
Cough	14 (14.9)	17 (18.3)	21 (9.6)
COVID-19	5 (5.3)	12 (12.9)	29 (13.3)
Diarrhea	17 (18.1)	18 (19.4)	30 (13.8)
Dissociation	27 (28.7)	27 (29.0)	68 (31.2)
Dizziness	31 (33.0)	36 (38.7)	59 (27.1)
Dysgeusia	29 (30.9)	24 (25.8)	52 (23.9)
Fatigue	21 (22.3)	12 (12.9)	34 (15.6)
Headache	39 (41.5)	39 (41.9)	83 (38.1)
Hypoesthesia	10 (10.6)	15 (16.1)	25 (11.5)
Hypoesthesia oral	12 (12.8)	11 (11.8)	22 (10.1)
Influenza	12 (12.8)	12 (12.9)	23 (10.6)
Insomnia	13 (13.8)	14 (15.1)	27 (12.4)
Nasal discomfort	13 (13.8)	9 (9.7)	29 (13.3)
Nasopharyngitis	30 (31.9)	20 (21.5)	48 (22.0)
Nausea	37 (39.4)	37 (39.8)	72 (33.0)
Oropharyngeal pain	15 (16.0)	8 (8.6)	28 (12.8)
Somnolence	25 (26.6)	21 (22.6)	43 (19.7)
Upper respiratory tract infection	5 (5.3)	11 (11.8)	26 (11.9)
Urinary tract infection	9 (9.6)	14 (15.1)	32 (14.7)
Vertigo	28 (29.8)	20 (21.5)	50 (22.9)
Vision blurred	8 (8.5)	12 (12.9)	30 (13.8)
Vomiting	20 (21.3)	14 (15.1)	33 (15.1)

IND, induction phase; TEAE, treatment emergent adverse event.

Limitations

- SUSTAIN-3 is an open-label study with no control group for comparison
- The majority of patients included in this analysis had participated in a previous ESK induction period
- 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 by potential bias related to which patients chose to continue (or not to continue) from the parent study into this study
- This analysis does not include characterization of the patient population in each subgroup through other variables
- This analysis reported time to first achievement of certain efficacy outcomes, and it cannot be assumed that patients maintained these achievements after week 52 of OP/M

Conclusions

- For patients who do not achieve full response to ESK after 28 days of induction therapy, many will achieve remission, response, clinically meaningful improvement, or clinically substantial improvement by week 52 of maintenance therapy
  - For IND nonresponders, the median time to clinically meaningful change in MADRS total score (6-point improvement) was 50 days into maintenance therapy whereas, for IND partial responders, the median time to clinically substantial change (12-point improvement) was 11 days into maintenance therapy
- IND (day 28) partial responders appear to be more likely to achieve response, remission, clinically meaningful improvement, or clinically substantial improvement than IND nonresponders; however, a large proportion of IND nonresponders still benefited from treatment with ESK up to week 52 of OP/M
- In general, rates of TEAEs were similar between IND nonresponders, IND partial responders, and IND full responders

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