Long-Term Safety and Efficacy of Esketamine Nasal Spray Maintenance Dosing After a Lapse in Treatment: A Post Hoc Analysis of the SUSTAIN-3 Study

John Zajecka[1], Dong-Jing Fu[2], Ibrahim Turkoz[2], Oliver Lopena[2], Lisa Lim[2], Brianne Brown[2], Muhammad Ahmed[2], Patricia Cabrera[2], Manish Patel[2]

[1]Rush University Medical Center, Chicago, IL; [2]Johnson & Johnson, Titusville, NJ

Introduction

- Esketamine nasal spray (ESK) is approved by the US Food and Drug Administration for the treatment of treatment-resistant depression (TRD) in adults, as monotherapy or in conjunction with an oral antidepressant (OAD), and for the treatment of depressive symptoms in adults with major depressive disorder with acute suicidal ideation or behavior, in conjunction with an OAD[1]
- SUSTAIN-3 was an open-label extension study that evaluated long-term safety and efficacy of flexibly dosed ESK in conjunction with an OAD for up to 6.5 years[2]
- Results from SUSTAIN-3 demonstrated that long-term safety of ESK was consistent with the known safety profile established in previous studies; improvements in depressive symptoms generally persisted in patients who remained on ESK maintenance treatment[2]
- It is unknown if patients who stop ESK treatment during maintenance dosing will benefit from resuming treatment at a maintenance dosing schedule[3]
  - According to the US prescribing information for ESK, for patients who miss treatment session(s), the dosing schedule of ESK should be adjusted per clinical judgment based on depressive symptoms upon continuation of maintenance treatment[1]

Objective

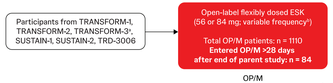
- This post hoc analysis of SUSTAIN-3 evaluated safety and efficacy of ESK maintenance dosing with an ongoing OAD in adults with TRD who had a >28-day lapse in ESK treatment

Methods

Study design

- SUSTAIN-3 (NCT02782104) was a multicenter, open-label, long-term extension study to evaluate safety and efficacy of flexibly dosed ESK, in conjunction with an OAD, in patients with TRD (**Figure 1**)

Figure 1: Study design



ESK, esketamine nasal spray; OP/M, optimization/maintenance phase.
[a]Results from the TRANSFORM-3 study (patients aged ≥65 years) were not included in this analysis.
[b]Dosing frequency was adjusted based on Clinical Global Impression-Severity scale score and tolerability.

- Patients entered SUSTAIN-3 from 1 of 5 parent studies and could enter the optimization/maintenance (OP/M) phase directly, bypassing a 4-week induction (IND) phase, when they had received induction and were a responder in the parent study or they were in the OP/M phase of the parent study
- This subgroup analysis included adult patients (aged 18-64) who entered OP/M with a >28-day lapse in ESK treatment from the end of the parent study; during OP/M, ESK was dosed according to US prescribing information and in conjunction with an ongoing OAD

Data analyses

- Montgomery-Åsberg Depression Rating Scale (MADRS) and Patient Health Questionnaire-9 (PHQ-9) total scores were used to evaluate disease severity throughout OP/M and from IND baseline to OP/M last visit
- Response was defined as a ≥50% improvement in MADRS or PHQ-9 total scores, compared with IND baseline
- Treatment-emergent adverse events (TEAEs) are summarized descriptively

Results

Demographics and baseline characteristics

- Of 1110 total patients who received treatment in the OP/M phase, 84 patients continued maintenance ESK in the OP/M phase >28 days from the end of the parent study and were included in this subgroup analysis; most patients were female (65.5%) and White (89.3%) and had an average age of 49.8 years, consistent with the overall study population[2] (**Table 1**)

Table 1: Patient demographics and baseline clinical characteristics

	Patients who had >28-day lapse in ESK maintenance n = 84
Mean age (SD), years	49.8 (11.28)
Female, n (%)	55 (65.5)
Race, n (%)	
White	75 (89.3)
Black or African American	4 (4.8)
Asian	1 (1.2)
Multiple	1 (1.2)
Ethnicity, n (%)	
Hispanic or Latino	12 (14.3)
Mean duration of current episode (range), weeks	131.1 (13-1144)
Duration of lapse in maintenance treatment, days[a]	
Mean (SD)	163.5 (135.2)
Median	119.5
Range	30-607
Mean baseline MADRS total score (SD)	
IND	36.65 (5.78)
Parent study last visit	11.6 (10.10)
OP/M	14.7 (10.67)
Mean baseline PHQ-9 total score (SD)	
IND	18.83 (4.05)
Parent study last visit	5.4 (5.21)
OP/M	8.5 (6.85)

ESK, esketamine nasal spray; IND, induction phase; MADRS, Montgomery-Åsberg Depression Rating Scale; OP/M, optimization/maintenance phase; PHQ-9, Patient Health Questionnaire-9.
[a]Time from the last visit of the parent study to the initiation of OP/M. This timeframe also includes the period during which patients received placebo during the maintenance phase of SUSTAIN-1.

- Mean (SD) time between the end of the parent study and the initiation of OP/M was 163.5 (135.2) days (median, 119.5 days; range, 30-607 days)
- At OP/M baseline, mean (SD) MADRS total score was 14.7 (10.67); this represented a mean (SD) increase in MADRS total score from the end of the parent study to OP/M baseline of 3.1 (6.79) during the >28-day lapse in ESK treatment
- At OP/M baseline, mean (SD) PHQ-9 total score was 8.5 (6.85); this represented a mean (SD) increase in PHQ-9 total score from the end of the parent study to OP/M baseline of 3.1 (5.04) during the >28-day lapse in ESK treatment

Efficacy

- Improvements from OP/M baseline in mean (SE) MADRS and PHQ-9 total scores were observed by week 3 and continued to improve through week 8; improvements were sustained throughout OP/M (**Figure 2**)
- Response rates over time per MADRS and PHQ-9 total scores are shown in **Figure 3**; response rates increased from OP/M baseline to week 8 and were sustained throughout OP/M
- Mean change (SD) from IND baseline to OP/M last visit for MADRS total score was −24.1 (10.82), and for PHQ-9 total score was −11.5 (7.26) (**Table 2**)
- At OP/M last visit, 72.6% of patients achieved response per MADRS total score, and 59.5% of patients achieved response per PHQ-9 total score (**Table 2**)

Table 2: Change from IND baseline in MADRS and PHQ-9 total score and response rate at OP/M last visit

	Patients who had >28-day lapse in ESK maintenance n = 84	
	MADRS	PHQ-9
Mean change from IND baseline (SD)[a]	−24.1 (10.82), *P* < 0.001	−11.5 (7.26), *P* < 0.001
Response, n (%)[b]	61 (72.6)	50 (59.5)

ESK, esketamine nasal spray; IND, induction phase; MADRS, Montgomery-Åsberg Depression Rating Scale; OP/M, optimization/maintenance phase; PHQ-9, Patient Health Questionnaire-9.
[a]Mean change in total score from IND baseline to OP/M last visit (last observation carried forward). *P*-value is for difference from 0 using a 1-sample *t* test.
[b]Response is defined as ≥50% reduction in score from IND baseline to OP/M last visit.

Safety

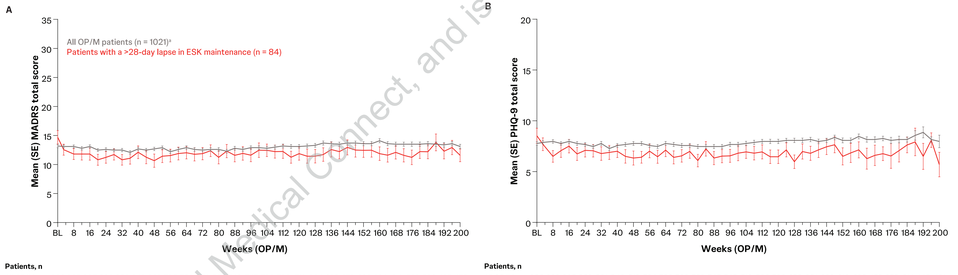
- The most common TEAEs experienced by patients with a >28-day lapse in maintenance treatment were dizziness, nausea, and headache; these were the most common TEAEs among all patients treated in OP/M (**Table 3**)

Table 3: Most common (≥10%) TEAEs[a]

TEAE, n (%)	Patients who had >28-day lapse in ESK maintenance n = 84	All OP/M patients[b] n = 1021
Dizziness	30 (35.7)	354 (34.7)
Nausea	23 (27.4)	351 (34.4)
Headache	21 (25.0)	382 (37.4)
Vertigo	19 (22.6)	195 (19.1)
Nasopharyngitis	21 (25.0)	235 (23.0)
Dysgeusia	18 (21.4)	221 (21.6)
Somnolence	16 (19.0)	241 (23.6)
Dissociation	14 (16.7)	270 (26.4)
Urinary tract infection	12 (14.3)	152 (14.9)
Influenza	11 (13.1)	126 (12.3)
Depression	10 (11.9)	82 (8.0)
Vomiting	10 (11.9)	166 (16.3)
Back pain	10 (11.9)	199 (19.5)
Arthralgia	10 (11.9)	164 (16.1)
Paresthesia	9 (10.7)	87 (8.5)

ESK, esketamine nasal spray; OP/M, optimization/maintenance phase; TEAE, treatment-emergent adverse event.
[a]Most common (≥10%) TEAEs reported in patients who initiated OP/M >28 days after the end of the parent study, and matching data for the overall study population for comparison.
[b]Patients who received ≥1 dose of study intervention in OP/M, consistent with US prescribing information.

Figure 2: Mean (SE) (A) MADRS and (B) PHQ-9 total scores during OP/M (observed cases)

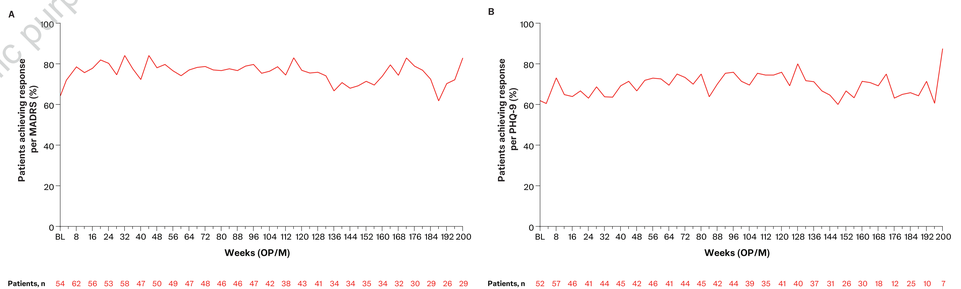


Patients, n	BL	8	16	24	32	40	48	56	64	72	80	88	96	104	112	120	128	136	144	152	160	168	176	184	192	200
All OP/M	986	935	907	862	863	843	822	795	789	771	753	749	747	723	708	711	684	689	672	663	634	611	560	526	497	472
>28-day lapse	84	79	72	66	69	65	64	64	64	61	61	60	60	59	55	51	56	54	51	50	49	46	43	38	40	37	35

Patients, n	BL	8	16	24	32	40	48	56	64	72	80	88	96	104	112	120	128	136	144	152	160	168	176	184	192	200
All OP/M	985	926	905	859	861	840	819	794	786	768	752	745	745	719	705	709	675	681	663	610	625	473	375	514	145	101
>28-day lapse	84	78	72	65	69	65	63	63	59	60	60	60	58	56	47	54	50	52	48	39	42	26	19	38	14	8

BL, baseline; ESK, esketamine nasal spray; MADRS, Montgomery-Åsberg Depression Rating Scale; OP/M, optimization/maintenance phase; PHQ-9, Patient Health Questionnaire-9.
Patients received ESK maintenance dosing in conjunction with an ongoing oral antidepressant.
[a]Patients who received ≥1 dose of study intervention in OP/M, consistent with US prescribing information.

Figure 3: Response rates per (A) MADRS and (B) PHQ-9 total scores during OP/M upon continuation of ESK maintenance treatment after a >28-day lapse (observed cases)



Patients, n	BL	8	16	24	32	40	48	56	64	72	80	88	96	104	112	120	128	136	144	152	160	168	176	184	192	200
	54	62	56	53	58	47	50	49	47	48	46	46	47	42	38	43	41	34	34	35	34	32	30	29	26	29

Patients, n	BL	8	16	24	32	40	48	56	64	72	80	88	96	104	112	120	128	136	144	152	160	168	176	184	192	200
	52	57	46	41	44	45	42	46	41	44	45	42	44	39	35	41	40	37	31	26	30	18	12	25	10	7

BL, baseline; ESK, esketamine nasal spray; IND, induction phase; MADRS, Montgomery-Åsberg Depression Rating Scale; OP/M, optimization/maintenance phase; PHQ-9, Patient Health Questionnaire-9.
Response is defined as ≥50% reduction in score from IND baseline.
Patients received ESK maintenance dosing in conjunction with an ongoing oral antidepressant.

Key Takeaways

- Patients who had a >28-day lapse in esketamine nasal spray treatment continued to receive benefit upon recontinuation of maintenance dosing
- These results provide clinicians with valuable insights into how to manage patients with lapses in treatment of esketamine nasal spray when given in conjunction with an ongoing OAD

Conclusions

- In this post hoc subgroup analysis of the open-label extension study SUSTAIN-3, patients with a >28-day lapse in esketamine nasal spray treatment benefited from recontinuation of esketamine nasal spray maintenance dosing when given in combination with an ongoing OAD
- TEAEs were consistent with the established safety profile of esketamine nasal spray

Limitations

- SUSTAIN-3 was an open-label study with no control group for comparison
- This is a post hoc subgroup analysis with a relatively small sample size
- Potential bias related to which patients chose to continue from the parent study into SUSTAIN-3, and the exclusion of patients with significant psychiatric or medical comorbidities, or substance dependence, may limit the generalizability of these findings

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