Long-Term Safety and Efficacy of Esketamine Nasal Spray by Dosing Frequency in Adults With Treatment-Resistant Depression: Analysis of the SUSTAIN-3 Study

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Introduction

- Treatment-resistant depression (TRD) affects 10% to 30% of patients with major depressive disorder (MDD)[1,2] and is commonly defined as an inadequate response to 2 or more oral antidepressants (OADs) of adequate dose and duration[3]
- The optimal goal of treatment for patients with MDD is to achieve and sustain full symptomatic remission early in the course of their illness[4,5]
- Esketamine nasal spray (ESK) is a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist approved by the US Food and Drug Administration for use in combination with an OAD for the treatment of adults with TRD as well as for depressive symptoms in adults with MDD with acute suicidal ideation or behavior[6]
- SUSTAIN-3 is an open-label, multicenter, phase 3 long-term extension study assessing the safety and efficacy of individualized and flexibly dosed ESK, in conjunction with an OAD, in patients with TRD
- The results of SUSTAIN-3 add to current understanding of the long-term safety and efficacy of ESK treatment from previous studies, including SUSTAIN-1, the first controlled maintenance study that showed that the flexible administration of ESK in combination with an OAD is more effective than an OAD in combination with placebo nasal spray at sustaining antidepressant effects in patients with TRD for up to 23 months[7]

Objective

- To describe long-term safety and efficacy of flexibly dosed ESK in patients with TRD from SUSTAIN-3 (NCT02782104)

Methods

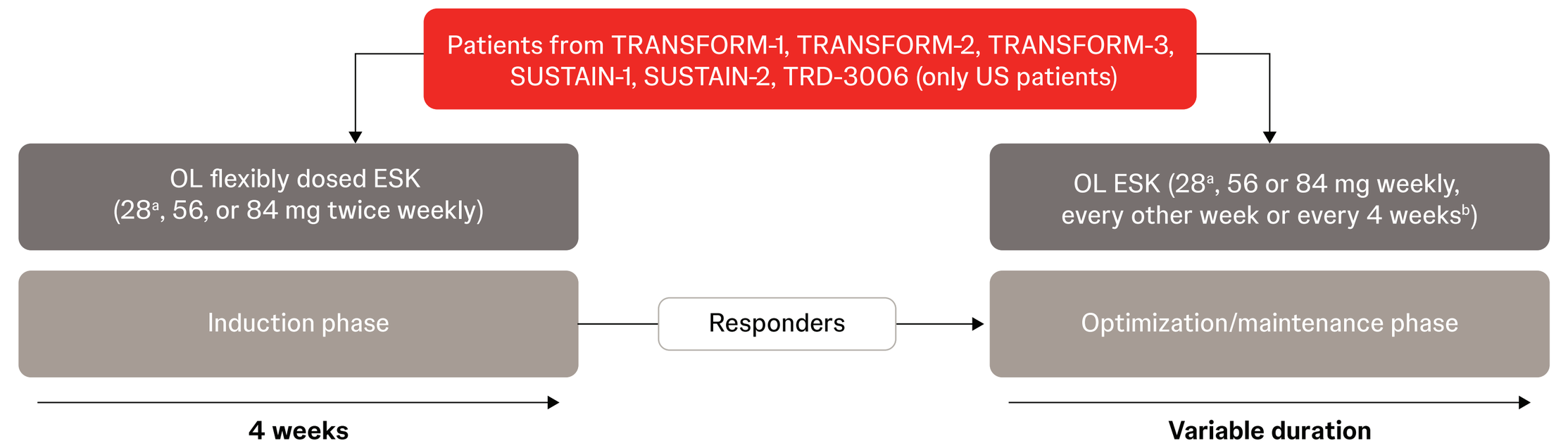
Study design and participants

- SUSTAIN-3 was conducted to assess the safety and efficacy of ESK treatment plus an OAD in adult patients with TRD for up to 6.5 years
- Patients from 6 phase 3 parent studies (TRANSFORM-1, -2, and -3; SUSTAIN-1 and -2; TRD3006) were enrolled in SUSTAIN-3, either into a 4-week induction (IND) phase or directly into an optimization/maintenance (OP/M) phase of variable duration (**Figure 1**)
- Patients could leave the study when ESK was approved and available in their local healthcare system
- Starting at week 4 of the OP/M phase, ESK planned treatment frequency was adjusted according to Clinical Global Impressions-Severity scale (CGI-S) scores at fixed 2- or 4-week intervals (**Table 1**)

Outcomes measures

- For this subgroup analysis, cohorts were assigned based on cumulative mode ESK planned dosing frequency of weekly, every other week, or every 4 weeks
- Depressive symptoms were assessed using the Montgomery–Åsberg Depression Rating Scale (MADRS) every 4 weeks and the 9-item Patient Health Questionnaire (PHQ-9) every 4 or 12 weeks
- Remission was defined as MADRS total score ≤12
- Treatment-emergent adverse events (TEAEs) were monitored throughout the study

FIGURE 1: SUSTAIN-3 study design



CGI-S, Clinical Global Impressions-Severity scale; ESK, esketamine nasal spray; OL, open-label.
[a]The 28 mg dose was only an option for patients aged ≥65 years.
[b]Based on CGI-S score and tolerability.

TABLE 1: Algorithm for adjusting ESK treatment frequency

Current Treatment Frequency[a]	CGI-S Score at Current Visit[b,c]	
	≤3	>3
Weekly	Change to every other week frequency	No change in frequency
Every other week	No change in frequency or change to every 4 weeks per clinical judgement	Change to weekly frequency
Every 4 weeks	No change in frequency	Change to weekly or every other week frequency per clinical judgement

CGI-S, Clinical Global Impressions-Severity scale; ESK, esketamine nasal spray; OP/M, optimization/maintenance.
[a]Starting from week 4 of the OP/M phase.
[b]CGI-S is a 7-point clinician-rated scale based upon observed and reported symptoms wherein 1 indicates normal, not at all ill; 2, borderline mentally ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; and 7, among the most extremely ill patients.
[c]The CGI-S is administered every 2 weeks from week 4 through the end of the OP/M phase, and adjustment of the intranasal treatment session frequency is only permitted at the fixed 2-week intervals (based on CGI-S score as assessed at that visit) and every 4 weeks for patients dosed at the 4-week interval.

Results

Baseline demographics and clinical characteristics

- A total of 1097 patients were included in the analysis; 591 patients (54%), 369 patients (34%), and 137 patients (12%) had an ESK mode dosing frequency of weekly, every other week, and every 4 weeks, respectively, during the OP/M phase
- Baseline demographics and clinical characteristics are shown in **Table 2**
- OP/M phase baseline mean (SD) MADRS total score was 16.2 (8.4), 10.0 (7.8), and 8.1 (7.3) for patients with mode ESK dosing frequency of weekly, every other week, and every 4 weeks, respectively (**Table 2**)
- OP/M baseline mean (SD) PHQ-9 total score was 9.3 (5.5), 5.8 (5.2) and 5.1 (4.7) for patients with mode ESK dosing frequency of weekly, every other week, and every 4 weeks, respectively (**Table 2**)

TABLE 2: Baseline demographics and clinical characteristics by mode ESK dosing frequency[a]

	Weekly n = 591	Every Other Week n = 369	Every 4 Weeks n = 137
Mean age (SD), years	48.5 (12.4)	51.5 (12.2)	50.5 (11.4)
Sex, n (%)			
Male	205 (34.7)	111 (30.1)	43 (31.4)
Female	386 (65.3)	258 (69.9)	94 (68.6)
Race, n (%)[b]			
White	502 (84.9)	329 (89.2)	120 (87.6)
Black or African American	29 (4.9)	12 (3.3)	2 (1.5)
Asian	22 (3.7)	15 (4.1)	8 (5.8)
Other	21 (3.6)	6 (1.6)	1 (0.7)
Not reported	11 (1.9)	5 (1.4)	5 (3.6)
Region, n (%)			
Europe	244 (41.3)	165 (44.7)	56 (40.9)
North America	205 (34.7)	92 (24.9)	18 (13.1)
Rest of world	142 (24.0)	112 (30.4)	63 (46.0)
Employment status, n (%)[c]			
Any type of employment	345 (58.4)	224 (60.7)	95 (69.3)
Any type of unemployment	155 (26.2)	87 (23.6)	23 (16.8)
Other	91 (15.4)	58 (15.7)	19 (13.9)
IND baseline MADRS total score	n = 302	n = 88	n = 23
Mean (SD)	30.1 (7.5)	25.6 (8.6)	28.8 (8.5)
OP/M baseline MADRS total score	n = 591	n = 369	n = 137
Mean (SD)	16.2 (8.4)	10.0 (7.8)	8.1 (7.3)
IND baseline PHQ-9 total score	n = 301	n = 88	n = 23
Mean (SD)	15.9 (5.3)	13.6 (5.7)	13.8 (7.1)
OP/M baseline PHQ-9 total score	n = 591	n = 368	n = 137
Mean (SD)	9.3 (5.5)	5.8 (5.2)	5.1 (4.7)

ESK, esketamine nasal spray; IND, induction phase; MADRS, Montgomery-Åsberg Depression Rating Scale; OP/M, optimization/maintenance phase; PHQ-9, 9-item Patient Health Questionnaire.
[a]Data are reported from parent study if they were not collected in SUSTAIN-3.
[b]Data from patients who identified as American Indian or Alaskan Native or multiple races are not reported (<1%).
[c]Any type of employment includes any category containing "employed" (sheltered work, housewife or dependent husband, and student); any type of unemployment includes any category containing "unemployed"; other includes retired and no information available.

Description of ESK treatment frequency, duration, and dose

- The distribution of ESK dosing frequency of weekly, every other week, and every 4 weeks over time during the OP/M phase is shown in **Figure 2**
- In general, during the OP/M phase, the most frequent dosing interval was weekly, followed by every other week and every 4 weeks (**Figure 2**)
- The mean (SD) duration of ESK treatment in patients treated at a mode dosing frequency of weekly, every other week, and every 4 weeks was 42.9 (23.87), 46.5 (21.42), and 46.4 (22.50) months, respectively (**Table 3**)
- The median mode dose of ESK received per treatment was 84, 84, and 56 mg for patients treated at a mode dosing frequency of weekly, every other week, and every 4 weeks, respectively (**Table 3**)

TABLE 3: Mean ESK treatment duration and dose in the OP/M phase by mode dosing frequency

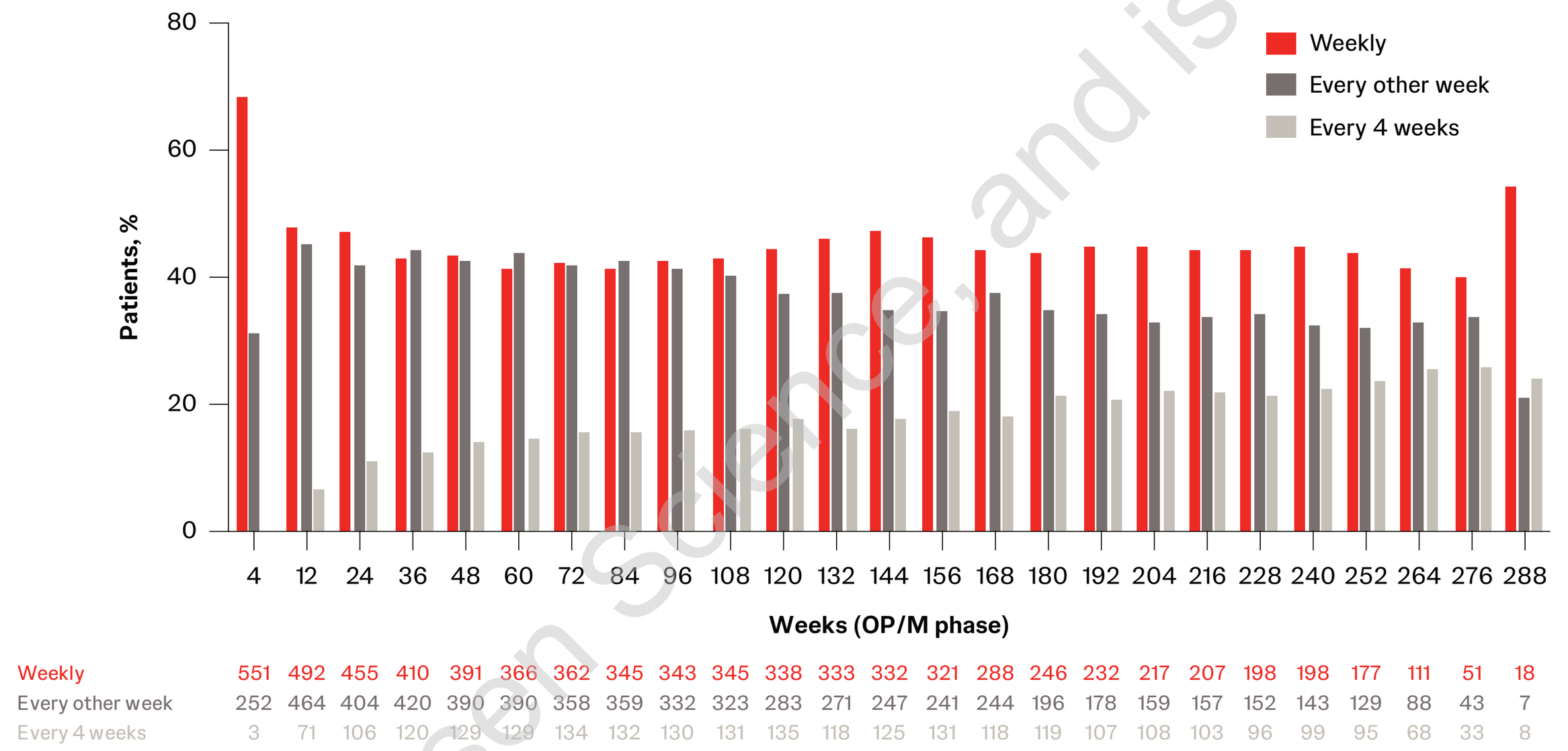
	Weekly n = 591	Every Other Week n = 369	Every 4 Weeks n = 137
ESK treatment duration, months			
Mean (SD)	42.9 (23.9)	46.5 (21.4)	46.4 (22.5)
Median	45.0	47.5	50.7
Range	0-77	1-78	1-72
Mean dose per patient, mg			
Mean (SD)	77.9 (11.1)	71.9 (14.5)	68.2 (14.6)
Median	83.9	82.6	65.0
Range	28-84	28-84	28-84
Mode dose per patient, mg			
Mean (SD)	78.2 (12.1)	72.2 (15.3)	68.5 (15.2)
Median	84.0	84.0	56.0
Range	28-84	28-84	28-84

ESK, esketamine nasal spray; OP/M, optimization/maintenance; SD, standard deviation.

Efficacy

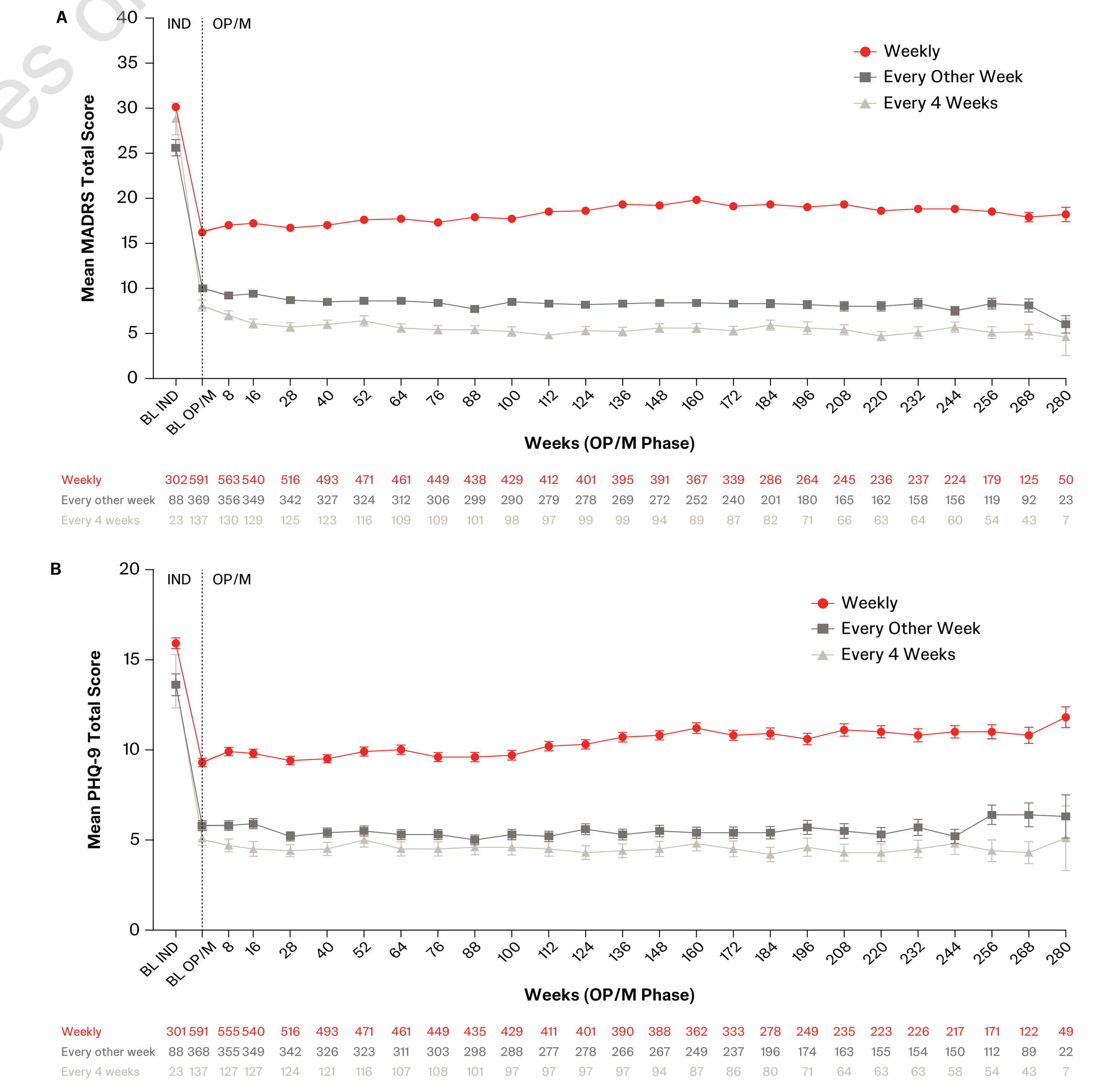
- Mean MADRS and PHQ-9 total scores remained stable over time for all dosing frequency subgroups (**Figure 3**)
- The mean (SD) MADRS total score change from OP/M phase baseline to the end of the study (312 weeks) based on last-observation-carried-forward (LOCF) data was 2.0 (10.4), −1.8 (8.7), and −2.2 (9.8) for patients treated at a mode dosing frequency of weekly, every other week, and every 4 weeks, respectively
- The mean (SD) PHQ-9 total score change from the OP/M phase baseline to the end of the study (312 weeks) based on LOCF data was 1.5 (6.6), −0.3 (5.4), and −0.8 (6.2) for patients treated at a mode dosing frequency of weekly, every other week, and every 4 weeks, respectively
- At the end of the OP/M phase, the proportion of patients in remission (defined as having a MADRS total score ≤12) based on LOCF data was 24.7%, 75.6%, and 88.3% for patients treated at a mode dosing frequency of weekly, every other week, and every 4 weeks, respectively

FIGURE 2: Distribution of ESK dosing frequency over time starting from week 4 of the OP/M phase



ESK, esketamine nasal spray; OP/M, optimization/maintenance.
Data are presented until week 288, when >20 patients were present in the study.

FIGURE 3: Mean (SE) (A) MADRS total score and (B) PHQ-9 total score over time by mode dosing frequency in observed cases



BL, baseline; IND, induction; MADRS, Montgomery–Åsberg Depression Rating Scale; OP/M, optimization/maintenance; PHQ-9, 9-item Patient Health Questionnaire.
MADRS total score ranges from 0 to 60; a higher score indicates greater depression severity.
PHQ-9 total score ranges from 0 to 27; a higher score indicates greater depression severity.
Data beyond week 280 were excluded due to reduced sample size.

Safety

- The most commonly reported TEAEs (>10% of patients) are shown in **Table 4**
- TEAEs were consistent with the established tolerability profile of ESK, with no new safety signals identified

TABLE 4: Most common TEAEs (>10%) by mode dosing frequency

	Weekly n = 591	Every Other Week n = 369	Every 4 Weeks n = 137
Total number subjects with TEAEs, n (%)	557 (94.2)	362 (98.1)	125 (91.2)
Headache	230 (38.9)	126 (34.1)	46 (33.6)
Nausea	193 (32.7)	112 (30.4)	50 (36.5)
Dizziness	169 (28.6)	132 (35.8)	63 (46.0)
Nasopharyngitis	142 (24.0)	94 (25.5)	31 (22.6)
Dissociation	133 (22.5)	101 (27.4)	36 (26.3)
Dysgeusia	134 (22.7)	57 (15.4)	26 (19.0)
Vertigo	128 (21.7)	60 (16.3)	11 (8.0)
Back pain	121 (20.5)	81 (22.0)	24 (17.5)
Somnolence	116 (19.6)	101 (27.4)	36 (26.3)
Anxiety	111 (18.8)	64 (17.3)	25 (18.2)
Diarrhea	109 (18.4)	61 (16.5)	14 (10.2)
Arthralgia	101 (17.1)	57 (15.4)	24 (17.5)
Urinary tract infection	97 (16.4)	58 (15.7)	21 (15.3)
Vomiting	95 (16.1)	59 (16.0)	21 (15.3)
Insomnia	86 (14.6)	40 (10.8)	23 (16.8)
Upper respiratory tract infection	83 (14.0)	45 (12.2)	14 (10.2)
Blood pressure increased	76 (12.9)	51 (13.8)	28 (20.4)
Fatigue	75 (12.7)	51 (13.8)	18 (13.1)
Cough	74 (12.5)	28 (7.6)	12 (8.8)
Vision blurred	71 (12.0)	33 (8.9)	12 (8.8)
COVID-19	70 (11.8)	52 (14.1)	19 (13.9)
Influenza	68 (11.5)	51 (13.8)	14 (10.2)
Oropharyngeal pain	67 (11.3)	20 (5.4)	8 (5.8)
Depression	62 (10.5)	19 (5.1)	6 (4.4)

TEAE, treatment-emergent adverse event.

Key takeaway

Flexible dosing of esketamine nasal spray, adjusted according to disease severity, is effective at maintaining long-term clinical stability in patients with TRD

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
- Sample size decreases at later time points and the size of the every 4 week dosing frequency subgroup may have implications for the generalizability of findings
- 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 may limit the generalizability of these findings

Conclusions

This subgroup analysis of SUSTAIN-3, an open-label, phase 3, long-term extension study of flexibly dosed esketamine nasal spray, in combination with an oral antidepressant, demonstrated durable long-term safety and efficacy in patients with a mode dosing frequency of weekly, every other week, or every 4 weeks

Acknowledgements
The authors thank Emily Spaulding, PhD, and Kevin O'Regan, PhD (ApotheCom, Yardley, PA), for editorial and writing assistance, which was funded by Janssen Scientific Affairs, LLC, a Johnson & Johnson company.

Disclosures
JZ has received funding from Boehringer-Ingelheim, Compass, ElMindA, Cheryl T. Herman Foundation, Hoffman-LaRoche, Jazz Pharmaceuticals, Janssen/Johnson & Johnson, LivaNova, Otsuka, Neurocrine, Novartis, SAGE Therapeutics, and Takeda and provided consulting or advisory board support to Alpha Sigma, ElMindA, Janssen/Johnson & Johnson, Lundbeck, and Takeda. DF, NZ, and IT are employees of Janssen Research & Development, LLC. PC, OL, MP, and SF are employees of Janssen Scientific Affairs, LLC, a Johnson & Johnson company. DF, NZ, IT, PC, OL, MP, and SF hold stock in Johnson & Johnson, Inc.

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Supported by Janssen Scientific Affairs, LLC, a Johnson & Johnson company

Presented at Psych Congress Elevate; May 30-June 2, 2024; Las Vegas, Nevada

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