

## REGULAR RESEARCH ARTICLE

# Managing Esketamine Treatment Frequency Toward Successful Outcomes: Analysis of Phase 3 Data

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## Abstract

**Background:** Esketamine nasal spray was recently approved for treatment-resistant depression. The current analysis evaluated the impact of symptom-based treatment frequency changes during esketamine treatment on clinical outcomes.

**Methods:** This is a post-hoc analysis of an open-label, long-term (up to 1 year) study of esketamine in patients with treatment-resistant depression (SUSTAIN 2). During a 4-week induction phase, 778 patients self-administered esketamine twice weekly plus a new oral antidepressant daily. In responders ( $\geq 50\%$  reduction in Montgomery-Åsberg Depression Rating Scale total score from baseline), esketamine treatment frequency was thereafter decreased during an optimization/maintenance phase to weekly for 4 weeks and then adjusted to the lowest frequency (weekly or every other week) that maintained remission (Montgomery-Åsberg Depression Rating Scale  $\leq 12$ ) based on a study-defined algorithm. The relationship between treatment frequency and symptom response, based on clinically meaningful change in Clinical Global Impression–Severity score, was subsequently evaluated 4 weeks after treatment frequency adjustments in the optimization/maintenance phase.

**Results:** Among 580 responders treated with weekly esketamine for the first 4 weeks in the optimization/maintenance phase (per protocol), 26% continued to improve, 50% maintained clinical benefit, and 24% worsened. Thereafter, when treatment frequency could be reduced from weekly to every other week, 19% further improved, 49% maintained benefit, and 32% worsened. For patients no longer in remission after treatment frequency reduction, an increase (every other week to weekly) resulted in 47% improved, 43% remained unchanged, and 10% worsened.

**Conclusions:** These findings support individualization of esketamine nasal spray treatment frequency to optimize treatment response in real-world clinical practice.

**Trial Registration:** ClinicalTrials.gov identifier: NCT02497287

**Key Words:** Esketamine, s-ketamine, dosing, treatment-resistant depression

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## Significance Statement

Esketamine nasal spray was recently approved by the US Food and Drug Administration, in conjunction with an oral antidepressant, for treatment-resistant depression (TRD). As the optimal treatment frequency of esketamine for long-term maintenance was unknown when phase 3 studies began, investigators adjusted treatment frequency based on level of depressive symptoms per protocol. Accordingly, after twice-weekly treatment for 4 weeks, all responders had esketamine treatment frequency reduced from twice weekly to weekly for the following 4 weeks, after which 76% either continued to improve or maintained clinical benefit. Thereafter, when treatment frequency could be further reduced from weekly to every other week, per algorithm based on the level of depressive symptomatology, most (68%) further improved or maintained clinical benefit, and among the remainder, most (90%) improved or remained unchanged following an increase from every other week back to weekly treatment. These results support individualization of esketamine nasal spray treatment frequency to optimize response in clinical practice.

## Introduction

Esketamine nasal spray is a first-in-class glutamatergic N-methyl-D-aspartate receptor antagonist, which was recently approved by the US Food and Drug Administration and European Medicines Agency for treatment-resistant depression (TRD) in adults, in conjunction with an oral antidepressant (Spravato Prescribing Information 2019; Spravato Summary of Product Characteristics 2019). The approval of esketamine nasal spray was based, in large part, on efficacy and safety findings from phase 2 and phase 3 studies in patients with TRD (Daly et al., 2018, 2019; Popova et al., 2019; Fedgchin et al., 2019; Wajs et al., 2020; Ochs-Ross et al., 2020).

Esketamine nasal spray is self-administered under the direct observation of a healthcare provider. Esketamine treatment starts with twice-weekly treatment of either 56 or 84 mg for 4 weeks during the induction phase. At the start of the phase III program in TRD, the optimal treatment frequency of esketamine nasal spray for long-term maintenance of individual patients was unknown. Therefore, in the phase III studies, a treatment frequency algorithm was implemented similar to the dosing regimen model applied in the electroconvulsive therapy literature (Russell et al., 2003; Odenberg et al., 2008). The algorithm was driven by symptom severity measured by the Montgomery-Åsberg Depression Rating Scale (MADRS) (Williams and Kobak, 2008) with decrease in treatment frequency on depressive symptom improvement ( $MADRS \leq 12$ ) and increase in treatment frequency on depressive symptom worsening ( $MADRS > 12$ ). The goal of treatment frequency adjustments was to optimize treatment outcomes in individual patients and to achieve and/or maintain remission at the lowest possible esketamine treatment frequency that prevents relapse.

A post-hoc analysis of data from one of the esketamine phase III studies (SUSTAIN-2; Wajs et al., 2020) was conducted to assess the effectiveness of symptom-based treatment frequency changes on improving, worsening, or maintaining clinical benefit. The aim of the post-hoc analysis reported herein is to inform clinical decision-making and optimization of esketamine therapy for patients with TRD.

## Materials and Methods

The methods of SUSTAIN-2 are published elsewhere (Wajs et al. 2020). Study methods salient to the work reported here are summarized below.

### Ethical Practices

An Institutional Review Board or Independent Ethics Committee, depending on the participating country, approved the study protocol and amendments. The study was conducted

in accordance with ethical principles of the Declaration of Helsinki, Good Clinical Practices, and applicable regulatory requirements. All individuals provided written informed consent before participating in the study.

### Study Design

SUSTAIN-2 was an open-label, long-term (up to 1 year of exposure), phase III study conducted across 21 countries from October 2015 to January 2018. SUSTAIN-2 included 4 phases: a 4-week screening phase (direct-entry patients only, as described below), a 4-week induction phase, an optimization/maintenance phase of up to 48 weeks, and a 4-week follow-up phase (results from the latter are not reported here).

### Study Population of SUSTAIN-2

Eligible patients had moderate-to-severe depression without psychotic features and met the study definition of TRD (i.e., nonresponse to an adequate trial of  $\geq 2$  antidepressants in the current episode of depression). Patients entered the study either directly (patients  $\geq 18$  years) or after completing the double-blind induction phase of a randomized, 4-week, phase III efficacy study in patients  $\geq 65$  years with TRD (TRANSFORM-3) (Ochs-Ross et al., 2020). Transfer-entry patients who were responders ( $\geq 50\%$  reduction in MADRS total score) in the short-term study joined the current study in the optimization/maintenance phase while nonresponders joined in the induction phase. Patients from the double-blind TRANSFORM-3 study who were responders and entered directly into the optimization/maintenance phase of the SUSTAIN-2 study were excluded ( $n=23$ ) from this post-hoc analysis, so data points from 580 patients of 603 for treatment frequency changes were analyzed.

### Study Drug Dosing

#### Induction Phase (4 weeks)

Patients self-administered a twice-weekly dose of esketamine nasal spray (patients aged 18–64 years: 56 or 84 mg; patients aged  $\geq 65$  years: 28, 56, or 84 mg) under the direct supervision of a healthcare provider. Direct-entry patients simultaneously initiated a new daily oral antidepressant, and transfer-entry (nonresponder) patients continued the daily oral antidepressant that was initiated in the short-term study. The oral antidepressant was 1 of a choice of 4 (duloxetine, escitalopram, sertraline, or venlafaxine XR) selected by the investigator. The dose of esketamine nasal spray was flexible until day 15, after which investigators were asked to not adjust the dose (56 or 84 mg)

unless in their clinical judgment, based on tolerability, the dose warranted a change.

### Optimization/Maintenance Phase (Up to 48 Weeks)

During the first 4 weeks of the optimization/maintenance phase, all patients received esketamine on a weekly basis (Figure 1); thereafter, treatment frequency was reevaluated every 4 weeks according to a treatment algorithm based on the principle of assignment to the lowest treatment frequency (weekly or every other week) that was adequate to maintain remission (defined as MADRS  $\leq 12$ ). If the MADRS total score was  $>12$  (i.e., depressive symptoms present), treatment frequency was either maintained at weekly or increased to weekly from every other week until the next assessment. If MADRS total score was  $\leq 12$  (i.e., remission), treatment frequency was maintained at every other week or reduced from weekly to every other week until the next assessment.

### Compliance

Study drug accountability was conducted for both esketamine and the oral antidepressant throughout the study. For esketamine, study drug accountability consisted of recording in the electronic case record all esketamine nasal spray devices dispensed and documenting the dose given at each dosing session. For the oral antidepressant, treatment compliance was assessed every 4 weeks by performing pill counts with documentation of drug accountability forms in the electronic case record. In addition, between visits patients completed a daily diary where the administration of oral antidepressant was captured.

### Key Outcome Assessments

Symptom improvement or worsening was evaluated using the investigator-assessed Clinical Global Impression–Severity (CGI-S) score (Guy, 1976). The CGI-S equates to the clinical judgment used by clinicians in real-world practice to assess the overall impact of treatment and is measured on a scale of 0 to 7. Considering the investigator's total clinical experience, a patient is globally assessed on severity of mental illness at the time of rating according to: 0=not assessed; 1=normal (not at all ill); 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among the most extremely ill patients.

Symptoms were also evaluated using the Patient Health Questionnaire–9 Item Depression Module (PHQ-9) (Spitzer et al., 1999), a patient-reported scale that covers the 9 symptom domains of major depression disorder (DSM 5 criteria). Each item was rated on a 4-point scale (0=not at all, 1=several days, 2=more than half the days, and 3=nearly every day). The patient's item responses were summed to provide a total score (range of 0 to 27), with higher scores indicating greater severity of depressive symptoms. The recall period was 2 weeks.

In the current post-hoc analysis, the CGI-S and PHQ-9 were used to evaluate changes in a clinically meaningful response: a 1-point change in CGI-S score and a 3-point change in PHQ-9 were considered clinically meaningful (Turkoz et al., 2018).

### Statistical Analyses

Patients in SUSTAIN-2 were classified into 3 treatment frequency cohorts for statistical analyses: (1) those who were treated weekly (high-frequency group); (2) those who had 1 change to every other week (low-frequency group); and (3) those who alternated back and forth from weekly to every other week (alternating frequency group). Baseline characteristics and psychiatric history were summarized and compared across these groups.

Clinical outcomes (CGI-S and PHQ-9) data from SUSTAIN-2 were extracted and changes in CGI-S and PHQ-9 scores from the day of treatment frequency change to 4 weeks after every treatment frequency change (Table 1) were summarized by esketamine treatment frequency cohort: (1) in pooled manner, irrespective of when the change (increase, decrease) occurred, and (2) based on timing of the change (Table 2). Subsequently, an analysis was performed to see if there were any differences in the probability of outcomes following the first change in treatment frequency to that following the second and third changes in treatment frequency.

### Results

A total of 778 patients were treated with esketamine in the 4-week induction phase (Figure 2); 198 patients discontinued after induction (84 did not meet criteria for continuing into the next phase, 52 due to adverse events, 22 due to withdrawal by patients, 21 due to lack of efficacy, and 19 for other reasons) and went to the 4-week follow-up phase, and 580 (75%) patients were

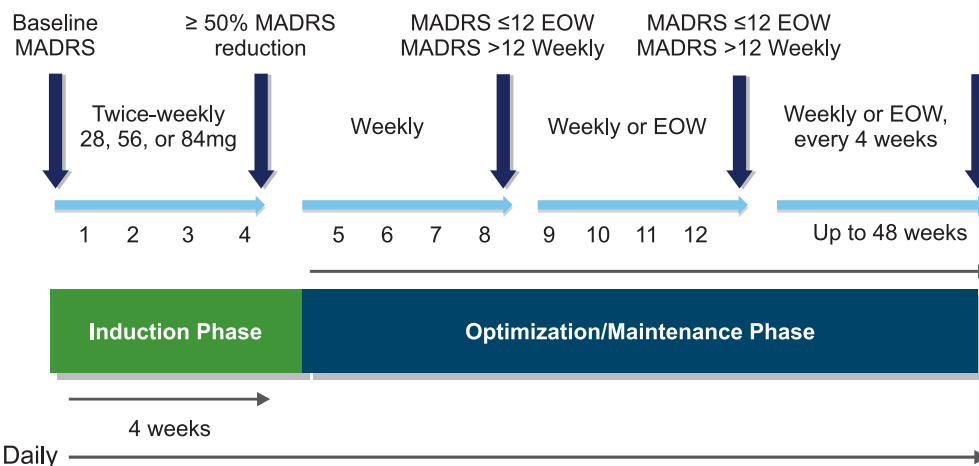


Figure 1. Study design: esketamine nasal spray treatment frequency. Abbreviations: AD, antidepressant; EOW, every other week; MADRS, Montgomery-Åsberg Depression Rating Scale. Note: Downward arrow indicates potential change in treatment frequency.

**Table 1.** Patient Classification Based on Change in CGI-S and PHQ-9 Score<sup>a</sup>

Change in dose frequency	Patient classification	Change in CGI-S	Change in PHQ-9
Increase	Symptom improvement	1 or more points	3 or more points
	Remained unchanged	No change	Less than 3 points
	Worsening	1 or more points	3 or more points
Decrease	Symptom improvement	1 or more points	3 or more points
	Maintained clinical benefit	No change	Less than 3 points
	Worsening	1 or more points	3 or more points

Abbreviations: CGI-S, Clinical Global Impression–Severity (CGI-S); PHQ-9, Patient Health Questionnaire–9 Item Depression Module.

<sup>a</sup>Change in score from the day of treatment frequency change to 4 weeks after the change.

Note: Decrease in CGI-S or PHQ-9 indicates improvement.

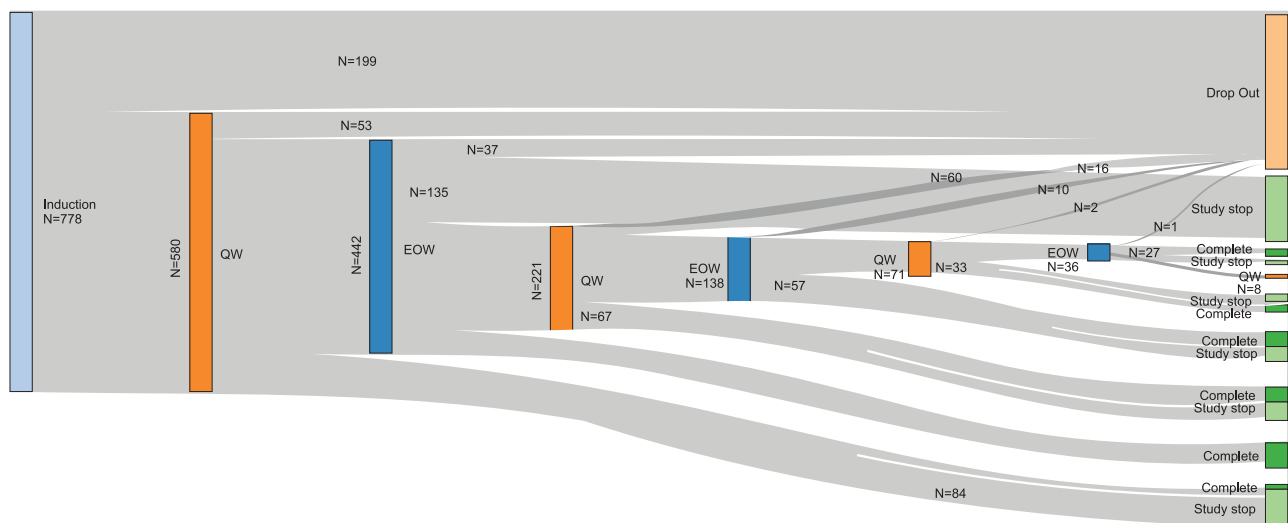
**Table 2.** Method of Pooled and Patient Cohort Analyses by Change in Esketamine Treatment Frequency

Change in dose frequency	Change	Pooled analysis <sup>a</sup>	Patient cohort analysis <sup>b</sup>
Decrease	Twice weekly to weekly	Not applicable <sup>c</sup>	Cohort after induction (week 4) for first decrease in treatment frequency
	Weekly to every other week	First, second, and third decreases to every-other-week treatment sessions combined	Separate cohorts for first decrease and second decrease to every-other-week treatment sessions
Increase	Every other week to weekly	First, second, and third increases to weekly treatment sessions combined	Separate cohorts for second and third increases to weekly treatment sessions

<sup>a</sup>Based on the number of frequency changes.

<sup>b</sup>Based on number of patients.

<sup>c</sup>Not applicable as the treatment algorithm included only 1 time point when treatment frequency decreased from twice weekly to weekly.



**Figure 2.** Patient flow based on frequency of treatment with esketamine nasal spray. The bars represent the number of patients: treatment frequency, light blue bar, twice weekly; orange bars, once weekly (QW); blue bars, every other week (EOW); dark green, study completers; light green, patients who had discontinued by study end. During the 4-week induction period, study drug was administered twice weekly.

responders (defined as  $\geq 50\%$  reduction in MADRS total score) at the end of the induction phase and proceeded to weekly dosing in the optimization/maintenance phase. Subsequently, 53 patients discontinued treatment, 84 patients remained on a weekly treatment regimen until the study end/completion, and 442 patients had their esketamine treatment frequency decreased to every other week. The proportion of patients on every-other-week dosing increased over time, with 50.8%, 58%, and 64% of patients dosed every other week at weeks 8, 24, and 44, respectively (Table 3). A total of 149 patients completed 1 year

of treatment with esketamine. Of note, the study was completed after predefined exposure criteria were met. Response and remission rates at study endpoint were 76.2% and 57.9%, respectively.

The mean age at induction baseline was 50.7 years, 63.4% patients were women, and 85.7% were Caucasian (Table 4). Patients in the 3 treatment frequency groups (i.e., weekly, every other week, and alternating between weekly and every other week) were generally similar with respect to baseline characteristics and psychiatric history, with the following noteworthy

**Table 3.** Shift of Treatment Frequency of Esketamine Nasal Spray from Week 4 to Week 8, Week 24, and Week 44 of the Optimization/Maintenance Phase

	Regimen at week 4		
	Every other week	Weekly	Total
<b>Regimen at week 8</b>			
Every other week,	189 (35.9%)	78 (14.8%)	267 (50.8%)
Weekly, and	61 (11.6%)	198 (37.6%)	259 (49.2%)
Total	250 (47.5%)	276 (52.5%)	526 (100.0%)
<b>Regimen at week 24</b>			
Every other week,	138 (39.4%)	65 (18.6%)	203 (58.0%)
Weekly, and	41 (11.7%)	106 (30.3%)	147 (42.0%)
Total	179 (51.1%)	171 (48.9%)	350 (100.0%)
<b>Regimen at week 44</b>			
Every other week,	71 (41.3%)	39 (22.7%)	110 (64.0%)
Weekly, and	17 (9.9%)	45 (26.2%)	62 (36.0%)
Total	88 (51.2%)	84 (48.8%)	172 (100.0%)

Note: Data presented as the number and percentage of patients within each week.

observations. History of suicidal ideation in the past 6 months was more common among patients in the alternating treatment frequency group compared with the high-treatment frequency (treated weekly) and low-treatment frequency (one change to every other week) groups. Baseline CGI-S score, PHQ-9 total score, and MADRS total score were similar across the esketamine treatment frequency groups.

There was no formal definition of adherence used during the treatment phase; however, overall compliance appeared to be good, with only 3 patients discontinuing the study because of missing consecutive dosing sessions.

In the treatment frequency pooled analysis, a total of 1332 changes in CGI-S score 4 weeks after change in esketamine treatment frequency were summarized (from 580 patients with a maximum of 5 switches reported [3 to weekly and 2 to every other week]): twice weekly to weekly, 547 CGI-S changes; weekly to every other week, 547 CGI-S changes; and every other week to weekly, 262 CGI-S changes.

After the induction phase, treatment frequency was decreased from twice weekly to weekly for 4 weeks, per protocol, and based on the CGI-S, 26% of patients continued to improve, 50% maintained clinical benefit, and 24% worsened at the end of the first 4 weeks of the optimization/maintenance phase (Figure 3a). Of all subsequent treatment frequency reductions observed from weekly to every other week, 19% resulted in further improvement, 49% in maintained clinical benefit, and 32% in symptom worsening (Figure 3b). When treatment frequency increase was required (driven by the algorithm based on worsening depressive symptoms) from every other week to weekly, 47% of patients improved, 43% remained unchanged, and 10% worsened (Figure 3c).

In the more granular analysis of outcome by timing of change in treatment frequency, the likelihood of worsening was higher after the second decrease (40%,  $n=121$ ) compared with the first decrease (29%,  $n=402$ ) from weekly to every-other-week treatment (Figure 3b). After an increase from every-other-week to weekly treatment, approximately one-half of both second and third switches resulted in improvement (Figure 3c).

The relationship between the algorithm-assigned treatment frequency of esketamine and change in PHQ-9 score was evaluated. Clinically meaningful changes (of 3 points) in PHQ-9 were evaluated 4 weeks after treatment frequency adjustment. After the induction phase, 21% of patients continued to improve, 55% maintained clinical benefit, and 23% worsened at the end of the

first 4 weeks of the optimization/maintenance phase based on PHQ-9 (Figure 4a). Of all subsequent treatment frequency reductions observed from weekly ( $\geq 4$  weeks later) to every other week, 14% resulted in further improvement, 61% in maintained clinical benefit, and 25% in symptom worsening (Figure 4b). When treatment frequency increase was necessary from every other week to weekly, 21% of patients improved, 55% remained unchanged, and 23% worsened (Figure 4c).

## Discussion

Esketamine nasal spray, in conjunction with an oral antidepressant, represents a new treatment paradigm for TRD. As esketamine is a pulsatile treatment, in real-world clinical practice clinicians can adjust both dose and treatment frequency rather than only the dose. According to the study protocol used in the phase 3 TRD program, treatment frequency was determined with a MADRS-based algorithm, not clinical judgment. In the current analysis, a strong correlation was found between the MADRS total score, CGI-S, and PHQ-9, indicating use of CGI-S and/or PHQ-9 may be considered as alternative measures for the purpose of judging treatment success and making treatment frequency decisions.

This analysis provides guidance to physicians on the average response rates achieved using individualized esketamine treatment frequency in the optimization/maintenance phase of treatment, potentially contributing to improved treatment outcomes in real-world practice. Patients evaluated for treatment frequency changes every 4 weeks had a high probability of improvement or maintaining benefit based on CGI-S. Symptom-based lowering of esketamine treatment frequency to weekly after induction was successful in 76% of patients. Towards the end of the optimization/maintenance phase, a higher proportion of patients remained in remission and were switched to every-other-week treatment compared with week 8 of the study; overall, 69% of regimen changes to every other week resulted in improvement/maintained clinical benefit. For patients who needed a temporary increase in treatment frequency, 47% of regimen changes back to weekly resulted in improvement.

The generalizability of our findings to clinical practice is limited by the fact that the treatment algorithm used in the study protocol dictated treatment frequency, with adjustments made no more often than every 4 weeks, and with a maximum of 3 changes from weekly to every-other-week treatment permitted during the optimization/maintenance phase. In addition, dose

**Table 4.** Baseline Characteristics and Psychiatric History by Treatment Frequency of Esketamine Nasal Spray in SUSTAIN-2

	Weekly n = 138	Switched once from weekly to every other week n = 221	Alternating between weekly and every other week n = 221	All patients n = 580 <sup>a</sup>
Age, mean (SD), y	51.6 (13.56)	51.2 (12.44)	49.7 (14.03)	50.7 (13.33)
Sex, n (% of all patients)				
Male	57 (41.3%)	76 (34.4%)	79 (35.7%)	212 (36.6%)
Female	81 (58.7%)	145 (65.6%)	142 (64.3%)	368 (63.4%)
Race, n (% of all patients)				
White	117 (84.8%)	195 (88.2%)	185 (83.7%)	497 (85.7%)
Asian	16 (11.6%)	20 (9.1%)	19 (8.6%)	55 (9.5%)
Black or African American	2 (1.4%)	3 (1.4%)	8 (3.6%)	13 (2.2%)
Other	0 (0.0%)	1 (0.5%)	6 (2.7%)	7 (1.2%)
Multiple	3 (2.2%)	1 (0.5%)	2 (0.9%)	6 (1.0%)
Not reported	0 (0.0%)	1 (0.5%)	1 (0.5%)	2 (0.3%)
Ethnicity, n (% of all patients)				
Hispanic or Latino	26 (18.8%)	68 (30.8%)	36 (16.3%)	130 (22.4%)
Not Hispanic or Latino	111 (80.4%)	151 (68.3%)	183 (82.8%)	445 (76.7%)
Not reported/unknown	1 (0.7%)	2 (0.9%)	2 (0.9%)	5 (0.9%)
Baseline BMI, mean (SD), kg/m <sup>2</sup>	28.4 (5.72)	27.7 (5.46)	28.2 (6.20)	28.0 (5.81)
Region, n (% of all patients)				
Europe	43 (31.2%)	88 (39.8%)	79 (35.7%)	210 (36.2%)
North America	25 (18.1%)	23 (10.4%)	47 (21.3%)	95 (16.4%)
Other	70 (50.7%)	110 (49.8%)	95 (43.0%)	275 (47.4%)
Oral antidepressant, n (% of all patients)				
Duloxetine	47 (34.1%)	72 (32.6%)	69 (31.2%)	188 (32.4%)
Escitalopram	37 (26.8%)	71 (32.1%)	61 (27.6%)	169 (29.1%)
Sertraline	24 (17.4%)	32 (14.5%)	40 (18.1%)	96 (16.6%)
Venlafaxine XR	30 (21.7%)	46 (20.8%)	51 (23.1%)	127 (21.9%)
Baseline CGI-S score, mean (SD)	4.9 (0.71)	4.7 (0.78)	4.8 (0.78)	4.8 (0.77)
Baseline MADRS total score, mean (SD)	31.9 (5.15)	30.3 (4.80)	31.1 (5.12)	31.0 (5.04)
Baseline PHQ-9 total score, mean (SD)	18.5 (4.89)	16.6 (4.74)	17.2 (5.11)	17.3 (4.96)
Age at MDD diagnosis, mean (SD), y	35.8 (14.24)	34.9 (12.64)	33.7 (12.33)	34.7 (12.93)
History of suicidal ideation <sup>b</sup> (based on C-SSRS) in the past 6 months, n (%)	33 (23.9)	41 (18.6)	71 (32.1)	145 (25.0)
Duration of current episode, wk				
Mean, median	175.9, 60	147.7, 52	153.1, 78	156.6, 63.5
Minimum–maximum	6–1872	6–2184	10–1196	6–2184
Previous MDD episodes, including current episodes, n (% of all patients)				
1	18 (13.0%)	26 (11.8%)	32 (14.5%)	76 (13.1%)
2–5	87 (63.0%)	161 (72.9%)	140 (63.3%)	388 (66.9%)
6–10	23 (16.7%)	27 (12.2%)	42 (19.0%)	92 (15.9%)
>10	10 (7.2%)	7 (3.2%)	7 (3.2%)	24 (4.1%)
Family history of bipolar disorder, n (% of all patients)				
Yes	2 (1.4%)	7 (3.2%)	6 (2.7%)	15 (2.6%)
No	136 (98.6%)	214 (96.8%)	215 (97.3%)	565 (97.4%)

Abbreviations: BMI, body mass index; CGI-S, Clinical Global Impression–Severity; C-SSRS, Columbia Suicide Severity Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, major depression disorder; PHQ-9, Patient Health Questionnaire 9-item.

<sup>a</sup>23 responders from TRANSFORM-3 were excluded from the analysis.

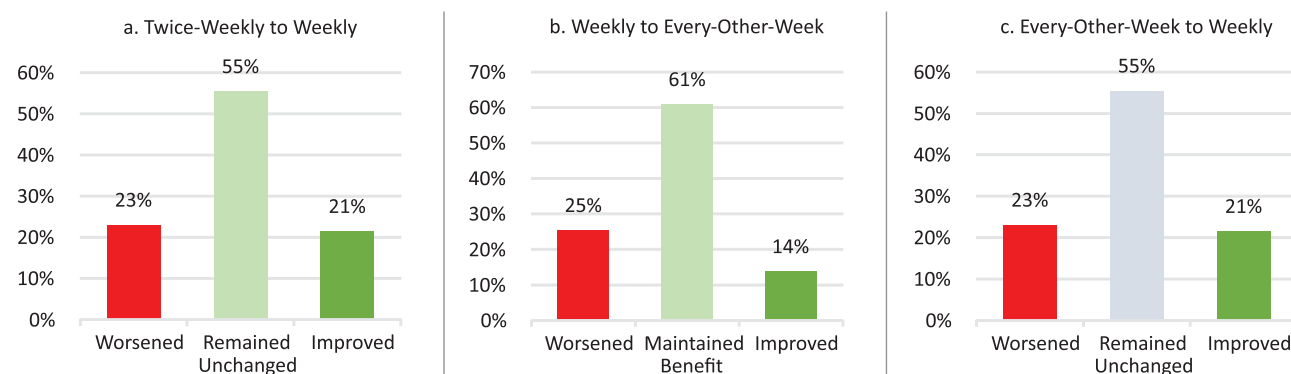
<sup>b</sup>Active suicidal ideation or behavior was an exclusion criterion for entry into the study.

changes (28 mg, 56 mg, or 84 mg) were not allowed during the optimization/maintenance phase. These constraints are not present in clinical practice. In real-world practice, if clinicians observe worsening of depressive symptoms, treatment frequency of esketamine would likely be adjusted prior to the 4 weeks used in this study setting. Furthermore, the MADRS total score cutoff determining adjustment in frequency from weekly to every other week, and vice versa, was prespecified as part of a study-defined algorithm. The impact of a lower cut-off on the MADRS total score cannot be determined retrospectively. Due to sample size limitations, no formal analyses of treatment frequency change by country were conducted. However, a post-hoc analysis of data

from the open-label induction phase of the main study, looking at change from baseline on the MADRS total score to the end of the 4-week phase, suggests that there was no significant difference in efficacy based on region. Similarly, no formal analyses of treatment frequency change by concomitant oral antidepressant were conducted. However, the proportion of patients on each oral antidepressant is consistent (Table 4) regardless of the treatment frequency required to maintain wellness on weekly dosing, switching once to every other week, and alternating between weekly and every other week. Additionally, no patients discontinued in the optimization/maintenance phase due solely to adverse events related to the oral antidepressant.



**Figure 3.** Change in Clinical Global Impression–Severity (CGI-S) score 4 weeks after change in treatment frequency (pooled and by switch analysis). (a) Change in CGI-S after reducing the treatment frequency to 4 weeks of weekly treatment. (b) Change in CGI-S after reducing the treatment frequency to 4 weeks of every-other-week (EOW) treatment (pooled analysis). (c) Change in CGI-S after increasing the treatment frequency to 4 weeks of weekly treatment (pooled analysis). Note: Denominator for the pooled analysis is the number of times patients changed treatment frequency.



**Figure 4.** Change in Patient Health Questionnaire–9 Item Depression Module (PHQ-9) score 4 weeks after change in treatment frequency (pooled analysis). (a) Change in PHQ-9 after reducing the treatment frequency to 4 weeks of weekly treatment. (b) Change in PHQ-9 after reducing the treatment frequency to 4 weeks of every-other-week (EOW) treatment. (c) Change in PHQ-9 after increasing the treatment frequency to 4 weeks of weekly treatment. Note: Denominator is the number of times patients changed treatment frequency.

The findings from SUSTAIN-2 support the benefits of continued individualization of esketamine nasal spray treatment frequency to optimize treatment response in real world clinical practice. Adjusting (increasing or decreasing) esketamine treatment frequency as a treatment strategy for individual patients with TRD is associated with a high likelihood of positive outcomes (i.e., decrease or maintaining of CGI-S score). Patients who worsen on every-other-week treatment of esketamine nasal spray may derive treatment benefits from switching to weekly treatment.

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## Contributors

Ibrahim Turkoz conducted the statistical analyses. All authors were involved in interpretation of the results and review of the manuscript. All authors meet ICMJE criteria and all those who fulfilled those criteria are listed as authors.

## Statement of Interest

Michel Nijs, Ewa Wajs, Leah Aluisio, Ibrahim Turkoz, Ella Daly, Adam Janik, Stephane Borentain, Allitia DiBernardo, and Frank Wiegand are employees of Janssen Research & Development, LLC and hold company equity. Jaskaran B. Singh was an employee of Janssen Research & Development at the time the SUSTAIN 2 study was conducted and this manuscript was written, and holds company equity. Dr. Singh is currently employed by Neurocrine Biosciences, San Diego, CA.

## Role of the Sponsor

Employees of the sponsor, as noted in author contributions, were involved in trial design; patient recruitment; data collection, analysis, or interpretation; and/or other aspects pertinent to the study. Authors had full access to all of the data in the study, were involved in writing and/or revising the manuscript, and had final responsibility for the decision to submit for publication.

## Previous Presentations

Data from this study were presented in poster sessions at the 2019 Annual Meeting of the American Psychiatric Association, San Francisco, CA, May 21, 2019; 2019 Annual Meeting of the American Society of Clinical Psychopharmacology (ASCP), Scottsdale, AZ, May 29, 2019; 2019 American Association of Nurse Practitioners (AANP) National Conference, Indianapolis, IN, June 20–22, 2019; and the 32nd ECNP Congress, Copenhagen, Denmark, September 8, 2019.

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