Longitudinal Course of Adverse Events With Esketamine Nasal Spray: A Post Hoc Analysis of Pooled Data From Phase 3 Trials in Patients With Treatment-Resistant Depression

David J. Williamson, PhD[a,h,*]; Jagadish P. Gogate, PhD[b]; Jennifer K. Kern Sliwa, PharmD[c]; Lewis S. Manera, MS[d,h]; Sheldon H. Preskorn, MD[e]; Andrew Winokur, PhD, MD[f]; H. Lynn Starr, MD[g]; and Ella J. Daly, MD[a,h]

ABSTRACT

Objective: To describe the tolerability of esketamine nasal spray based on the adverse event profile observed during treatment sessions occurring early and later over the course of treatment.

Methods: In 2 long-term, phase 3 studies (NCT02493868, October 1, 2015–February 16, 2018; NCT02497287, September 30, 2015–October 28, 2017), patients with treatment-resistant major depressive disorder (per *DSM-5*) and nonresponse to ≥ 2 oral antidepressants received esketamine nasal spray (56 or 84 mg) twice weekly during a 4-week induction phase, weekly for weeks 5–8, and weekly or every 2 weeks thereafter as maintenance treatment, in conjunction with a new oral antidepressant. A post hoc analysis using descriptive statistics evaluated occurrence (incidence, frequency, severity) and recurrence (incidence and severity) of events of specific interest.

Results: In patients treated with esketamine nasal spray plus a newly initiated oral antidepressant (n = 928), spontaneously reported adverse events of dizziness, nausea, sedation, vertigo, and increased blood pressure were more likely to recur after the first week of treatment if they occurred more frequently (twice > once > none) during the first week. The same pattern was observed when these events were assessed by structured instruments. Incidences of dizziness, dissociation, increased blood pressure, nausea, vertigo, and sedation were highest in week 1 of treatment (20.6%, 16.7%, 4.3%, 14.0%, 12.1%, and 3.8%, respectively) and decreased thereafter. Initial occurrences and subsequent recurrences of events were mostly mild or moderate in severity.

Conclusions: Adverse events during treatment with esketamine nasal spray plus an oral antidepressant generally become less frequent with ongoing treatment, and the majority are mild or moderate in severity.

Trial Registration: ClinicalTrials.gov identifiers: NCT02493868; NCT02497287

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[a]Field-Based Medical Affairs, Janssen Scientific Affairs, LLC, Titusville, New Jersey

[b]Statistics and Decision Sciences, Janssen Research & Development, LLC, Titusville, New Jersey

[c]Neuroscience Medical Information, Janssen Scientific Affairs, LLC, Titusville, New Jersey

[d]Janssen Medical Information, Janssen Scientific Affairs, LLC, Titusville, New Jersey

[e]Department of Psychiatry and Behavioral Sciences, University of Kansas School of Medicine, Wichita, Kansas

[f]Department of Psychiatry, UConn Health, Farmington, Connecticut

[g]Clinical Development, Janssen Scientific Affairs, LLC, Titusville, New Jersey

[h]Drs Williamson and Daly and Mr Manera were affiliated with Janssen Scientific Affairs, LLC, at the time the trial was conducted.

**Corresponding author:* David J. Williamson, PhD, University of South Alabama College of Medicine, 2450 Old Shell Rd, Ste A, Mobile, AL 36607 (dr.williamson@comcast.net).

Medication management for an individual patient is optimized by balancing the potential for benefit versus harm. Patients are not equally susceptible to every adverse event (AE) listed in a product's prescribing information; rates provided therein generally do not provide information about how the rate and severity of specific AEs change over time with repeated dosing.

Esketamine nasal spray (ESK) is a noncompetitive *N*-methyl-D-aspartate receptor antagonist approved, in conjunction with an oral antidepressant (OAD), for the treatment of adults with treatment-resistant major depressive disorder (TRD) or major depressive disorder with acute suicidal ideation or behavior.[1–8] The US Food and Drug Administration (FDA) requires a Risk Evaluation and Mitigation Strategy (REMS) for ESK to ensure its benefits outweigh the risks of misuse, abuse, and serious adverse outcomes from sedation and dissociation, which includes a requirement of post-administration monitoring for ≥ 2 hours.[9] Two notable characteristics of the ESK treatment paradigm are discrete treatment sessions lasting ≥ 2 hours and treatment-associated AEs that are transient and generally resolve within 90 minutes.[6,10–13] A pooled analysis of patients who participated in the TRANSFORM-1 (NCT02417064) and TRANSFORM-2 (NCT02418585) studies, two 4-week, phase 3, double-blind, placebo-controlled, multicenter studies of ESK in patients with treatment-resistant depression, found that across treatment sessions, ≥ 90% of patients were considered ready for discharge at 90 minutes after administration, with an additional 2%–7% ready at 2 hours.[11] The ≥ 2-hour ESK treatment sessions and transient AEs associated with ESK treatment provide a valuable opportunity to determine how a patient's early experience of AEs may impact the likelihood of recurrence with subsequent administrations. In addition to assessing the patterns of AE occurrence over time

Clinical Points

- The 5 most common adverse events (AEs; dissociation, dizziness, nausea, sedation, vertigo) associated with esketamine nasal spray plus an oral antidepressant in patients with treatment-resistant major depressive disorder are more likely to recur after week 1 if they occurred more frequently during the first week of treatment.
- Most patients did not report AEs in week 1 and were stratified into the groups with the lowest recurrence risk.
- Recurrence of AEs after week 4 (the end of the induction period) was more closely related to the frequency of the same AEs during week 4 than during week 1.
- The reported severity of dissociation, dizziness, nausea, sedation, vertigo, and increased blood pressure was mostly mild and rarely severe, in terms of both initial incidence and recurrence.

following repeated administrations of ESK, we investigated the following questions:

- Does the frequency of AEs observed during the initial weeks of treatment (induction) provide any indication of the rates of AEs observed later in treatment?
- Does the severity of AEs reported during the initial weeks of treatment provide any indication of the reported severity of AE recurrences, should they occur?
- Do the incidence and severity of AEs occurring during the last week of induction treatment (week 4) provide a better indication of recurrence and/or severity with longer-term treatment than those observed during week 1?
- To the extent that later AE frequency or severity differ according to what is observed early in treatment, does ESK dose or medications given to prevent or attenuate these AEs appear to affect an observed pattern?

METHODS

Patients

Data were pooled from adults (aged 18–64 years) with TRD enrolled in the SUSTAIN-1[1] (NCT02493868, October 1, 2015–February 16, 2018) and SUSTAIN-2[7] (NCT02497287, September 30, 2015–October 28, 2017) studies. Patients had recurrent or single-episode (≥ 2 years) major depressive disorder (*Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition) and met study-defined criteria for TRD. In the relapse prevention study, SUSTAIN-1, at screening, depressive symptoms had been nonresponsive to adequate trials of ≥ 1 and ≤ 5 OADs in the current depressive episode.[1] Nonresponse to a different, ongoing OAD was confirmed at the end of the 4-week screening prospective observational phase (defined as ≤ 25% improvement in Montgomery-Asberg Depression Rating Scale [MADRS] total score from week 1 to week 4 and a MADRS total score of ≥ 28 on week 2 and week 4).[1] In contrast, in the open-label safety study, SUSTAIN-2, patients must have had ≥ 2 prior OAD failures in the current episode (determined retrospectively) and a MADRS total score of ≥ 22.[7]

Study Designs

The SUSTAIN studies, and the 2 short-term trials (TRANSFORM-1 and -2 in adults aged < 65 years) from which patients transferred into SUSTAIN-1, have been previously reported[1,2,6,7] and were conducted in accordance with the Declaration of Helsinki, Good Clinical Practices, and applicable regulatory requirements. Protocols were approved by relevant institutional review boards and independent ethics committees. All patients provided written informed consent.[1,2,6,7]

SUSTAIN-1 was a double-blind, placebo-controlled, relapse-prevention trial that compared the efficacy of ESK versus placebo (PBO) nasal spray, both in conjunction with an OAD, in delaying relapse of depressive symptoms in patients with TRD who were in stable remission or stable response after 4 months of treatment with ESK plus OAD.[1] SUSTAIN-2 was an open-label multicenter study that assessed the long-term safety and efficacy of ESK plus OAD in patients with TRD.[7]

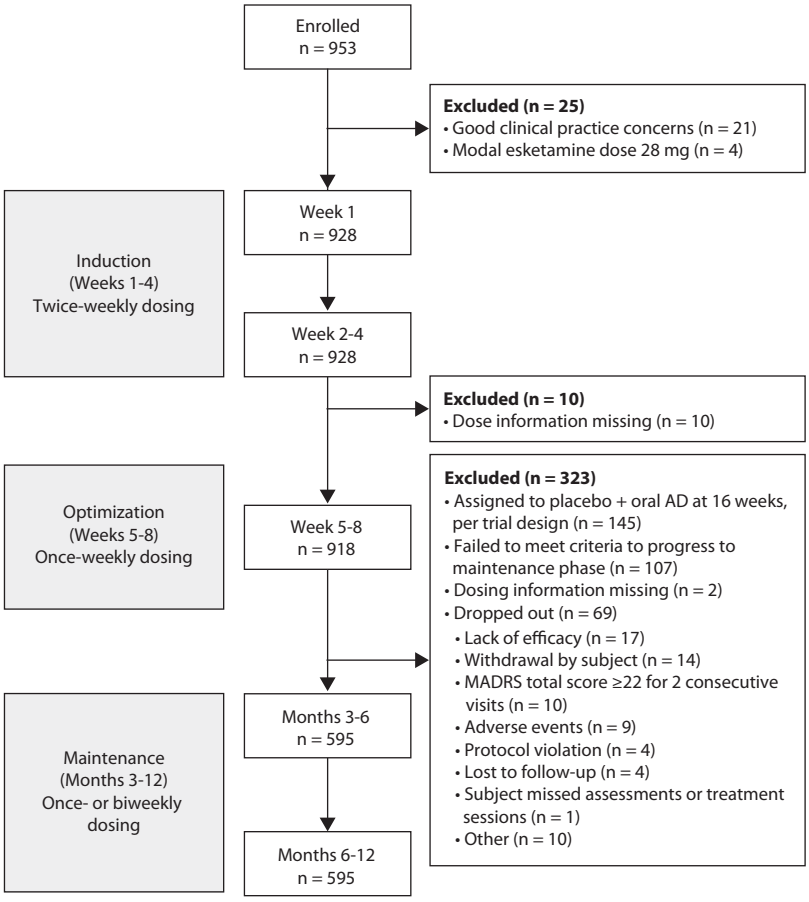
The present analysis was limited to the 2 doses of ESK (56 and 84 mg) approved for use by the FDA in patients with TRD. Patients received ESK (56 or 84 mg) or PBO nasal spray (SUSTAIN-1 only), in conjunction with a newly initiated OAD. In SUSTAIN-1, after week 16 as part of the randomized withdrawal design, a subset of patients previously assigned to ESK were switched to PBO nasal spray and thus excluded from the current analysis after this time. Nasal spray treatment occurred twice weekly during the induction phase (weeks 1–4), once weekly during weeks 5–8, and thereafter once weekly or every other week in the optimization/maintenance phase, with dosing frequency individualized according to the severity of depressive symptoms (MADRS total score ≤ vs > 12) and tolerability.[1,7] It was recommended that, on dosing days, patients take their OADs ≥ 3 hours after the ESK or PBO treatment session.

Safety Assessments

Patients were monitored for ≥ 90 minutes after ESK administration; afterward, they could leave the site if deemed clinically stable by the clinician. AEs were monitored and reported; safety assessments were conducted throughout the study. Clinician-reported AEs were categorized as mild, moderate, or severe per clinical judgment (Supplementary Table 1).

Vital signs, the Clinician-Administered Dissociative States Scale (CADSS), and the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) were assessed at baseline and at all treatment sessions (predose, 40 minutes, 1 hour [vital signs only], and 1.5 hours after dose). Abnormal CADSS and MOAA/S scores could be reported as AEs based on clinician judgment. Blood pressure (BP) readings were conducted at each treatment session, with elevations

Figure 1. Patients Included in the Analysis



Abbreviations: AD = antidepressant, MADRS = Montgomery-Asberg Depression Rating Scale.

reported as AEs if clinically significant based on clinician judgment. The CADSS consists of 23 questions, each coded on a 5-point scale (0, not at all; 4, extreme), yielding a total score of 0–92.[14,15] A CADSS total score of >4 was used to indicate the presence of dissociative symptoms.[15] Although the extent to which this score represents a clear marker for dissociation is debated,[16] this cutoff has precedence in the literature and was determined as acceptable for use in the package labeling by FDA.[8] Scores on the MOAA/S range from 0 (no response to painful stimulus) to 5 (readily responds to name spoken in normal tone).[17] Any decrease in MOAA/S from predose (score < 5) indicated some degree of sedation. Additionally, acute hypertension was defined per protocol as systolic BP of ≥ 180 mm Hg and ≥ 20 mm Hg higher than baseline and/or diastolic BP of ≥ 105 mm Hg and ≥ 15 mm Hg higher than baseline. This analysis included any treatment sessions in which patients received ESK. We first looked for any discernable patterns in the occurrence of AEs over time following repeated administrations of ESK, stratified according to whether the respective AEs occurred once, twice, or not at all during the index week. Weeks 1 and 4 were set a priori as index weeks because they represent the beginning and end of the induction period, and previous reports have documented that the frequency and/or severity of at least some of the AEs decline over the first 4 weeks of treatment.[7] We also examined whether the maximum reported AE severities during the index week provided an indication of the severities of AE recurrences.

Recurrence and severity of AEs were assessed from week 2–4, month 2 (weeks 5–8), months 3–6, and months 6–12. Study investigators rated AE severity as 0 (no AE), 1 (mild), 2 (moderate), or 3 (severe) based on the clinician's judgment. To examine AEs in individual patients over time, only patients who received ≥ 1 ESK dose in the subsequent period were included in the analyses of each respective period.

The 5 most commonly reported treatment-emergent AEs occurring with ESK plus OAD (dissociation, dizziness, nausea, sedation, and vertigo) were evaluated, each having an incidence of ≥ 5% and at least a 2-fold greater incidence compared with PBO nasal spray plus an OAD.[8] Observed increases in BP were also examined at each dosing session.

Patients who received medication to treat an emergent AE or prevent re-emergence of an AE were identified; however, given the low numbers, additional analysis to assess potential impact was not possible. Patients identified as having adequately controlled hypertension before initiation of treatment were instructed to take their hypertension medication before nasal spray dosing. Incidence of BP-related

Table 1. Rates of Adverse Event Recurrence With Esketamine Nasal Spray According to Frequency of Adverse Events in Week 1, % (n/N)[a]

	Overall rate for timeframe	No AE in week 1	AE once in week 1[b]	AE twice in week 1[b]	Overall rate for timeframe	No AE in week 1	AE once in week 1[b]	AE twice in week 1[b]	Overall rate for timeframe	No AE in week 1	AE once in week 1[b]	AE twice in week 1[b]
	Clinician-reported dissociation				CADSS-defined dissociation[c]				Dizziness			
Week 1	16.7 (159/949)				55.3 (525/949)				20.6 (196/949)			
Weeks 2–4	15.7 (149/949)	5.6 (44/790)	48.2 (41/85)	86.5 (64/74)	52.0 (493/949)	23.6 (100/424)	59.1 (146/247)	88.8 (247/278)	18.8 (178/946)	6.1 (46/753)	51.9 (56/108)	86.4 (76/88)
Weeks 5–8	12.6 (116/918)	6.1 (46/759)	29.8 (25/84)	60.0 (45/75)	34.9 (320/918)	15.6 (62/398)	32.5 (79/243)	64.6 (179/277)	12.5 (115/918)	3.7 (27/723)	30.8 (33/107)	62.5 (55/88)
Months 3–6	14.5 (86/595)	7.6 (36/476)	26.2 (17/65)	61.1 (33/54)	38.7 (230/595)	19.4 (49/252)	42.7 (67/157)	61.3 (114/186)	15.6 (93/595)	7.5 (34/452)	31.2 (24/77)	53.0 (35/66)
Months 6–12	8.7 (52/595)	4.6 (22/476)	18.5 (12/65)	33.3 (18/54)	25.9 (154/595)	15.9 (40/252)	26.8 (42/157)	38.7 (72/186)	8.1 (48/595)	4.0 (18/452)	20.8 (16/77)	21.2 (14/66)
	Clinician-reported sedation				MOAA/S-defined sedation[d]				Nausea			
Week 1	3.8 (36/949)				37.3 (354/949)				14.0 (133/949)			
Weeks 2–4	4.0 (38/949)	2.1 (19/913)	36.8 (7/19)	70.6 (12/17)	43.2 (410/949)	21.2 (126/595)	65.7 (119/181)	95.4 (165/173)	9.2 (87/949)	5.1 (42/816)	28.6 (32/112)	61.9 (13/21)
Weeks 5–8	2.6 (24/918)	1.2 (11/883)	22.2 (4/18)	52.9 (9/17)	33.1 (304/918)	15.8 (90/570)	42.0 (74/176)	81.4 (140/172)	4.0 (37/918)	1.7 (13/786)	16.1 (18/112)	30.0 (6/20)
Months 3–6	3.5 (21/595)	3.0 (17/575)	0 (0/9)	36.4 (4/11)	37.5 (223/595)	23.8 (90/378)	47.7 (51/107)	74.5 (82/110)	7.2 (43/595)	4.5 (23/506)	20.8 (16/77)	33.3 (4/12)
Months 6–12	2.5 (15/595)	1.7 (10/575)	0 (0/9)	45.5 (5/11)	28.4 (169/595)	18.8 (71/378)	38.3 (41/107)	51.8 (57/110)	6.7 (40/595)	4.9 (25/506)	18.2 (14/77)	8.3 (1/12)
	Clinician-reported increased blood pressure				Measure-based increased blood pressure				Vertigo			
Week 1	4.3 (41/949)				5.6 (53/949)				12.1 (115/949)			
Weeks 2–4	5.1 (48/949)	2.3 (21/908)	56.5 (13/23)	77.8 (14/18)	10.4 (99/949)	8.0 (72/896)	48.9 (23/47)	66.7 (4/6)	14.6 (139/949)	5.4 (45/834)	67.4 (29/43)	90.3 (65/72)
Weeks 5–8	3.9 (36/918)	1.9 (17/878)	40.9 (9/22)	55.6 (10/18)	9.6 (88/918)	8.3 (72/867)	26.7 (12/45)	66.7 (4/6)	9.9 (91/918)	3.0 (24/805)	45.2 (19/42)	67.6 (48/71)
Months 3–6	4.2 (25/595)	3.0 (17/574)	36.4 (4/11)	40.0 (4/10)	12.8 (76/595)	11.7 (66/565)	30.8 (8/26)	50.0 (2/4)	8.2 (49/595)	3.4 (18/532)	28.6 (6/21)	59.5 (25/42)
Months 6–12	2.2 (13/595)	1.7 (10/574)	9.1 (1/11)	20.0 (2/10)	10.2 (61/595)	9.9 (56/565)	19.2 (5/26)	0 (0/4)	5.0 (30/595)	1.7 (9/532)	23.8 (5/21)	38.1 (16/42)

[a]In each cell, n/N represents the number of patients who experienced a recurrence of the given AE/number of patients who contributed data (based on the time period described in the row title and the occurrence in week 1 described in the column title). Patient data were retained (1) in week 1 if the patient received ≥ 1 esketamine nasal spray (ESK) dose in weeks 2–4, (2) in weeks 2–4 if the patient received ≥ 1 ESK dose in weeks 5–8, (3) in weeks 5–8 if the patient received ≥ 1 ESK dose in months 3–6, and (4) in months 3–6 if the patient received ≥ 1 ESK dose in months 6–12.
[b]Shaded cells depict ≥ 10% difference in AE recurrence rates between occurrence twice vs once per week in week 1 (dark gray) and once per week versus none in week 1 (light gray).
[c]CADSS was coded on a 5-point scale as follows: 0 = not at all, 1 = mild, 2 = moderate, 3 = severe, 4 = extreme.[10]
[d]MOAA/S uses a 6-point scale in which 0 = no response painful stimulus, 1 = responds to painful stimulus, 2 = purposeful response to mild prodding or mild shaking, 3 = response after name called loudly or repeatedly, 4 = lethargic response to name called in normal tone, and 5 = readily responds to name spoken in normal tone.[13]
Abbreviations: AE = adverse event, CADSS = Clinician-Administered Dissociative States Scale, MOAA/S = Modified Observer's Assessment of Alertness/Sedation.

AEs was examined in patients with a history of hypertension according to whether they were taking medication to manage their hypertension.

RESULTS

This analysis included 928 patients in weeks 1–4, 918 in weeks 5–8, and 595 in months 3–6 and 6–12 (Figure 1). The mean age of the patients was 46 years; approximately two-thirds were female (Supplementary Table 2). Discontinuations, including those due to AEs, were low during the first 4 weeks of treatment (5%–7%).[1,7]

AE Rates Observed by Frequency of AEs During Week 1

The more frequently an AE occurred during the first week of treatment, the higher was the percentage of patients who experienced recurrence in subsequent time periods (Table 1). For example, the rate of dissociation based on spontaneous AE reporting during weeks 2–4 for the overall patient population was 15.7%. However, the corresponding rate for those in whom dissociation was reported twice as an AE during week 1 was 86.5% (64/74), whereas the rates in those for whom dissociation was reported once or not at all during week 1 were 48.2% (41/85) and 5.6% (44/790), respectively (Table 1). The same pattern (recurrence rates increasing with week 1 AE frequency) was observed for each examined AE and for corresponding rates of dissociation, sedation, and elevated BP based on standardized measures (Supplementary Figure 1).

AE Rates Observed by Frequency in Week 1 vs Frequency in Week 4

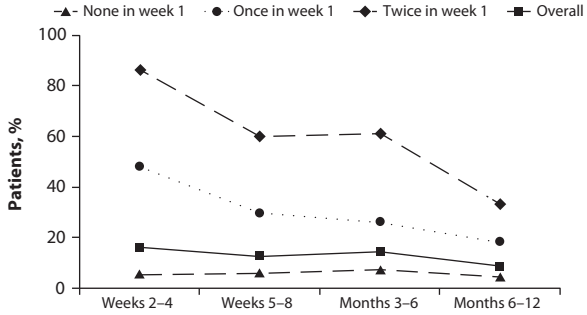
AE rates after week 4 appeared more like those observed in week 4 than those in week 1. When an AE did not occur in week 1 or week 4, there was little difference between the rates observed thereafter for clinician-reported AEs of dissociation, sedation, and increased BP (Figure 2); in these groups, there were few recurrences. Relationships for other AEs, including scale-based rates of dissociation, sedation, and acute hypertension, followed a similar pattern (Supplementary Figure 1), although the differences for acute hypertension were relatively small.

Does the Severity of an AE Experienced Early (ie, Week 1 or Week 4) Provide an Indication of AE Severity Later in Treatment?

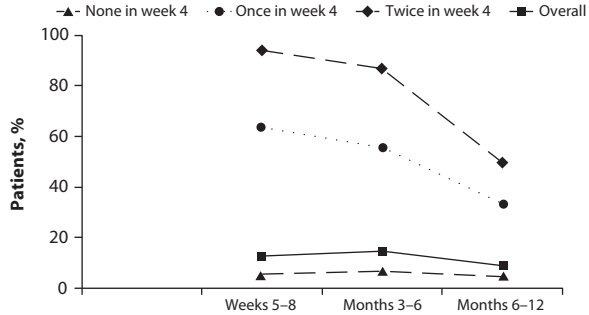
The ability to explore if AE severity in weeks 1 or 4 could be used to inform subsequent AE severity was limited by the low number of patients with moderate or severe AEs. For all

Figure 2. Percentage of Esketamine-Treated Participants With Adverse Events Based on Frequency of Week 1 and Week 4 Occurrence, for Clinician-Reported (A) Dissociation, (B) Sedation, and (C) Increased Blood Pressure

A. Clinician-reported dissociation

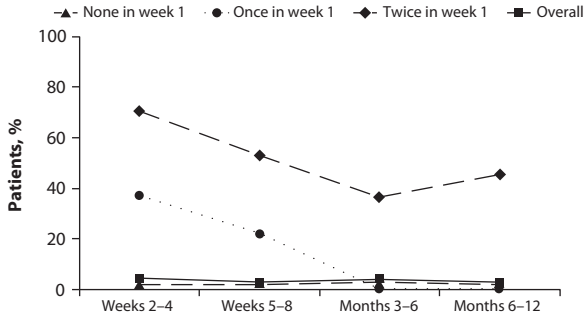


Patients (N)				
None in week 1	790	759	476	476
Once in week 1	85	84	65	65
Twice in week 1	74	75	54	54
Overall	949	918	595	595

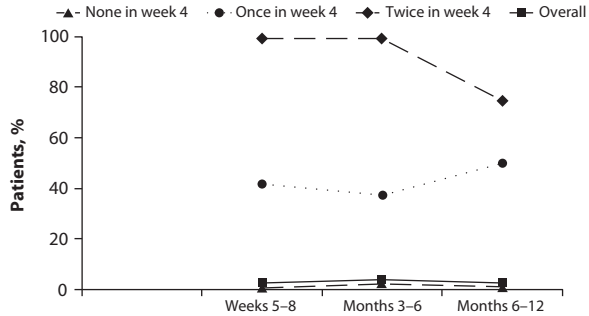


Patients (N)			
None in week 4	833	530	530
Once in week 4	33	27	27
Twice in week 4	52	38	38
Overall	918	595	595

B. Clinician-reported sedation

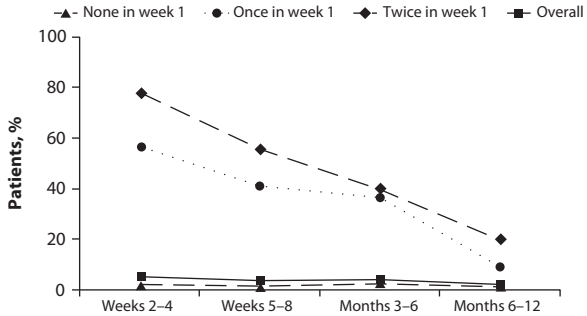


Patients (N)				
None in week 1	913	883	575	575
Once in week 1	19	18	9	9
Twice in week 1	17	17	11	11
Overall	949	918	595	595

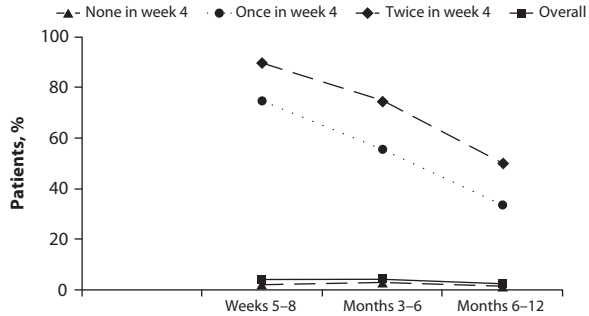


Patients (N)			
None in week 4	897	583	583
Once in week 4	12	8	8
Twice in week 4	9	4	4
Overall	918	595	595

C. Clinician-reported increased blood pressure



Patients (N)				
None in week 1	908	878	574	574
Once in week 1	23	22	11	11
Twice in week 1	18	18	10	10
Overall	949	918	595	595



Patients (N)			
None in week 4	896	582	582
Once in week 4	12	9	9
Twice in week 4	10	4	4
Overall	918	595	595

spontaneously reported AEs (except dissociation), < 5 patients for whom the respective AEs were reported as severe in weeks 1 or 4 had a recurrence reported as severe during any subsequent observation period. Likewise, for AEs other than dissociation, dizziness, vertigo, or nausea, < 10 patients for whom the AEs were reported in weeks 1 or 4 experienced recurrences of a moderately severe event.

AEs that recurred were generally mild or moderate in severity. Furthermore, the initial severity of an AE provided little indication of future severity, most likely due to minimal variance in AE severity. There were no consistent differences in the severity of respective AEs when comparing patients without a reported AE during weeks 1 or 4 versus those with mild AEs. When comparing patients whose AEs of

dissociation were characterized as moderate (score: 1) or severe (score: 2) in week 1, for those reporting a recurrence in subsequent weeks, mean AE severity scores were 1.5 and 2.1 in weeks 2–4, 1.3 and 1.8 in weeks 5–8, 1.4 and 1.2 in months 3–6, and 1.5 and 1.6 in months 6–12, respectively. In comparison, the mean AE severity score reported in patients who experienced their first reported dissociation after week 1 was 1.3.

In patients with evidence of mild-to-moderate levels of dissociation per CADSS (total score ≤ 14),[16] there were no obvious differences in the severity of subsequent spontaneously reported AEs of dissociation (mean scores: 1.2–1.4) across the different follow-up timeframes. Mean severity scores in patients with maximum CADSS total scores 15–24 and 24–42 were 1.3–2.1 across the different follow-up timeframes, and < 3 patients had a maximum CADSS score of > 42.

Finally, even when stratifying patients according to their most marked level of sedation observed during weeks 1 or 4, the average severity observed in recurrences was indicative of mild sedation (MOAA/S scores: 3.5–4.0), except for 1 patient with a mean recurrence score of 3.25, reflecting moderate sedation.

What Is the Impact of ESK Dose and Concomitant Medications on AEs?

Because flexible dosing (56 or 84 mg) was permitted in the first 2 weeks of the studies' induction phases, patients were stratified by modal dose during the respective periods. A small dose effect was most pronounced with dissociation and dizziness (Supplementary Figure 2); however, the impact of dose on AE recurrence rates was of a much smaller magnitude than the effect of week 1 AE frequency. Among patients who exhibited the most frequently observed AEs during week 1, few received prophylactic or symptomatic treatment for these AEs in later treatment sessions (Supplementary Table 3). BP-related AEs were also examined in patients with a history of hypertension and stratified according to whether the hypertension was managed with medication. As with other AEs, the number of patients for whom BP-related AEs were reported was too small to draw meaningful conclusions (Supplementary Table 4).

DISCUSSION

This post hoc analysis of adults treated with ESK plus OAD for TRD revealed that patients who experienced one of the most commonly reported AEs once or twice during the first week of treatment were more likely to experience a recurrence of the same AE compared to those who did not. Overall, recurrence rates diminished over time. If an AE occurred in week 4, its recurrence thereafter was more closely linked to its week 4 frequency than its week 1 frequency. The restricted range of observed AE severity, with most being mild or moderate, limited the ability to predict the severity of recurring AEs.

These findings suggest that the likelihood of AE recurrence may increase along with the frequency with which the AE occurs early in treatment. Nevertheless, the severity for such recurrences is likely to be mild to moderate and tends to diminish over time. Machine-learning–based algorithms using more variables may outperform this practical single-indicator clinical approach,[18] but these are typically not used in clinical practice due to complexity, lack of transparency of underlying criteria, and perceived additional effort.[19] Although it is impossible to predict whether a particular adverse event will or will not occur in a patient, our results may help inform shared decision-making between patient and clinician during treatment with ESK, within the guidelines of the REMS.[9] Because the original studies were not designed to formally evaluate potential factors impacting adverse event occurrence, it is unknown whether this occurrence is influenced by baseline patient factors, such as symptom severity, personality[20] or psychiatric factors,[21] or by the magnitude of improvement in depressive symptoms, but these relationships could be explored in future studies.

Differences between formally measured versus spontaneously reported rates of AEs of dissociation, sedation, and abnormally elevated BP are evident, with formally measured (scale-based) rates being higher than clinician-reported rates. These measurement approaches are inherently calibrated to different standards: clinicians were encouraged to report any AE they believed was clinically relevant or merited treatment, whereas the solicited formal measures assessed at each treatment session (eg, CADSS, MOAA/S, BP measurement) simply detect deviations from an accepted standard of "normal" values. Therefore, higher rates are more often revealed by the formal measures obtained by solicited reporting than by clinician report. Nevertheless, the same fundamental relationships between early and later tolerability were observed across measurement modalities.

A recent comprehensive analysis of cardiovascular safety from the phase 3 TRD program described BP elevations after administration of ESK plus OAD (in patients with no or controlled hypertension) as transient (maximum elevation within 40 minutes of ESK dosing; typically returning to predose range ≤ 1.5 hours after dosing), asymptomatic, self-limiting, not warranting rescue medications, and not associated with serious cardiovascular safety sequalae.[13] Although lower in patients who had not previously experienced the same AE, rates of objectively measured dissociation, sedation, and elevated BP never reached zero; therefore, consistent with prescribing recommendations, patients who experienced one of these AEs should be monitored after dosing to ensure sedation and dissociation are resolved before discharge, and BP must be assessed before ESK administration, at approximately 40 minutes after receiving a dose, and subsequently as clinically warranted.[8]

Regarding study limitations, this was a post hoc analysis of pooled data from 2 long-term studies with differing designs (SUSTAIN-1, double-blind; SUSTAIN-2, open-label) where the minimum required monitoring period per

protocol was 90 minutes, in contrast to the ≥ 2-hour post-administration monitoring required by the REMS. Study exclusion criteria may have skewed the sample to patients with fewer comorbidities than observed in real-world clinical settings. Analyses are limited to specific events as measured or reported by clinical trial sites during postdose monitoring. The consistency with which an AE is reported may vary over time and between sites. For instance, a clinician may consider an AE as having minimal clinical impact on a patient and thus be less likely to report it; conversely, an individual patient may find a given AE more troubling than other patients, even at mild levels, so a clinician's threshold for reporting the AE may shift reactively over time. These dynamics would impact reported recurrence rates in opposite directions and are difficult to quantify. Few patients (0.8%–5%; Supplementary Table 3) received prophylactic or symptomatic treatment for AEs during the respective timeframes, suggesting that these treatments had minimal impact on the observed patterns.

Finally, because AE *recurrence* was central to this post hoc analysis, we prospectively chose to limit our sample to patients who had ≥ 1 treatment session in the "next" timeframe to ensure we were examining patients in whom AEs had an opportunity to recur. This raises the potential for completer selection bias, whereby a systematic difference in patients who do not continue through the various stages of treatment may be missed. Given the low discontinuation rate during the first month of treatment (5%–7% by week 4), it is probable this potential bias had minimal impact on the rates of AEs observed during the first 2 months of treatment. The design of SUSTAIN-1 (whereby patients who did not meet criteria for stable response or stable remission at week 16 did not continue, and half of those remaining who were originally assigned to ESK were transitioned to placebo nasal spray in the subsequent randomized withdrawal phase) prevented a substantial number of patients from being followed after month 4 of treatment.

Overall, this post hoc analysis provides additional information for prescribers that can assist in clinician-patient discussions regarding the tolerability of ESK, setting expectations regarding AEs, and the likelihood and potential management of their recurrence. Clinicians should initiate discussions with patients about possible AEs that may occur with ESK treatment while recognizing that AEs are rarely severe and become less frequent with ongoing treatment.

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See supplementary material for this article at PSYCHIATRIST.COM.

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Supplementary Material

Article Title: Longitudinal Course of Adverse Events With Esketamine Nasal Spray: A Post Hoc Analysis of Pooled Data From Phase 3 Trials in Patients With Treatment-Resistant Depression

Authors: David J. Williamson, PhD; Jagadish P. Gogate, PhD; Jennifer K. Kern Sliwa, PharmD; Lewis S. Manera, MS; Sheldon H. Preskorn, MD; Andrew Winokur, PhD, MD; H. Lynn Starr, MD; and Ella J. Daly, MD

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List of Supplementary Material for the article

Disclaimer

This Supplementary Material has been provided by the authors as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Material

Supplementary Table 1. Classification of Clinician-Reported Adverse Events

Severity	Description
None	No adverse event reported
Mild	Awareness of symptoms that are easily tolerated, causing minimal discomfort, and not interfering with everyday activities
Moderate	Sufficient discomfort present that causes some interference with normal activity
Severe	Extreme distress, causing significant impairment of functioning or incapacitation and preventing normal everyday activities

Supplementary Table 2. Patient Demographics and Baseline Characteristics

	Patients included in weeks 1–4 n = 928	**Patients included in month 3–12 n = 595**
Mean age, years (SD)	46.3 (11.1)	46.4 (11.2)
Males, n (%)	328 (35.3)	215 (36.1)
Race, n (%)		
White	807 (87.0)	509 (85.5)
Black or African American	31 (3.3)	18 (3.0)
Asian	53 (5.7)	47 (7.9)
Other/unknown	36 (3.9)	21 (3.5)
Ethnicity		
Hispanic	175 (18.9)	125 (21.0)
Non-Hispanic	740 (79.7)	462 (77.6)
Other/unknown	13 (1.4)	8 (1.3)
Mean body mass index, kg/m^2, (SD)	28.3 (6.0)	28.2 (6.0)
History of hypertension, n (%)	194 (20.9)	124 (20.8)

Abbreviation: SD = standard deviation.

Supplementary Table 3. Patients Receiving Concomitant Medications for Clinician-Reported Adverse Events

Patients, n/N (%)[a]	Dizziness	Dissociation	Sedation	Vertigo	Nausea	Increased Blood Pressure
Weeks 2–4						
Prophylactic	0	2/159 (1.3)	0	0	0	1/41 (2.4)
Symptomatic	2/196 (1)	0	0	0	4/133 (3.0)	2/41 (4.9)
Weeks 5–8						
Prophylactic	0	2/159 (1.3)	0	0	0	1/40 (2.5)
Symptomatic	0	2/159 (1.3)	0	0	1/132 (0.8)	2/40 (5.0)
Months 3–6						
Prophylactic	0	2/119 (1.7)	0	0	0	0
Symptomatic	0	2/119 (1.7)	0	0	3/89 (3.4)	0
Months 6–12						
Prophylactic	0	2/119 (1.7)	0	0	0	0
Symptomatic	0	1/119 (0.8)	0	0	1/89 (1.1)	0

[a]Denominator is number of patients experiencing the adverse event in the respective timeframe.

Supplementary Table 4. Summary of Patients with Hypertension at Study Baseline According to Treatment of Hypertension Within Each Treatment Period

	Not receiving hypertension medication during treatment period							
	Clinician-reported increased blood pressure, % (n/N)				Measured-based increased blood pressure, % (n/N)			
	Overall rate for timeframe	No AE in week 1	AE once in week 1	AE twice in week 1	**Overall rate for timeframe**	No AE in week 1	AE once in week 1	AE twice in week 1
Week 1	**3.9 (7/177)**	–			**1.1 (3/177)**	–		
Weeks 2–4	**4.5 (8/177)**	2.9 (5/170)	25.0 (1/4)	66.7 (2/3)	**2.8 (5/177)**	2.3 (4/174)	50.0 (1/3)	0
Weeks 5–8	**2.5 (4/162)**	0.6 (1/155)	25.0 (1/4)	66.7 (2/3)	**1.8 (3/162)**	1.9 (3/160)	0 (0/2)	0
Months 3–6	**3.0 (3/100)**	2.1 (2/96)	50.0 (1/2)	0 (0/2)	**2.0 (2/100)**	2.0 (2/99)	0 (0/1)	0
Months 6–12	**2.0 (2/100)**	1.0 (1/96)	50.0 (1/2)	0 (0/2)	**2.0 (2/100)**	2.0 (2/99)	0	0

	Receiving hypertension medication during treatment period							
	Clinician-reported increased blood pressure, % (n/N)				Measured-based increased blood pressure, % (n/N)			
	Overall rate for timeframe	No AE in week 1	AE once in week 1	AE twice in week 1	**Overall rate for timeframe**	No AE in week 1	AE once in week 1	AE twice in week 1
Week 1	**6.2 (2/32)**	–			**6.2 (2/32)**	–		
Weeks 2–4	**3.1 (1/32)**	3.3 (1/30)	0	0 (0/2)	**6.2 (2/32)**	6.7 (2/30)	0 (0/2)	0
Weeks 5–8	**9.3 (4/43)**	7.3 (3/41)	0	50.0 (1/2)	**2.3 (1/43)**	2.4 (1/40)	0 (0/3)	0
Months 3–6	**12.1 (4/33)**	9.4 (3/32)	0	100 (1/1)	**3.0 (1/33)**	3.2 (1/31)	0 (0/2)	0
Months 6–12	**3.0 (1/33)**	0 (0/32)	0	100 (1/1)	**0 (0/33)**	0 (0/31)	0 (0/2)	0

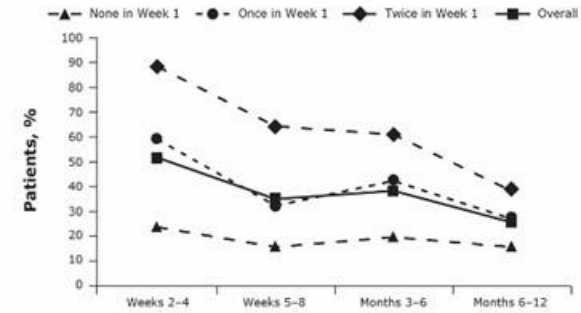
In each cell, n/N represents the number of patients who experienced a recurrence of the given AE / number of patients who contributed data (based on the time period described in the row title and the occurrence in week 1 described in the column title). Patient data were retained: (1) in week 1 if the patient received ≥1 ESK dose in weeks 2–4, (2) in weeks 2–4 if the patient received ≥1 ESK dose in weeks 5-8; (3) in weeks 5–8 if the patient received ≥1 ESK dose in months 3–6, and (4) in months 3–6 if the patient received ≥1 ESK dose in months 6–12.

Shaded cells depict ≥10% difference in AE recurrence rates between occurrence twice vs once per week in week 1 (dark gray) and once per week versus none in week 1 (light gray).

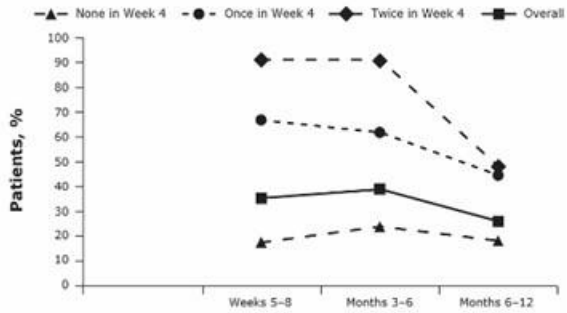
Abbreviation: AE = adverse event

Supplementary Figure 1. Percentage of Esketamine-Treated Participants With Adverse Events Based on Frequency of Week 1 and Week 4 Occurrence for (A) CADSS-Based Dissociation, (B) MOAA/S-Based Sedation, (C) Measure-Based Increased Blood Pressure, and Clinician-Reported (D) Dizziness, (E) Nausea, and (F) Vertigo

A. Dissociation (CADSS >4)

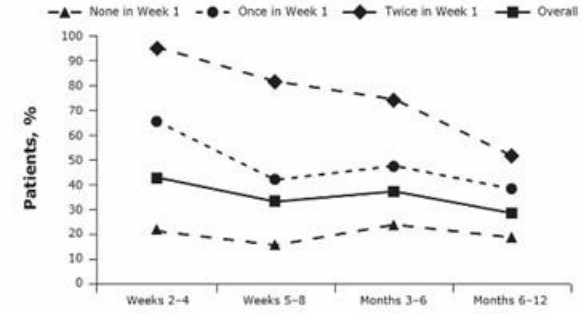


Patients (N)				
None in Week 1	424	398	252	252
Once in Week 1	247	243	157	157
Twice in Week 1	278	277	186	186
Overall	949	918	595	595

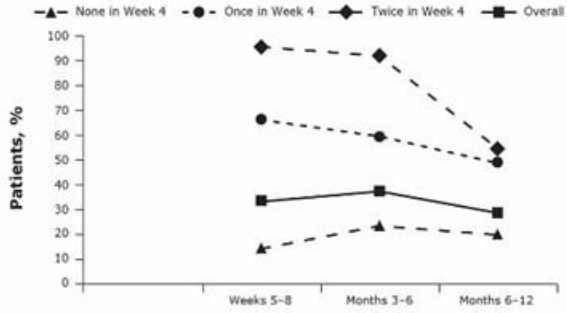


Patients (N)			
None in Week 4	655	421	421
Once in Week 4	139	97	97
Twice in Week 4	124	77	77
Overall	918	595	595

B. Sedation (MOAA/S <5)

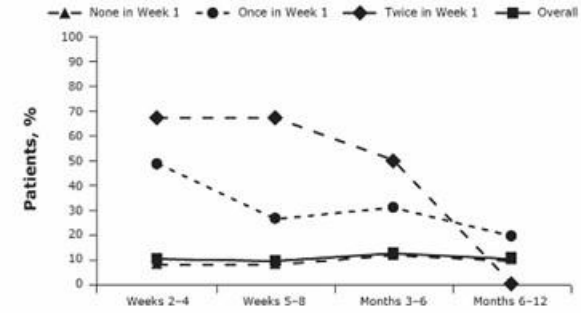


Patients (N)				
None in Week 1	595	570	378	378
Once in Week 1	181	176	107	107
Twice in Week 1	173	172	110	110
Overall	949	918	595	595

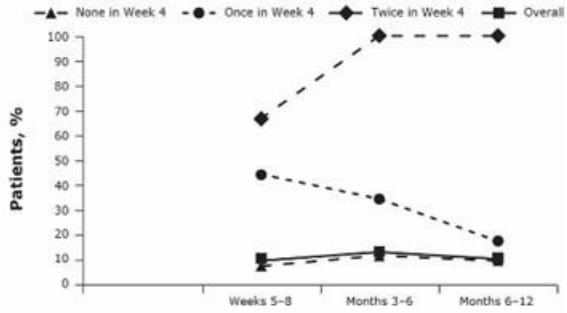


Patients (N)			
None in Week 4	657	432	432
Once in Week 4	131	86	86
Twice in Week 4	130	77	77
Overall	918	595	595

C. Increased Blood Pressure (Measured)

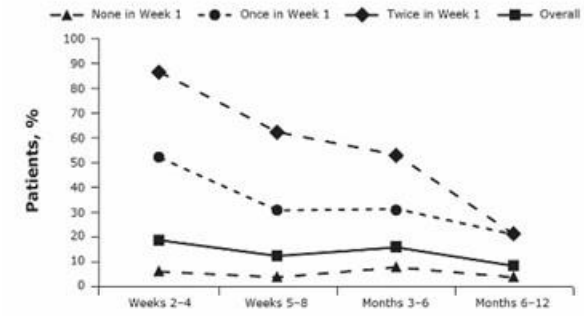


Patients (N)				
None in Week 1	896	867	565	565
Once in Week 1	47	45	26	26
Twice in Week 1	6	6	4	4
Overall	949	918	595	595

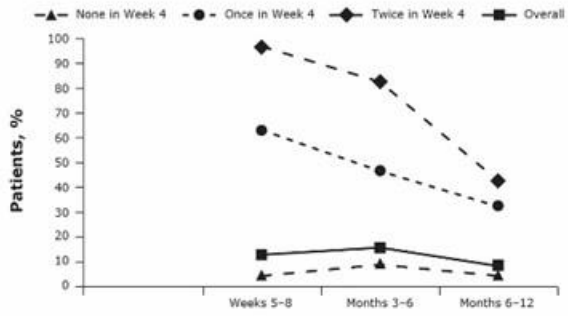


Patients (N)			
None in Week 4	874	570	570
Once in Week 4	38	23	23
Twice in Week 4	6	2	2
Overall	918	595	595

D. Clinician-Reported Dizziness

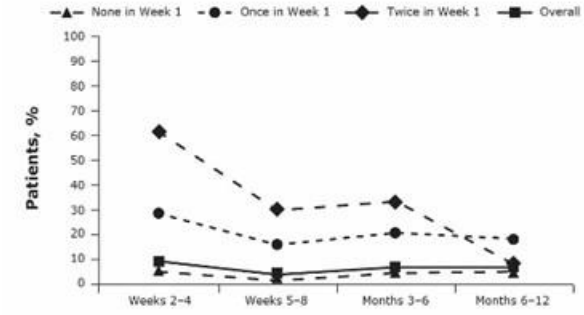


Patients (N)				
None in Week 1	753	723	452	452
Once in Week 1	108	107	77	77
Twice in Week 1	88	88	66	66
Overall	949	918	595	595

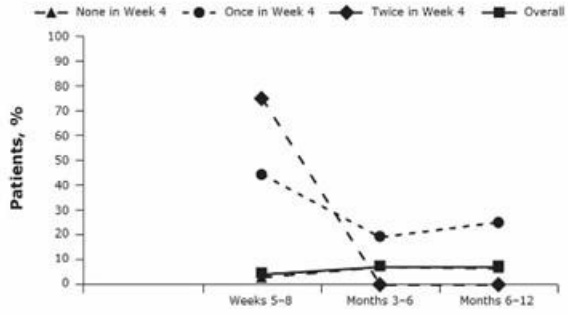


Patients (N)			
None in Week 4	820	527	527
Once in Week 4	43	28	28
Twice in Week 4	55	40	40
Overall	918	595	595

E. Clinician-Reported Nausea

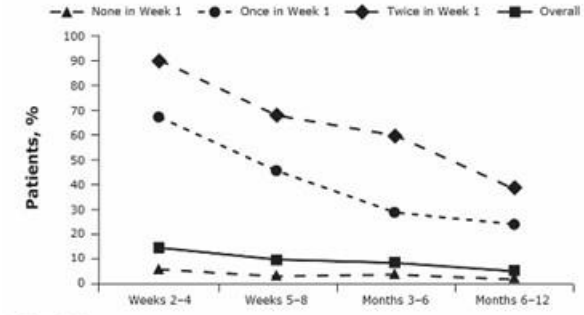


Patients (N)				
None in Week 1	816	786	506	506
Once in Week 1	112	112	77	77
Twice in Week 1	21	20	12	12
Overall	949	918	595	595

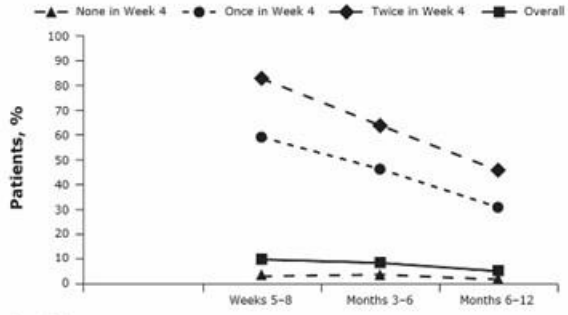


Patients (N)			
None in Week 4	889	577	577
Once in Week 4	25	16	16
Twice in Week 4	4	2	2
Overall	918	595	595

F. Clinician-Reported Vertigo



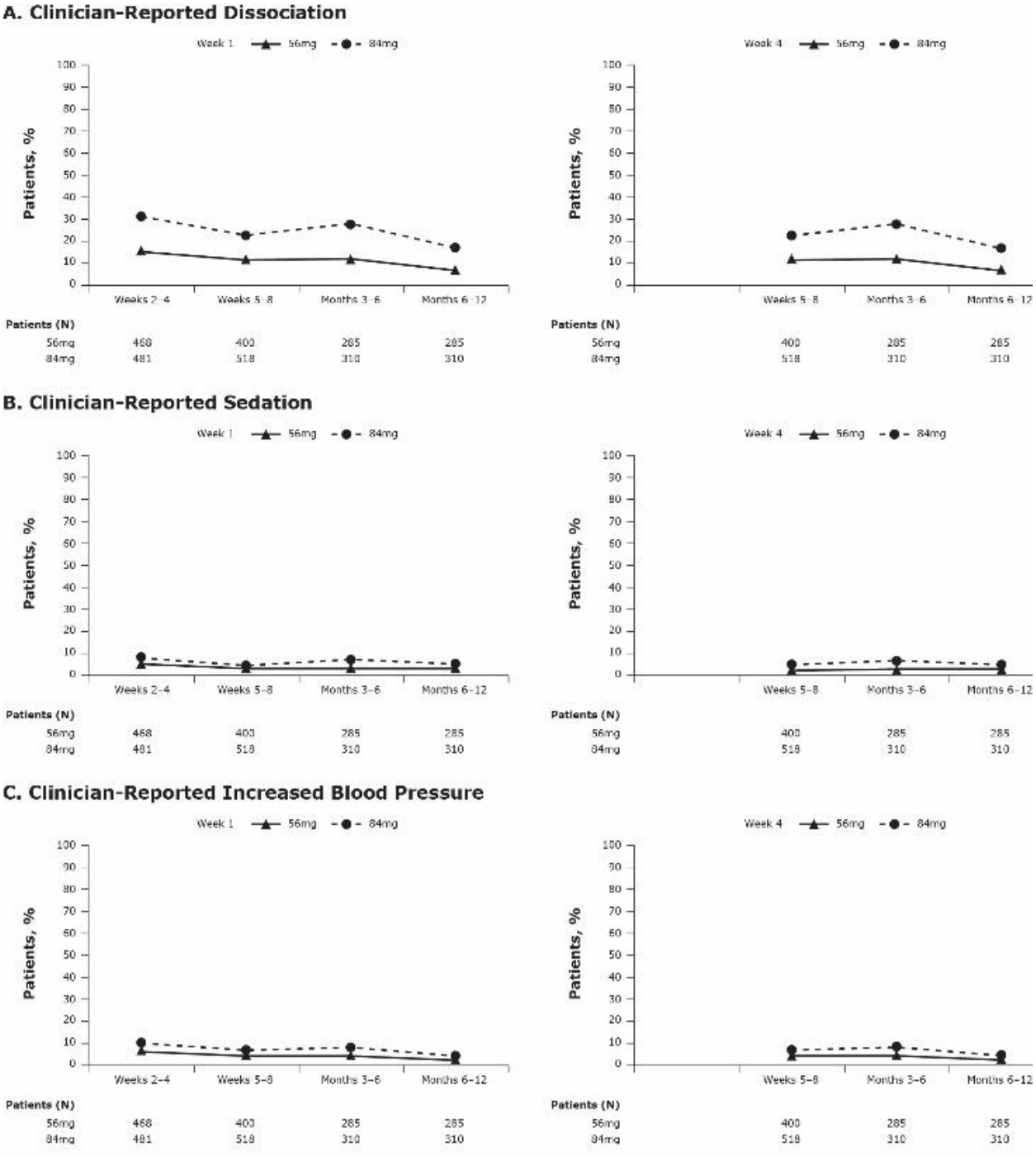
Patients (N)				
None in Week 1	834	805	532	532
Once in Week 1	43	42	21	21
Twice in Week 1	72	71	42	42
Overall	949	918	595	595



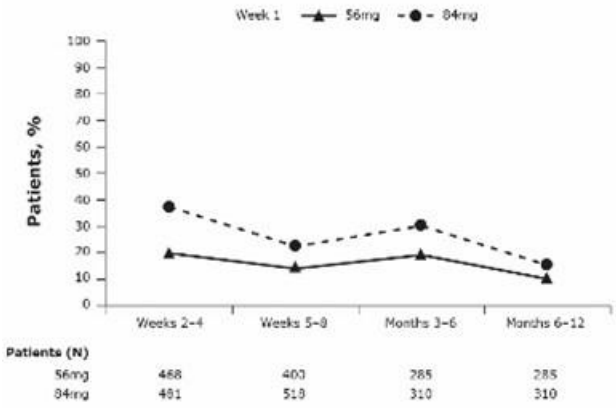
Patients (N)			
None in Week 4	827	549	549
Once in Week 4	39	13	13
Twice in Week 4	52	33	33
Overall	918	595	595

CADSS = Clinician-Administered Dissociative States Scale; MOAA/S = Modified Observer's Assessment of Alertness/Sedation.

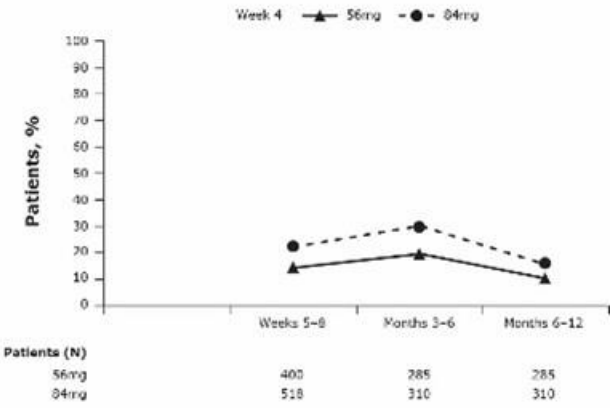
Supplementary Figure 2. Percentage of Esketamine-Treated Patients With Adverse Events Based On Esketamine Nasal Spray Dose, for Clinician-Reported (A) Dissociation, (B) Sedation, (C) Increased Blood Pressure, (D) Dizziness, (E) Nausea, (F) Vertigo, (G) CADSS-Based Dissociation, (H) MOAA/S-Based Sedation, and (I) Measure-Based Increased Blood Pressure



D. Clinician-Reported Dizziness

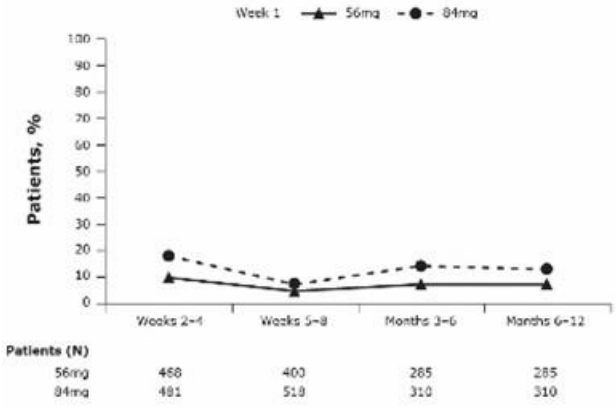


Patients (N)				
56mg	468	400	285	285
84mg	481	518	310	310

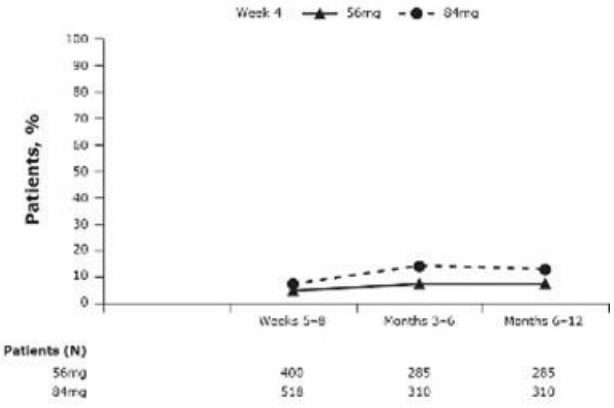


Patients (N)			
56mg	400	285	285
84mg	518	310	310

E. Clinician-Reported Nausea

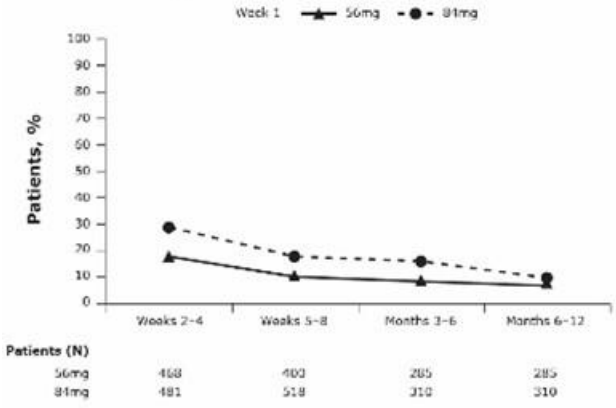


Patients (N)				
56mg	468	400	285	285
84mg	481	518	310	310

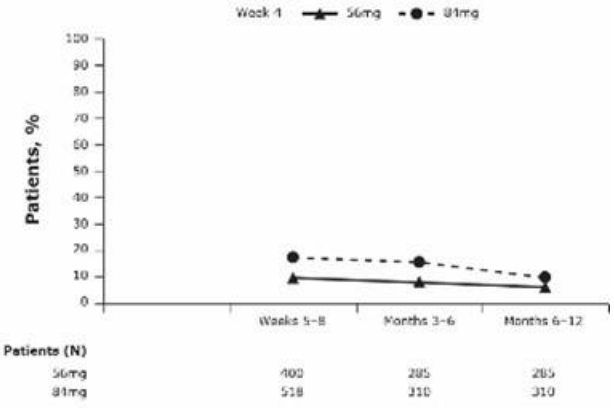


Patients (N)			
56mg	400	285	285
84mg	518	310	310

F. Clinician-Reported Vertigo

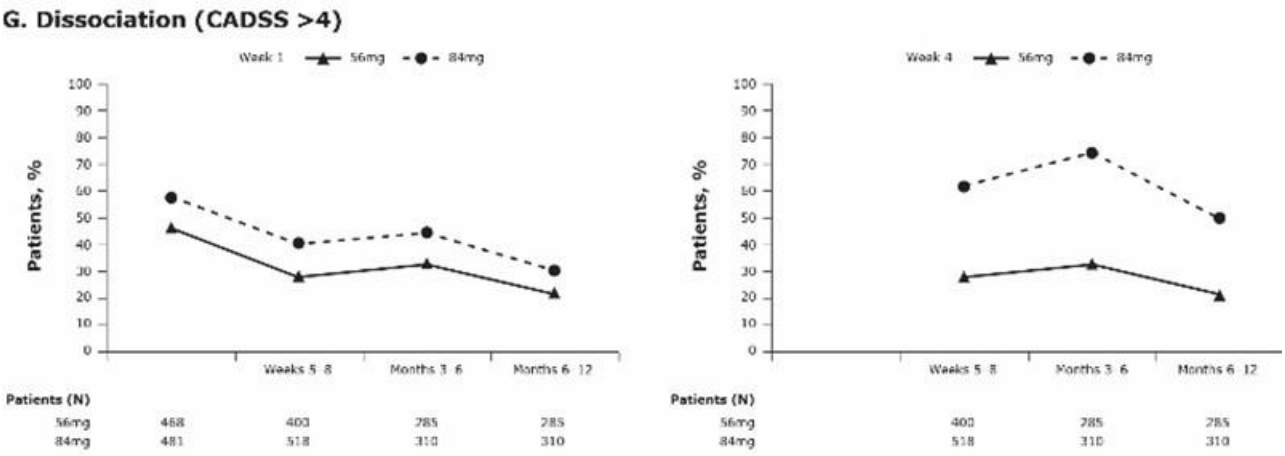


Patients (N)				
56mg	468	400	285	285
84mg	481	518	310	310

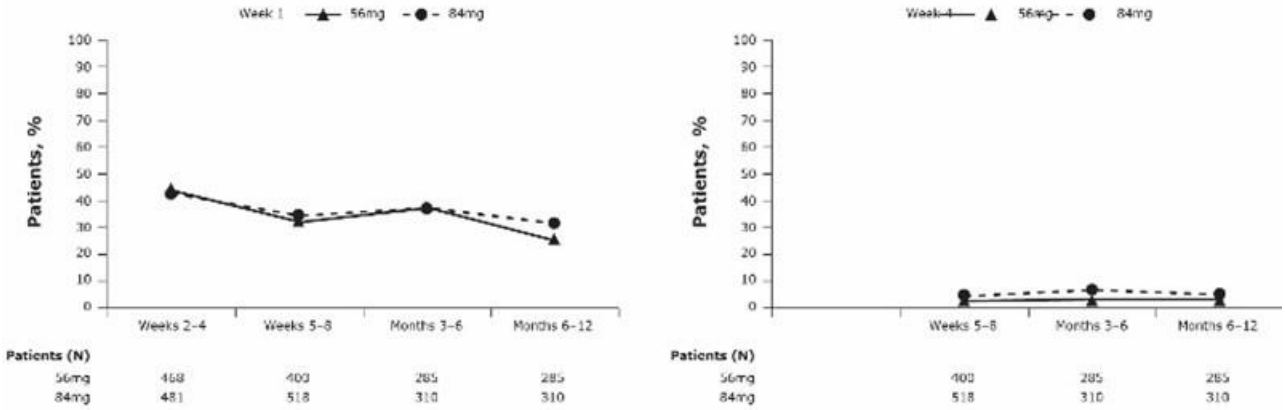


Patients (N)			
56mg	400	285	285
84mg	518	310	310

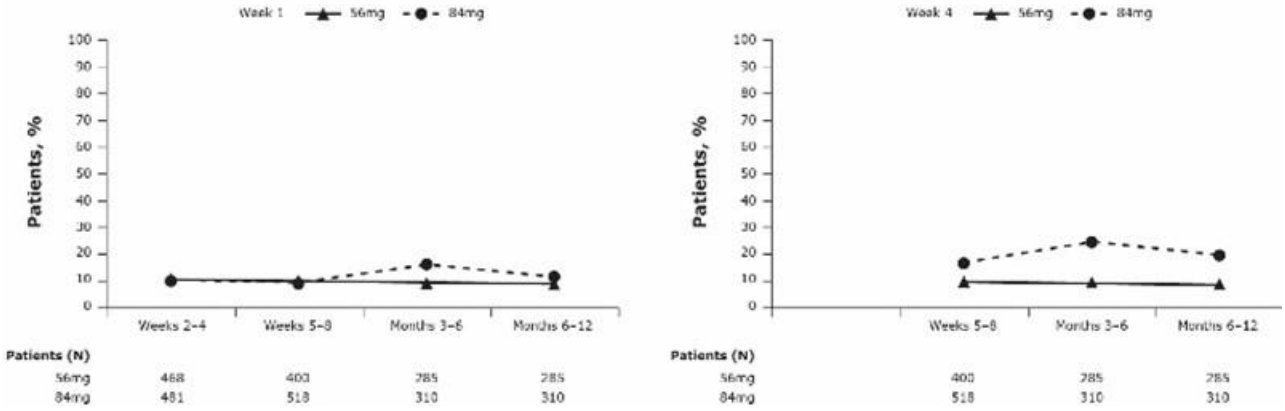
G. Dissociation (CADSS >4)



H. Sedation (MOAA/S <5)



I. Increased Blood Pressure (Measured)



CADSS = Clinician-Administered Dissociative States Scale; MOAA/S = Modified Observer's Assessment of Alertness/Sedation.