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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

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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

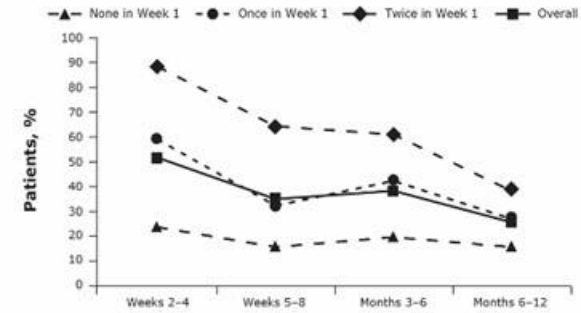
In each cell, n/N represents the number of patients who experienced a recurrence of the given AE / number of patients who contributed data (based on the time period described in the row title and the occurrence in week 1 described in the column title). Patient data were retained: (1) in week 1 if the 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).

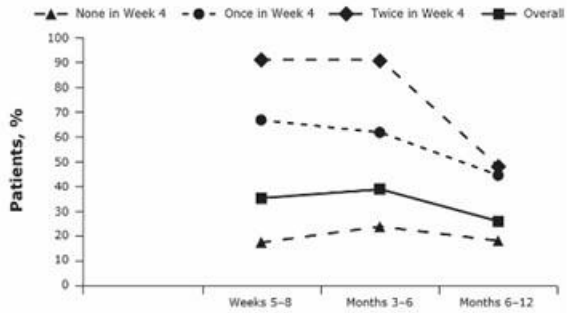
Abbreviation: AE = adverse event

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)

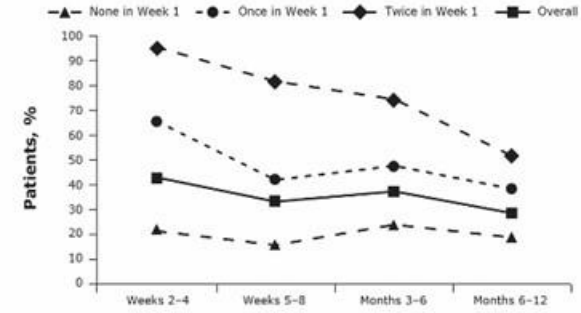


Patients (N)				
None in Week 1	424	398	252	252
Once in Week 1	247	243	157	157
Twice in Week 1	278	277	186	186
Overall	949	918	595	595

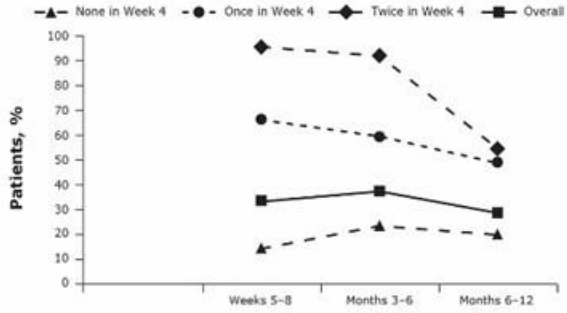


Patients (N)			
None in Week 4	655	421	421
Once in Week 4	139	97	97
Twice in Week 4	124	77	77
Overall	918	595	595

B. Sedation (MOAA/S <5)

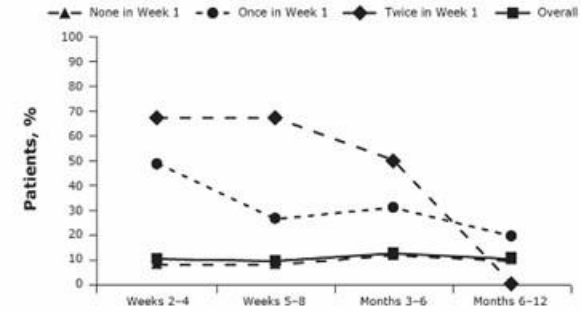


Patients (N)				
None in Week 1	595	570	378	378
Once in Week 1	181	176	107	107
Twice in Week 1	173	172	110	110
Overall	949	918	595	595

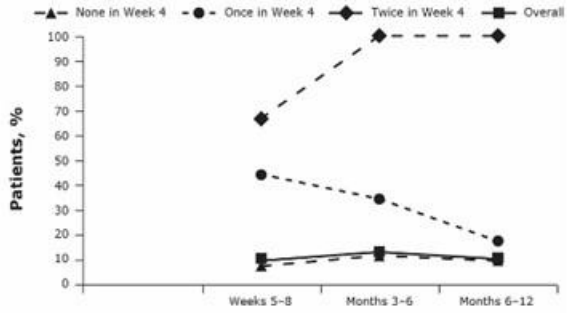


Patients (N)			
None in Week 4	657	432	432
Once in Week 4	131	86	86
Twice in Week 4	130	77	77
Overall	918	595	595

C. Increased Blood Pressure (Measured)

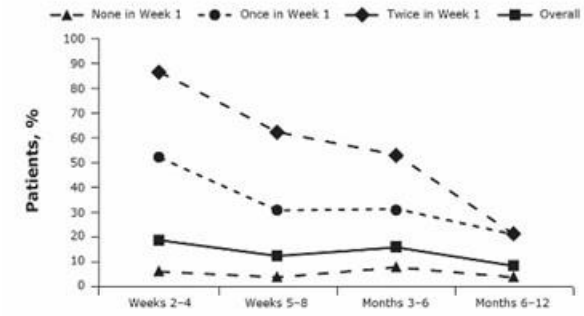


Patients (N)				
None in Week 1	896	867	565	565
Once in Week 1	47	45	26	26
Twice in Week 1	6	6	4	4
Overall	949	918	595	595

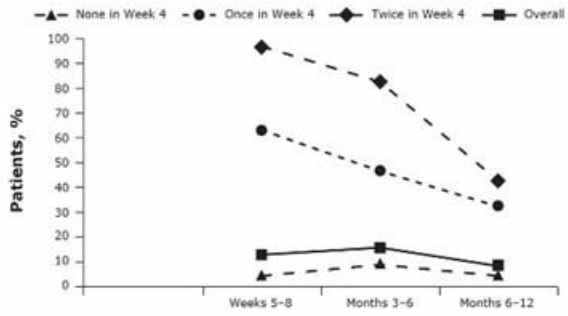


Patients (N)			
None in Week 4	874	570	570
Once in Week 4	38	23	23
Twice in Week 4	6	2	2
Overall	918	595	595

D. Clinician-Reported Dizziness

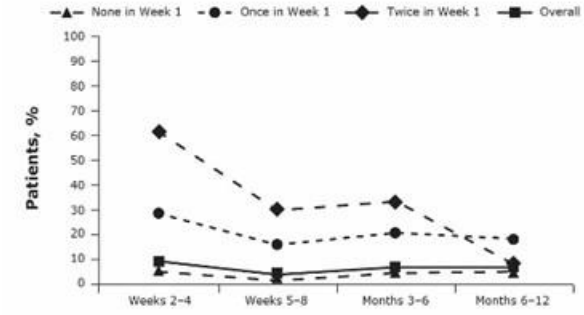


Patients (N)				
None in Week 1	753	723	452	452
Once in Week 1	108	107	77	77
Twice in Week 1	88	88	66	66
Overall	949	918	595	595

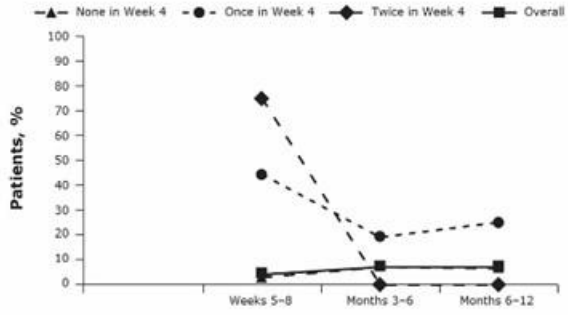


Patients (N)			
None in Week 4	820	527	527
Once in Week 4	43	28	28
Twice in Week 4	55	40	40
Overall	918	595	595

E. Clinician-Reported Nausea

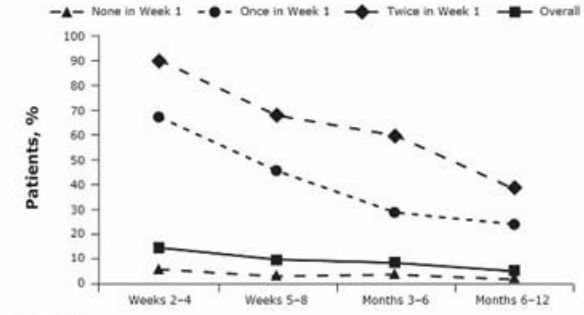


Patients (N)				
None in Week 1	816	786	506	506
Once in Week 1	112	112	77	77
Twice in Week 1	21	20	12	12
Overall	949	918	595	595

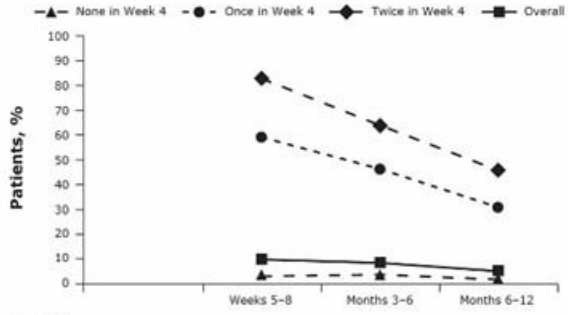


Patients (N)			
None in Week 4	889	577	577
Once in Week 4	25	16	16
Twice in Week 4	4	2	2
Overall	918	595	595

F. Clinician-Reported Vertigo



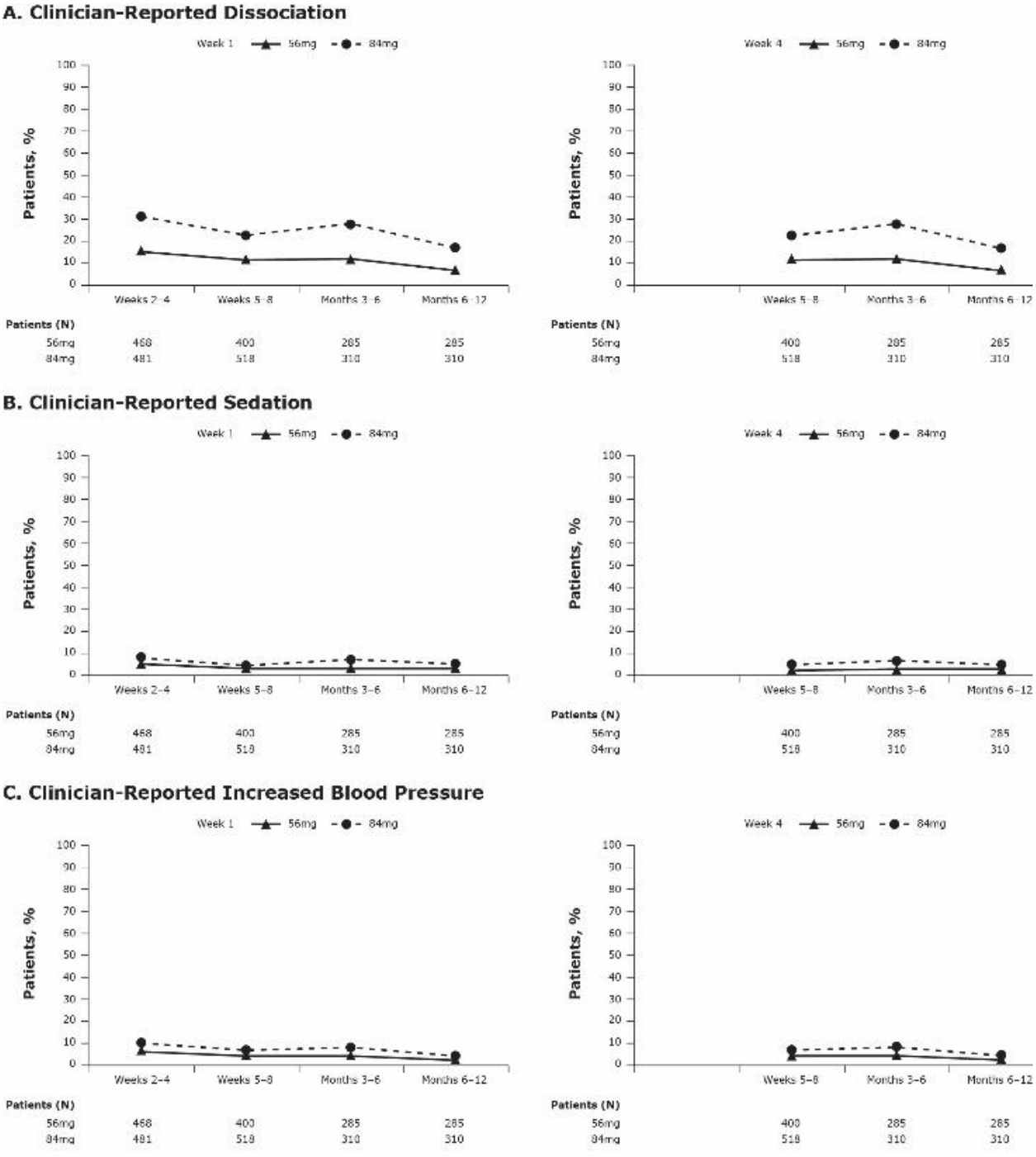
Patients (N)				
None in Week 1	834	805	532	532
Once in Week 1	43	42	21	21
Twice in Week 1	72	71	42	42
Overall	949	918	595	595



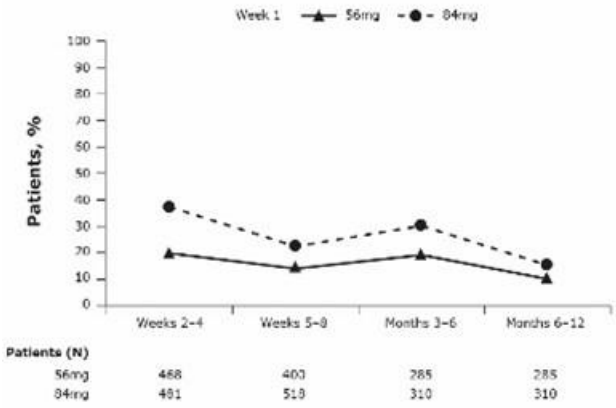
Patients (N)			
None in Week 4	827	549	549
Once in Week 4	39	13	13
Twice in Week 4	52	33	33
Overall	918	595	595

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

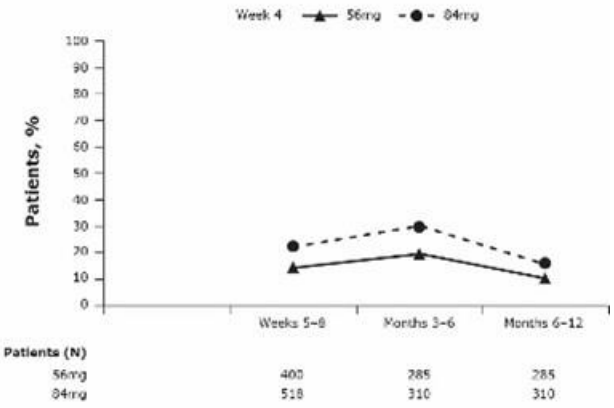
Supplementary Figure 2. Percentage of Esketamine-Treated Patients With Adverse Events Based On Esketamine Nasal Spray Dose, for Clinician-Reported (A) Dissociation, (B) Sedation, (C) Increased Blood Pressure, (D) Dizziness, (E) Nausea, (F) Vertigo, (G) CADSS-Based Dissociation, (H) MOAA/S-Based Sedation,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



D. Clinician-Reported Dizziness

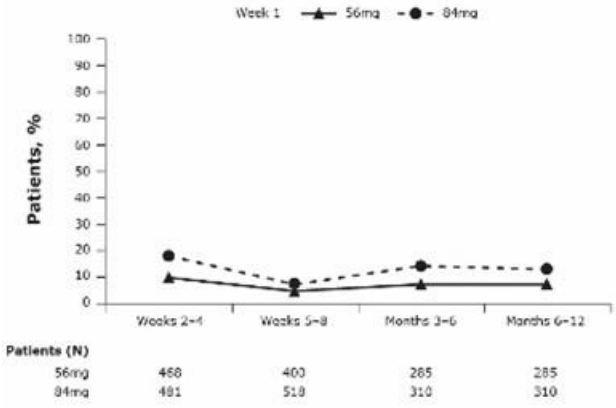


Patients (N)				
56mg	468	400	285	285
84mg	481	518	310	310

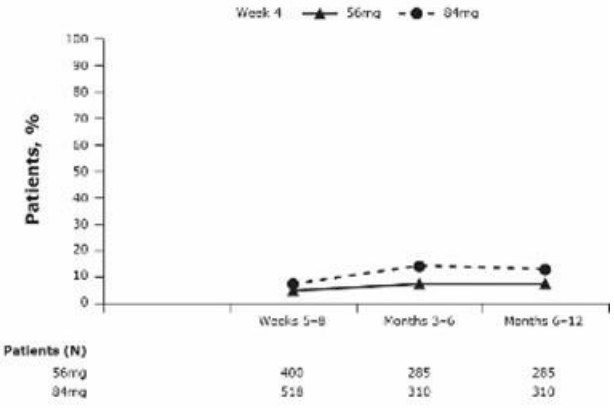


Patients (N)			
56mg	400	285	285
84mg	518	310	310

E. Clinician-Reported Nausea

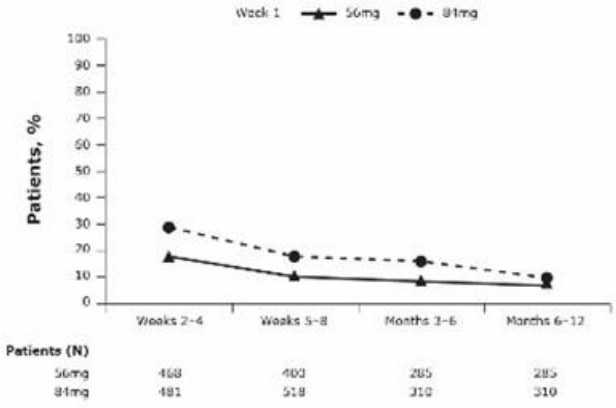


Patients (N)				
56mg	468	400	285	285
84mg	481	518	310	310

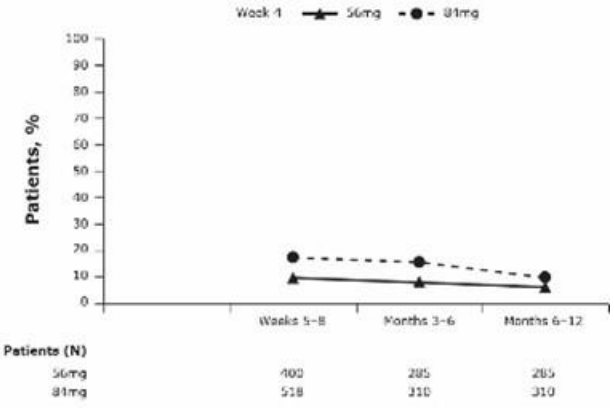


Patients (N)			
56mg	400	285	285
84mg	518	310	310

F. Clinician-Reported Vertigo

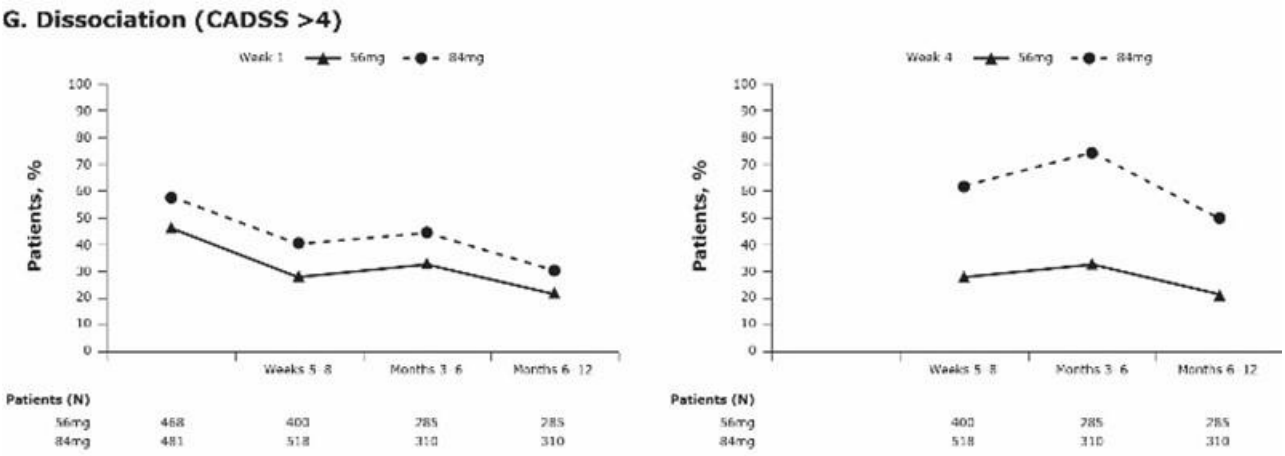


Patients (N)				
56mg	468	400	285	285
84mg	481	518	310	310

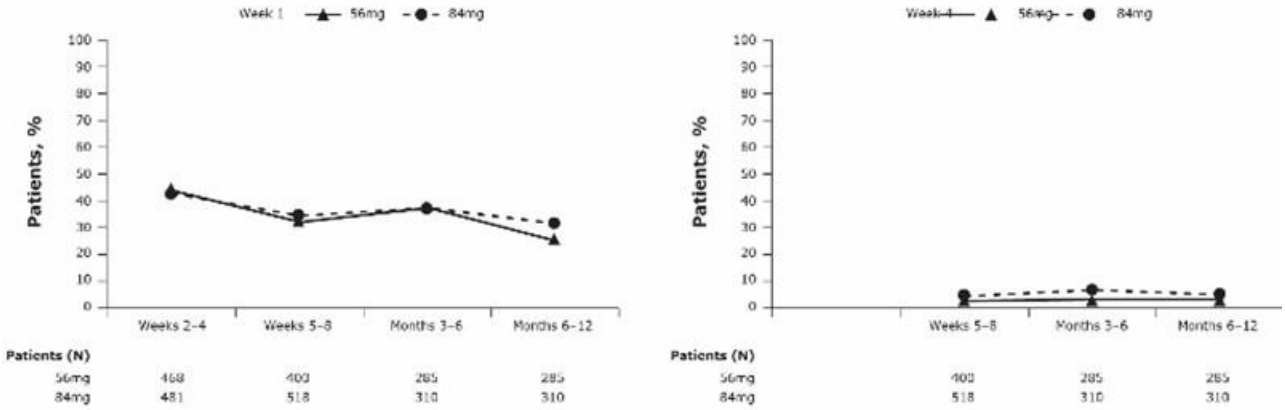


Patients (N)			
56mg	400	285	285
84mg	518	310	310

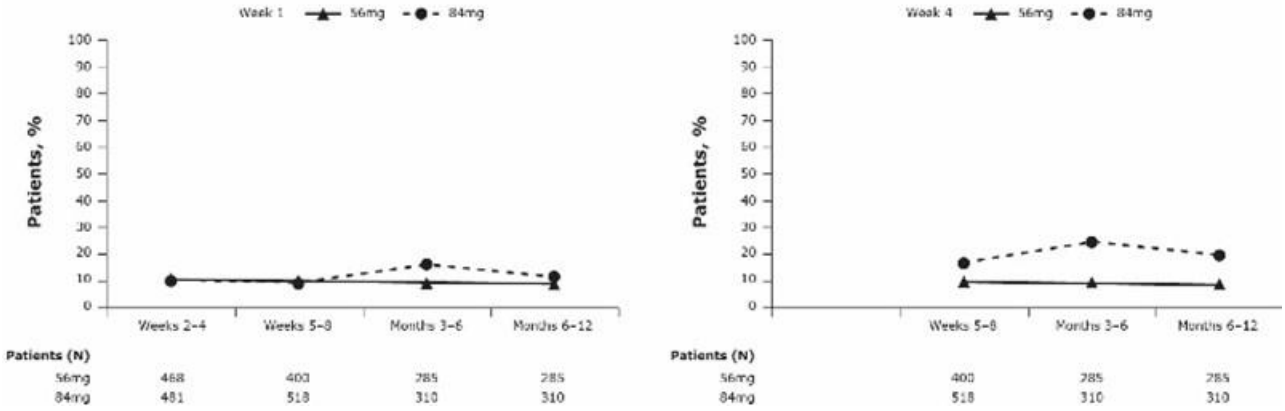
G. Dissociation (CADSS >4)



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.