Patients who received ESK as monotherapy without

a concurrent OAD for ≥12 months had long-term

stable depressive symptoms with no new safety

Patients who received esketamine nasal spray

Improvements in depressive symptoms were

esketamine nasal spray monotherapy and the

Esketamine nasal spray monotherapy may be

a viable treatment option for those who receive

little or no benefit from OADs, or who experience

SUSTAIN-3 is an open-label study with no control

This is a subgroup analysis with a small sample size,

Patients' ESK treatment history differed depending

on which parent study they participated in prior to

ESK monotherapy for a continuous time period was

started at different stages of the study and was of

Patients had different reasons for initiating

and continuing monotherapy treatment

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variable duration (although ≥12 consecutive months)

which may limit the interpretation of the results

a tolerable safety profile, and no new safety signals

similarly maintained in patients receiving

Esketamine nasal spray monotherapy had

overall SUSTAIN-3 study population

treatment-limiting TEAEs from OADs

group for comparison

optimization/maintenance phase

monotherapy for ≥12 consecutive months at any

point during the study remained stable during the

**Key Takeaway** 

Conclusions

Limitations

signals identified

# Long-Term Efficacy and Safety of Esketamine Nasal Spray as Monotherapy: A Post Hoc Analysis of the SUSTAIN-3 Study

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# Introduction

- Prior to January 2025, esketamine nasal spray (ESK) was approved for treatmentresistant depression (TRD) in adults and for depressive symptoms in adults with major depressive disorder with acute suicidal ideation or behavior, both in conjunction with an oral antidepressant (OAD)<sup>1</sup>
- Primary findings from a phase 4, multicenter, double-blind, randomized, placebo-controlled trial (TRD4005, NCT04599855) demonstrated that ESK as monotherapy led to a rapid and superior improvement in Montgomery-Åsberg Depression Rating Scale (MADRS) total score compared with placebo at day 28, and as early as 24 hours after the first dose<sup>2</sup>
- Based on these results. ESK was approved in the United States as the first and only monotherapy for adults with TRD<sup>1,3</sup>
- Some patients enrolled in SUSTAIN-3, a long-term open-label ESK efficacy and safety study, received ESK treatment without a concurrent OAD for a prolonged period (≥12 consecutive months) at the investigators' discretion<sup>4,5</sup>
- Data from these patients can provide additional evidence to inform the long-term efficacy and safety of ESK monotherapy

### Objective

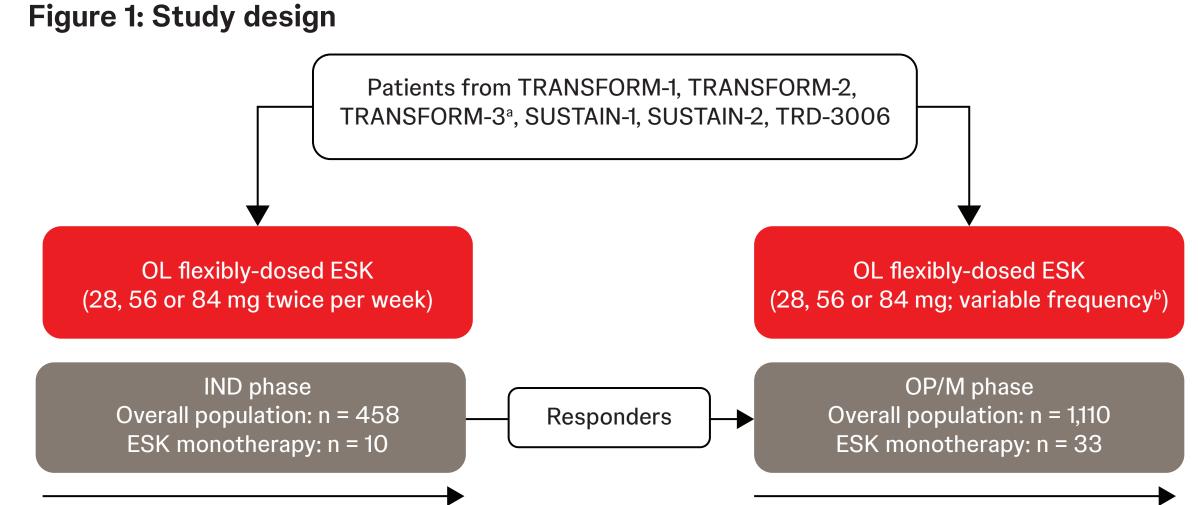
To describe the long-term efficacy and safety of ESK in adults with TRD who received ESK as monotherapy for ≥12 consecutive months in a long-term open-label study

# Methods

### Study design

- SUSTAIN-3 was a phase 3, open-label, long-term extension study comprised of 2 phases: a 4-week induction phase (IND) and a variable duration optimization/ maintenance phase (OP/M) (Figure 1)
- SUSTAIN-3 enrolled patients with TRD (≥2 prior OAD treatment failures) from 1 of 6 parent studies
- Patients entered either the IND or OP/M phase, based on their status at the end of the parent study
- Patients in SUSTAIN-3 received open-label, flexibly-dosed ESK, with a concurrent OAD: however, this post hoc subgroup analysis included patients who either never received an OAD or stopped OAD treatment but continued with ESK for variable durations
- Patients who discontinued OAD treatment may have reinitiated OAD treatment at a later point, but received ESK monotherapy for ≥12 consecutive months during the study period During the IND phase, ESK was flexibly-dosed twice weekly for 4 weeks;
- for patients who proceeded to the OP/M phase, ESK dosing frequency was individualized based on depression severity and tolerability to weekly, every other week, or every 4 weeks<sup>1</sup>

- Efficacy outcomes included changes in disease severity, evaluated per the MADRS and the 9-item Patient Health Questionnaire (PHQ-9)
- The proportions of patients who attained remission status were determined For MADRS, remission was defined as a total score ≤12
- For PHQ-9, remission was defined as a total score <5
- Treatment-emergent adverse events (TEAEs) were monitored throughout the duration of the study



ESK, esketamine nasal spray; IND, induction; OAD, oral antidepressant; OL, open-label; OP/M, optimization/

ESK monotherapy patients were defined as patients who did not receive OADs for ≥12 consecutive months

<sup>a</sup>Results from the TRANSFORM-3 study (patients aged ≥65 years) were not included in this subgroup analysis <sup>b</sup>Dosing frequency adjusted based on Clinical Global Impression-Severity scale score and tolerability. Dosing frequency during OP/M could be weekly, every other week, or every 4 weeks.

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# Table 1: Baseline characteristics

	ESK monotherapy patients N = 33	Overall SUSTAIN-3 patients N = 1,148
Mean age (SD), years	44.5 (11.27)	49.6 (12.28)
Sex, n (%)		
Female	18 (54.5)	764 (66.6)
Male	15 (45.5)	384 (33.4)
Race, n (%)		
American Indian or Alaskan Native	0	1 (0.1)
Asian	4 (12.1)	45 (3.9)
Black or African American	2 (6.1)	45 (3.9)
White	25 (75.8)	996 (86.8)
Other	1 (3.0)	29 (2.5)
Multiple	0	10 (0.9)
Not reported	1 (3.0)	22 (1.9)
Mean duration of current MDD episode (SD), weeks	197.9 (229.95)	162.8 (257.21)
Mean (SD) baseline MADRS total score <sup>a</sup>		
IND baseline	33.8 (3.82)b	29.1 (7.96) <sup>d</sup>
OP/M baseline	11.2 (9.51)°	13.1 (8.79)e
Mean (SD) baseline PHQ-9 total score <sup>a</sup>		
IND baseline	17.2 (4.39)b	15.4 (5.59) <sup>d</sup>
OP/M baseline	6.0 (4.82)°	7.6 (5.60) <sup>e</sup>

ESK, esketamine nasal spray; IND, induction phase; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; OAD, oral antidepressant; OP/M, optimization/maintenance phase; PHQ-9, 9-item Patient Health Questionnaire.

ESK monotherapy patients were defined as patients who did not receive OADs for ≥12 consecutive months <sup>a</sup>Patients could enter SUSTAIN-3 at either the IND phase or OP/M phase, based on their status at the end of the parent study.  ${}^{b}N = 10$ .  ${}^{c}N = 33$ .  ${}^{d}N = 458$ .  ${}^{e}N = 1{,}110$ .

# Table 2: Most common TEAEs

References

TEAE, n (%)	ESK monotherapy patients N = 33
Dizziness	18 (54.6)
Headache	17 (51.5)
Nausea	13 (39.4)
Upper respiratory tract infection	12 (36.4)
Back pain	9 (27.3)
Diarrhea	9 (27.3)
Anxiety	8 (24.2)
Dissociation	8 (24.2)
Arthralgia	7 (21.2)
Dysgeusia	7 (21.2)
Fatigue	7 (21.2)
Insomnia	7 (21 2)

ESK, esketamine nasal spray; OAD, oral antidepressant; TEAE, treatment-emergent adverse event. ESK monotherapy patients were defined as patients who did not receive OADs for ≥12 consecutive months at any point during ESK treatment.

# Results

# **Baseline characteristics**

- A total of 1,148 patients were enrolled in SUSTAIN-3; this subgroup analysis included 33 patients who received ESK monotherapy for ≥12 consecutive months
- Of these, 21 patients never received OAD treatment, and 12 patients discontinued OAD treatment for ≥12 consecutive months during SUSTAIN-3 (Figure 2) Mean (SD) and median duration from study start to the start of the ESK monotherapy
- For the monotherapy group, the mean (SD) and median duration of exposure to ESK was 1,241 (550) days and 1,221 days, respectively, with a maximum duration of ESK exposure of 2,149 days (almost 6 years)

period was 242.9 (329.14) days and 84.0 days, respectively (range: 0-1,167 days)

Mean (SD) and median duration of ESK monotherapy treatment was 926.2 (434.45) days and 875.0 days, respectively (range: 366-1,924 days)

Figure 3: Change in (A) MADRS and (B) PHQ-9 total scores over time for patients receiving ESK monotherapy (LOCF)

Week 2300
Week 296
Week 296
Week 288
Week 266
Week 166
Week 224
Week 166
Week 166
Week 166
Week 166
Week 224
Week 166
Week 226
We

Week 2336

Week 266

Week 166

Week

BL, baseline; ESK, esketamine nasal spray; IND, induction phase; LOCF, last observation carried forward; MADRS, Montgomery-Åsberg Depression Rating Scale; OP/M, optimization/

Patients could enter SUSTAIN-3 at either the IND phase or OP/M phase, based on their status at the end of the parent study.

Baseline characteristics are shown in **Table 1** 

### Clinician- and patient-reported disease severity

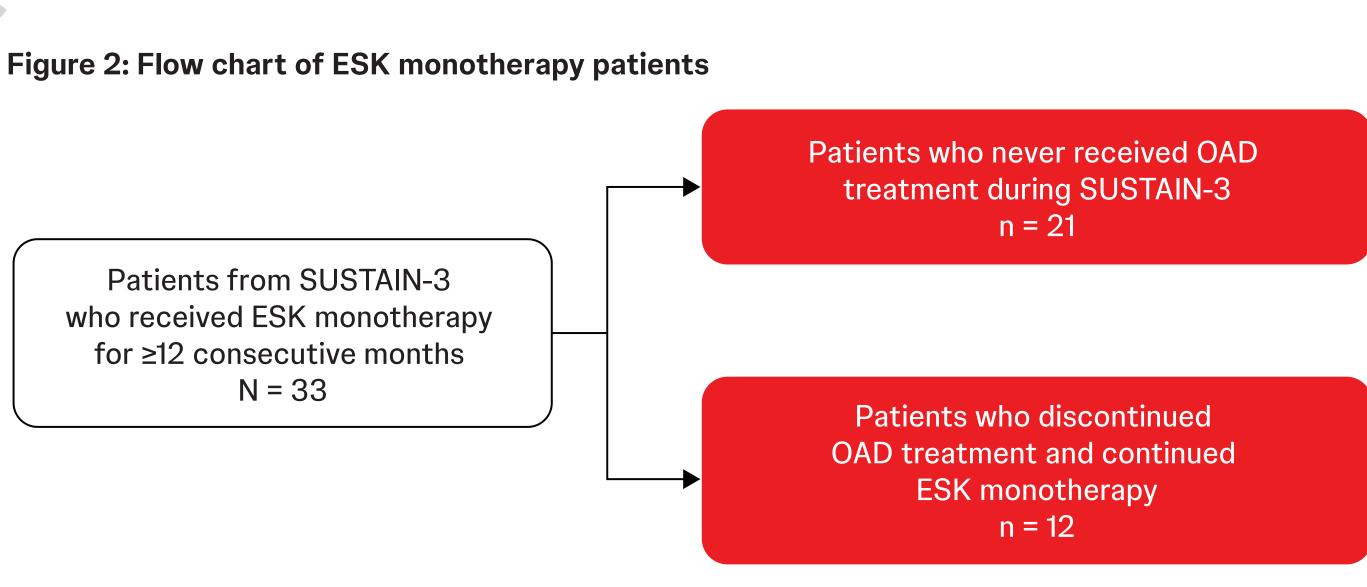
OP/M

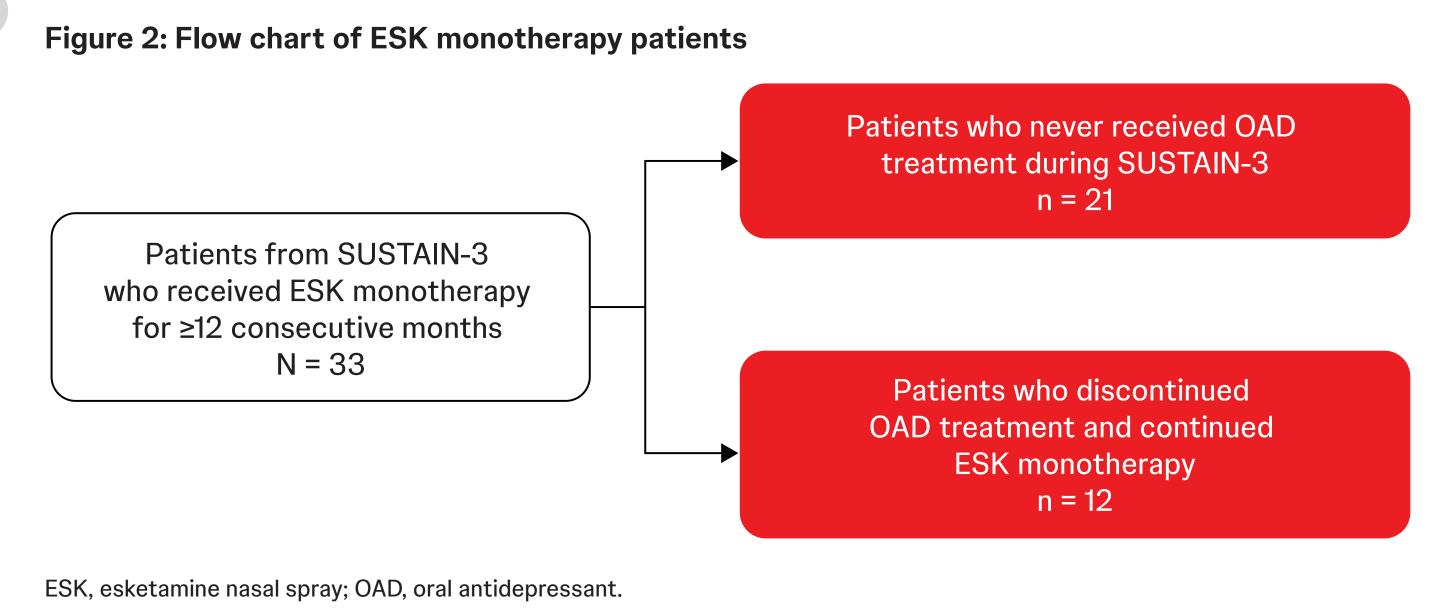
• Changes in MADRS and PHQ-9 scores throughout the study period are shown in **Figure 3** and demonstrate that measures of depression severity remained stable throughout OP/M for patients receiving ESK monotherapy

Mean changes in MADRS and PHQ-9 total scores from OP/M baseline to study end were similar between patients receiving ESK monotherapy and the overall population,4 with mean (SD) changes in MADRS and PHQ-9 scores from OP/M baseline to endpoint of 0.5 (5.88) and 1.5 (4.72), respectively, in patients receiving ESK monotherapy, comparable to 0.2 (9.93) and 0.6 (6.22) in the overall SUSTAIN-3 population

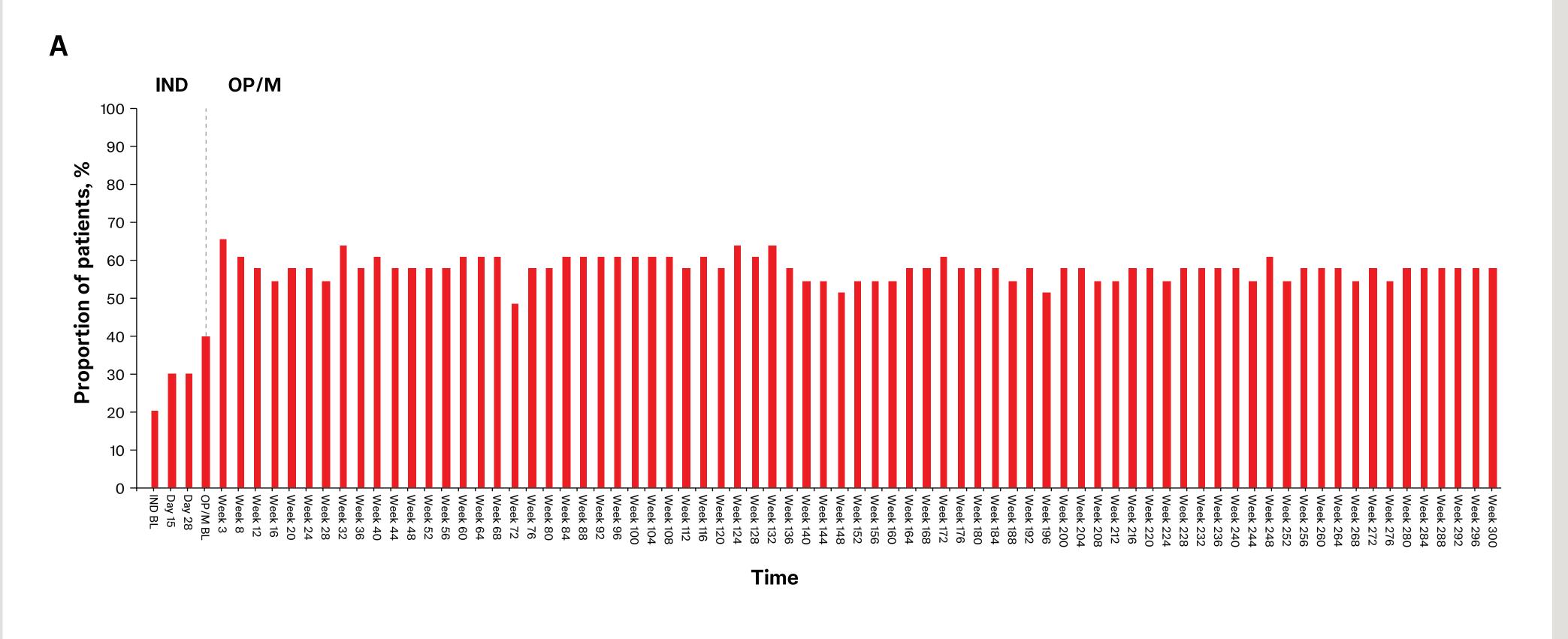
- The proportion of patients who had received ESK monotherapy who achieved remission remained stable throughout the OP/M phase (Figure 4)
- By study end, 57.6% of patients who had received ESK monotherapy were in remission based on MADRS total score, compared with 49.6% of the overall SUSTAIN-3 population
- For remission based on PHQ-9, 42.4% of patients who had received ESK monotherapy were in remission by study end, compared with 33.9% of the overall SUSTAIN-3 population

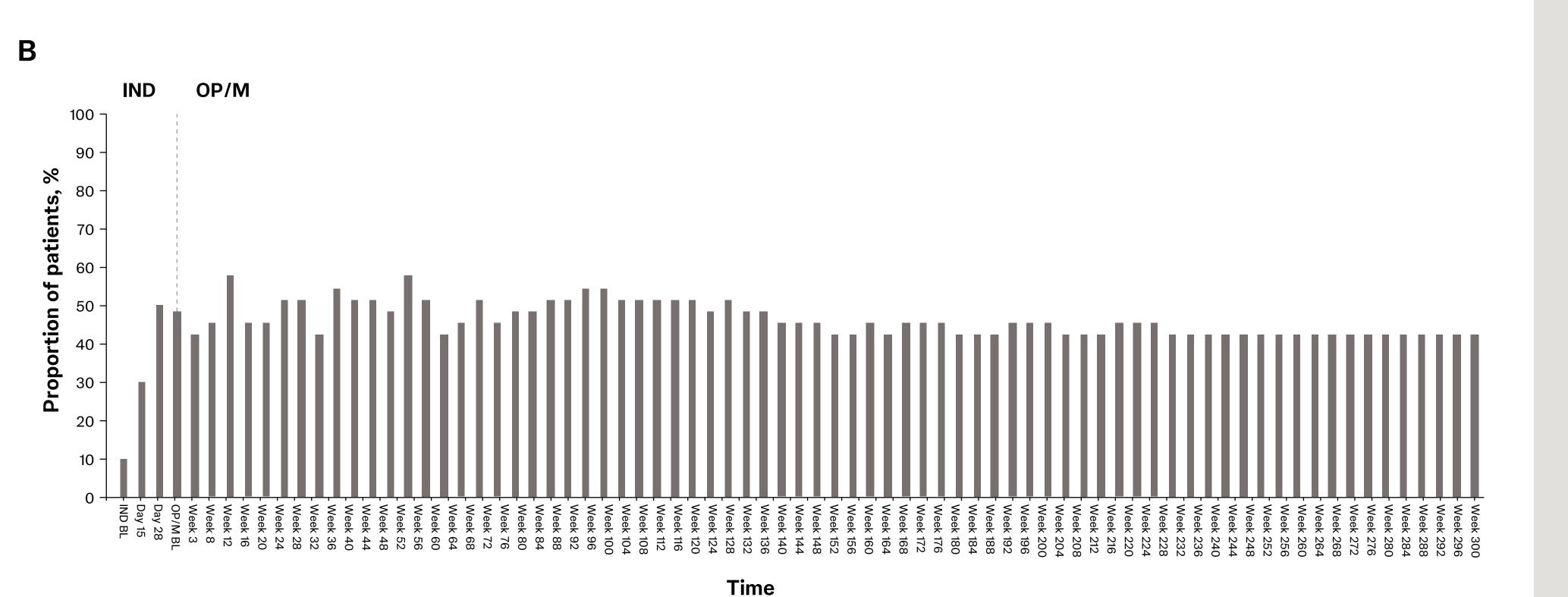
- Overall, 72.7% (n = 24) of patients who had received ESK monotherapy experienced TEAEs possibly related to study drug, and 15.2% (n = 5) experienced ≥1 serious TEAE
- The most common TEAEs (≥20% of patients) are shown in **Table 2**
- Results from this subgroup analysis were consistent with the established safety and tolerability profile of ESK, with no new safety signals identified<sup>6</sup>





# Figure 4: Proportion of patients receiving ESK monotherapy in remission based on (A) MADRS and (B) PHQ-9 total scores (LOCF)





BL, baseline; ESK, esketamine nasal spray; IND, induction phase; LOCF, last observation carried forward; MADRS, Montgomery-Åsberg Depression Rating Scale; OP/M, optimization/ maintenance phase; PHQ-9, 9-item Patient Health Questionnaire. Patients could enter SUSTAIN-3 at either the IND phase or OP/M phase, based on their status at the end of the parent study.

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# Previous presentation

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Novel Pathways in Depression





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