Esketamine Nasal Spray for Relapse Prevention in Patients With Treatment-Resistant Depression: A Post Hoc Analysis of Predictors of Relapse in Placebo-Treated Patients in SUSTAIN-1

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Introduction

- Depression is a common chronic illness that affects up to 6% of the adult population globally[1]
- Achieving and maintaining remission is the ultimate goal of treatment and leads to better daily functioning and long-term outcomes in patients with depression[2]
- Esketamine nasal spray (ESK) is approved by the US Food and Drug Administration for the treatment of treatment-resistant depression (TRD) in adults, as monotherapy or in conjunction with an oral antidepressant (OAD), and for the treatment of depressive symptoms in adults with major depressive disorder with acute suicidal ideation or behavior in conjunction with an OAD[3]
- SUSTAIN-1 (NCT02493868) was a phase 3, double-blind, multicenter, randomized withdrawal study evaluating the efficacy of continuing treatment with ESK + OAD compared with switching to placebo nasal spray (PBO) + OAD in delaying relapse of depressive symptoms in adults with TRD[4]
  - Continued treatment with ESK + OAD significantly delayed relapse compared with treatment with OAD alone (HR 0.49; 95% CI: 0.29, 0.84; $P = 0.003$)[4]
- Identifying predictors of relapse after discontinuation of ESK can inform individualized risk assessment and guide treatment decisions, helping to optimize maintenance strategies and improve sustained remission and long-term outcomes

Objective

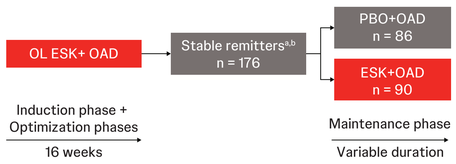
- In this post hoc analysis, we evaluated potential predictors of relapse among patients randomly assigned to the PBO + OAD arm of SUSTAIN-1, focusing on baseline demographics and disease-related characteristics that may increase vulnerability to relapse following discontinuation of ESK

Methods

Study design

- In SUSTAIN-1, adults with TRD were treated with ESK (56 or 84 mg) + OAD for 16 weeks in the induction and optimization phases (**Figure 1**)
- Patients who experienced stable remission were randomly assigned 1:1 to continue ESK + OAD treatment or discontinue ESK and switch to PBO + OAD in the maintenance phase
- Montgomery-Åsberg Depression Rating Scale (MADRS) assessments were performed weekly in the maintenance phase
- Relapse was defined as MADRS total score ≥22 for 2 consecutive assessments and/or hospitalization for suicidality or worsening depression, or any other clinically relevant event (assessed by the investigator)

Figure 1: SUSTAIN-1 study design



ESK, esketamine nasal spray; OAD, oral antidepressant; OL, open label; PBO, placebo nasal spray.
[a]Stable remission was defined as MADRS total score ≤12 for at least 3 of the last 4 weeks of the optimization phase.
[b]One patient with stable response was incorrectly randomized to the group with stable remission.

Data analyses

- A total of 45 variables describing baseline demographics and psychiatric history were assessed as candidate predictors of relapse
- Variables were examined descriptively for the relapse and nonrelapse groups, and differences between groups were compared using a *t* test (continuous) or chi-square test (categorical)
- Initial screening of candidate predictors used univariate Cox proportional hazards models; variables with nominal significance ($P < 0.3$) were advanced with no multiplicity adjustment
- Candidate predictors were then entered into a stepwise multivariate Cox proportional hazards model, with candidates entered sequentially and removed if they became nonsignificant; the final model retained predictors with $P < 0.05$
- Hazard ratios and 95% confidence intervals are reported

Results

Baseline demographics and clinical characteristics

- A total of 176 patients experienced stable remission after 16 weeks of ESK + OAD treatment and were randomized to either continue ESK + OAD (n = 90) or switch to PBO + OAD (n = 86)
- More patients experienced relapse in the PBO + OAD arm (45.3%, n = 39/86) compared with the ESK + OAD arm (26.7%, n = 24/90)
- For patients who discontinued ESK (randomized to the PBO + OAD arm), baseline demographics and clinical characteristics for relapsed and nonrelapsed patients are described in **Table 1** (variables shown represent a proportion of the total variables assessed)
- Variables with a statistically significant difference between groups were age ($P = 0.040$), number of previous antidepressants ($P = 0.046$), class of OAD ($P = 0.047$), and baseline Clinical Global Impression-Severity (CGI-S) category ($P < 0.001$)

Table 1: Patient demographics and baseline clinical characteristics

	Nonrelapse n = 47	Relapse n = 39	*P* value[a]
Mean age (SD), years	48.4 (10.98)	43.5 (10.91)	**0.040**
Female, n (%)	33 (70.2)	26 (66.7)	0.724
Race, n (%)			0.565
Black or African American	4 (8.5)	2 (5.1)	
Other/multiple races	3 (6.4)	1 (2.6)	
White	40 (85.1)	36 (92.3)	
Ethnicity, n (%)			0.326
Hispanic or Latino	8 (17.8)	4 (10.3)	
Mean baseline BMI (SD)	29.6 (6.34)	29.4 (6.23)	0.870
Hypertension status, n (%)			0.059
Yes	14 (29.8)	5 (12.8)	
No	33 (70.2)	34 (87.2)	
Employment status, n (%)			0.518
Employed	28 (59.6)	26 (66.7)	
Unemployed	10 (21.3)	9 (23.1)	
Other	9 (19.2)	4 (10.3)	
Mean age when diagnosed with MDD (SD), years	35.3 (11.62)	31.1 (10.85)	0.088
Mean duration of current episode (range), weeks	100.5 (12-884)	122.5 (9-649)	0.495
Number of previous antidepressants, n (%)			**0.046**
2	39 (83.0)	25 (64.1)	
≥3	8 (17.0)	14 (35.9)	
Class of OAD, n (%)			**0.047**
SNRI	36 (76.6)	22 (56.4)	
SSRI	11 (23.4)	17 (43.6)	
OAD, n (%)			0.053
Escitalopram	5 (10.6)	9 (23.1)	
Sertraline	6 (12.8)	8 (20.5)	
Venlafaxine extended-release	9 (19.2)	11 (28.2)	
Duloxetine	27 (57.5)	11 (28.2)	
Screening C-SSRS, lifetime, n (%)			0.200
Suicidal behavior	4 (8.5)	3 (7.7)	
Suicidal ideation	6 (12.8)	11 (28.2)	
No event	37 (78.7)	25 (64.1)	
Screening C-SSRS, past 6 or 12 months, n (%)			0.702
Suicidal ideation and behavior	7 (14.9)	7 (18.0)	
No event	40 (85.1)	32 (82.1)	
Mean screening IDS-30 total score (SD)	48.3 (7.16)	47.0 (8.48)	0.444
Mean baseline MADRS total score (SD)	37.9 (4.80)	37.3 (4.52)	0.582
Mean baseline PHQ-9 total score (SD)	19.6 (3.48)	20.0 (3.41)	0.654
Mean baseline CGI-S score (SD)	5.0 (0.88)	5.2 (0.43)	0.449
Baseline CGI-S category, n (%)			**<0.001**
Mildly and moderately ill	13 (27.7)	1 (2.6)	
Markedly ill	20 (42.6)	31 (79.5)	
Severely and most extremely ill	14 (29.8)	7 (18.0)	

BMI, body mass index; CGI-S, Clinical Global Impression-Severity; C-SSRS, Columbia Suicide Severity Rating Scale; IDS-30, 30-item Inventory of Depressive Symptomatology; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; OAD, oral antidepressant; PHQ-9, 9-item Patient Health Questionnaire; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.
[a]*P* values of continuous variables are based on a *t* test, and *P* values of categorical variables are based on a chi-square test. Bold font indicates $P < 0.05$.

Predictors of relapse

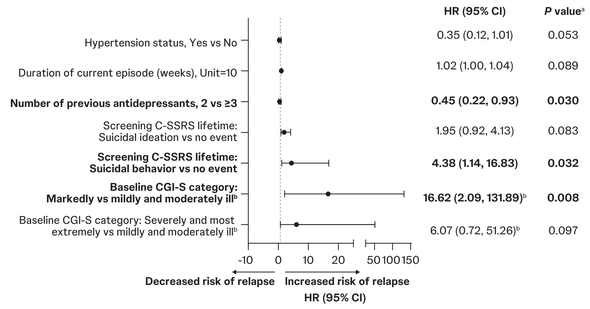
- Potential predictors of relapse were initially screened using univariate Cox proportional hazards models for time to relapse, and variables with nominal significance ($P < 0.3$) were advanced (**Table 2**)
- Potential independent predictors of relapse were identified using a stepwise multivariate Cox proportional hazards model; baseline clinical characteristics associated with relapse included number of prior antidepressant treatments (2 vs ≥3; HR 0.45; 95% CI: 0.22, 0.93; $P = 0.030$), Columbia Suicide Severity Rating Scale score at screening (lifetime history of suicidal behavior vs no event; HR 4.38; 95% CI: 1.14, 16.83; $P = 0.032$), and baseline CGI-S scale category (markedly ill vs mildly and moderately ill; HR 16.62; 95% CI: 2.09, 131.89; $P = 0.008$; only 1 patient experienced relapse in the CGI-S mildly and moderately ill category) (**Figure 2**)

Table 2: Screening of variables associated with increased risk of relapse using univariate Cox proportional hazards models

	Hazard ratio estimate[a] (95% CI)	*P* value[b]
Age, years, Unit = 10	**0.78 (0.59, 1.02)**	**0.074**
Sex, male vs female	1.02 (0.52, 1.99)	0.949
Race		0.862
Black or African American vs White	0.70 (0.17, 2.90)	0.621
Other vs White	0.78 (0.11, 5.74)	0.806
Ethnicity		
Hispanic or Latino vs Not Hispanic or Latino	0.77 (0.27, 2.16)	0.613
Baseline BMI	1.00 (0.95, 1.06)	0.995
Hypertension status		
Yes vs no	**0.51 (0.20, 1.32)**	**0.166**
Employment status		0.528
Unemployed vs employed	1.00 (0.47, 2.14)	0.998
Other vs employed	**0.55 (0.19, 1.58)**	**0.266**
Age when diagnosed with MDD (years), Unit = 10	**0.77 (0.58, 1.03)**	**0.076**
Duration of current episode (weeks), Unit = 10	**1.01 (1.00, 1.03)**	**0.129**
Number of previous antidepressants		
2 vs ≥3	**0.48 (0.25, 0.93)**	**0.031**
Class of OAD		
SNRI vs SSRI	**0.53 (0.28, 1.00)**	**0.051**
OAD		
Escitalopram vs duloxetine	**2.74 (1.13, 6.65)**	**0.026**
Sertraline vs duloxetine	**2.30 (0.92, 5.72)**	**0.074**
Venlafaxine extended-release vs duloxetine	**1.99 (0.86, 4.61)**	**0.106**
Screening C-SSRS, lifetime		**0.122**
Suicidal ideation vs no event	**2.11 (1.03, 4.35)**	**0.042**
Suicidal behavior vs no event	1.53 (0.46, 5.14)	0.490
Screening C-SSRS, past 6 or 12 months		
Suicidal ideation and behavior vs no event	1.37 (0.60, 3.12)	0.459
Screening IDS-30 total score, Unit = 10	0.81 (0.52, 1.27)	0.363
Baseline MADRS total score, Unit = 10	0.81 (0.41, 1.58)	0.528
Baseline PHQ-9 total score	1.02 (0.92, 1.12)	0.736
Baseline CGI-S	1.06 (0.70, 1.61)	0.774
Baseline CGI-S category		**0.023**
Markedly vs mildly and moderately ill	**9.75 (1.33, 71.58)**	**0.025**
Severely and most extremely vs mildly and moderately ill	4.66 (0.57, 37.91)	0.150

BMI, body mass index; CGI-S, Clinical Global Impression-Severity; C-SSRS, Columbia Suicide Severity Rating Scale; IDS-30, 30-item Inventory of Depressive Symptomatology; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; OAD, oral antidepressant; PHQ-9, 9-item Patient Health Questionnaire; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.
[a]A hazard ratio of >1 represents an increased risk of relapse, <1 represents a decreased risk of relapse.
[b]Variables with a nominal significance ($P < 0.3$) are in bold font.

Figure 2: Variables associated with increased risk of relapse using a stepwise multivariate Cox proportional hazards model



CGI-S, Clinical Global Impression-Severity; C-SSRS, Columbia Suicide Severity Rating Scale; HR, hazard ratio.
[a]Variables with nominal significance ($P < 0.05$) are in bold font.
[b]Only 1 patient experienced relapse in the CGI-S mildly and moderately ill category.

Key Takeaways

In this post hoc analysis, potential predictors of relapse for patients who discontinued treatment with esketamine nasal spray included having ≥3 prior antidepressant treatments, a lifetime history of suicidal behavior, or being categorized as "markedly ill" by CGI-S

These results support continued esketamine nasal spray treatment or more vigilant monitoring strategies for patients with these baseline clinical characteristics who may have a higher risk of relapse

Limitations

The generalizability of these findings may be limited by the exclusion of patients with significant psychiatric or medical comorbidities and substance dependence

This analysis was not prespecified, and small sample sizes may limit the statistical power and interpretation of the results

The use of univariate screening followed by multivariate modeling (without multiplicity adjustment) may subject data to overfitting and selection bias

Conclusion

This post hoc analysis identified baseline clinical characteristics that may be associated with higher risk of relapse after discontinuing esketamine nasal spray in patients with treatment-resistant depression who had previously achieved stable remission

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