

# Plain Language Summary

## 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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### What do these results mean for individuals with treatment-resistant depression (TRD)?

Patients with certain baseline factors (more severe illness and more treatment-resistant disease) may be at higher risk of relapse after stopping esketamine, suggesting potential benefit of continued treatment or closer monitoring in higher-risk individuals.

### Purpose of the study

To identify potential baseline clinical and demographic factors associated with relapse risk in patients with TRD who discontinued esketamine after achieving stable remission in the SUSTAIN-1 trial.



- **Treatment-resistant depression:** major depressive disorder that has not adequately responded to at least two antidepressants.
- **Esketamine:** A nasal spray approved for treatment-resistant depression in adults.
- **Clinical Global Impressions-Severity of illness:** 7-point scale assessing how mentally ill the patient is at the time of evaluation by a clinician.

### How was the study conducted?

This post hoc analysis evaluated 45 baseline factors in patients who were randomized to placebo + oral antidepressant after achieving stable remission on esketamine.

### What is the design of the study?

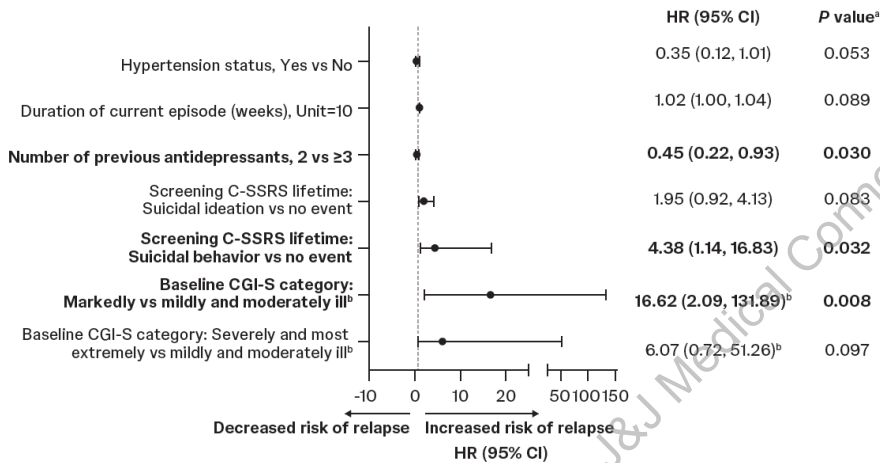
SUSTAIN-1 was a phase 3, randomized withdrawal trial. Patients received esketamine + oral antidepressant

for 16 weeks; remitters were randomized to continue treatment or switch to placebo + oral antidepressant during maintenance.

### What were the results of the study?

Relapse occurred more frequently after discontinuation (45.3%) of esketamine vs continued treatment (26.7%). Predictors of relapse included  $\geq 3$  prior antidepressants, history of suicidal behavior, and higher baseline illness severity (Clinical Global Impressions-Severity of illness, CGI-S).

Potential independent predictors of relapse using stepwise multivariate Cox proportional hazards model:



CGI-S, Clinical Global Impression-Severity; C-SSRS, Columbia Suicide Severity Rating Scale; HR, hazard ratio.

<sup>a</sup>Variables with nominal significance ( $P < 0.05$ ) are in bold font.

<sup>b</sup>Only 1 patient experienced relapse in the CGI-S mildly and moderately ill category.

### What were the limitations of the analysis?

Analysis is limited to the subset who achieved stable remission and then discontinued esketamine. Predictors identified may not generalize to all TRD patients or to those who never reached stable remission. The sample size was relatively small, limiting statistical power. Lack of multiplicity adjustment and stepwise modeling may introduce overfitting. Baseline factors available in the trial data may omit important clinical, biological, social, or treatment-adherence variables that influence relapse risk. For instance, generalizability is limited due to exclusion of patients with significant comorbidities or substance use disorders.