Effect of Benzodiazepines on Esketamine Nasal Spray for Treating Patients with Major Depressive Disorder with Active Suicidal Ideation and Intent

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INTRODUCTION

The American Psychiatric Association Task Force on Treatment-Resistant Depression (TRD) recommended 14 days of hospitalization for suicide attempts with imminent risk of suicide or severe ideation. 

METHODS

Study Overview

The ASPIRE studies were 3 randomized, placebo-controlled, double-blind, phase 3 studies conducted between June 2017 and April 2019 in North America, Europe, and South America. 

Eligible patients were randomized to either esketamine or placebo in the absence of current or recent benzodiazepine use, including sublingual. 

Patients were excluded if they had a history of substainal exposure to benzodiazepine (>1 mg/kg/day) during the study, or if they were using >1 mg/day of benzodiazepine during screening and randomization. 

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Efficacy and Safety Assessments

Efficacy

Esketamine was administered as a single intranasal dose at the start of an inpatient hospitalization. 

Safety

Clinical assessments were performed pre-dose and 40 minutes and 1.5 hours post-dose on dosing days 1 and 2. 

Statistical Analyses

Statistical outcomes analyses included (vs. placebo): 

• Dissociative symptoms were assessed pre-dose and 40 minutes and 1.5 hours post-dose on dosing days 1 and 2. 

Analysis Set

All randomized patients (Intention-to-Treat cohort) were evaluated for safety, and the on-treatment efficacy population for efficacy. 

Limitations

• The ASPIRE studies did not allow concurrent benzdiazepine use for 8 hours of dosing during and 48 hours after dosing. 

• The analyses reported herein are confined to effects following the first dose of esketamine, informing the effect of esketamine on the efficacy or safety of benzdiazepines if used concomitantly. 

• The impact of previous nouncement is on the long-term efficacy of esketamine nasal spray. 

DISCUSSION AND CONCLUSIONS

• Findings from the ASPIRE studies support the efficacy and safety of esketamine nasal spray for major depressive disorder with active suicidal ideation and intent. 

• Esketamine nasal spray, given as a single intranasal dose, reduced suicidal ideation and intent and resulted in a statistically significant reduction in the percentage of patients that met criteria for treatment-refractory depression, as compared to placebo. 

• Antidepressant monotherapy (Recommended 5 days)

• Current DSM-5 diagnosis of bipolar (or related disorders), obsessive compulsive disorder, antisocial personality disorder, drug use disorder, or serious psychiatric disorder (e.g., schizophrenia or schizoaffective disorder). 

• Montgomery–Åsberg Depression Rating Scale (MADRS) total score of >28 predose on day 1.

• Standard-of-Care antidepressant treatment (Recommended 14 days)

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