Title: Outlier Safety Data with Esketamine Nasal Spray Plus an Oral Antidepressant in Treatment-Resistant Depression (SUSTAIN-2 Study)

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Methodological Question Being Addressed: What is the nature of outlier data observed for identified safety parameters during long-term treatment with esketamine nasal spray (ESK) in patients with treatment-resistant depression (TRD)?

Introduction: ESK, a novel glutamate modulator, is currently being developed for TRD. Given the unique safety profile, clinicians and patients are interested in knowing what to expect following ESK administration on dosing days, particularly effects on blood pressure, dissociation, sedation, and potential for respiratory depression.

Methods: Based on data from an open-label, long-term, multicenter, phase 3 study (NCT02497287, SUSTAIN-2) that evaluated the safety and tolerability of ESK plus a newly initiated oral antidepressant for up to 1 year, this post hoc analysis assessed specific safety parameters occurring on dosing days in patients over the initial 4-week induction phase as well as during the subsequent (up to 48-week) optimization phase/maintenance phase (OP/MP). Clinically significant treatment-emergent events of interest were: blood pressure increase (vital sign data and/or adverse event [AE]), severe dissociative symptoms (AE data/ Clinician-Administered Assessment of Dissociative States Scale [CADSS]), deep sedation (using the Modified Observer's Assessment of

Alertness/Sedation [MOAA/S] and/or AE) and potential for respiratory depression. For each event, frequency of occurrence, rates of discontinuation, hospitalizations, or related serious AEs (SAEs) and use of concomitant medications will be presented.

Results: During the 4-week induction phase (n=779), 18 (2.3%) patients met criteria for transient treatment-emergent hypertension (ie, postdose SBP ≥180 mm Hg and or DBP ≥110 mm Hg). Four patients (0.5%) discontinued study medication because of increased blood pressure/hypertension; no patient was hospitalized; and no deaths or SAEs occurred due to these events. During the same period, 11 (1.4%) patients reported severe dissociation, 5 (0.6%) patients discontinued study medication, and no patients were hospitalized because of dissociation. Based on the MOAA/S, 4 (0.5%) patients had a score of 0 or 1 (corresponding to deep sedation) during the induction phase, 2 (0.3%) patients discontinued because of sedation, and 1 (0.1%) patient discontinued because of depressed consciousness. No patients were hospitalized for these events, and there were no cases of respiratory depression.

During the 48-week OP/MP phase (n=603), 18 (3.0%) patients met criteria for transient treatment-emergent hypertension, 3 (0.5%) discontinued study medication because of increased blood pressure/hypertension, and no patients were hospitalized. Four patients (0.7%) had severe dissociation, and no patients discontinued study medication or were hospitalized because of dissociation. Based on the MOAA/S, 1 (0.2%) patient had deep sedation at one of the dosing visits, and no patients discontinued study medication or were hospitalized because of sedation. There were no cases of respiratory depression

during this phase. One subject, who had an SAE of delirium, experienced transient deep sedation without reactivity to pain; MOAA/S was not completed.

Conclusions: In SUSTAIN-2, clinically significant increased blood pressure, severe dissociation and deep sedation were relatively uncommon; one patient was hospitalized (delirium) and very few required treatment discontinuation for these events. There were no cases of respiratory depression. These data support the tolerability of long term intermittent esketamine dosing in patients with TRD.

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