The Relationship Between Adverse Event Reporting and Events Identified by Scales/Vital Sign Measurement With Esketamine Nasal Spray Plus an Oral Antidepressant in Treatment-Resistant Depression (SUSTAIN-2 Study)

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INTRODUCTION

- There is a significant unmet need for more effective treatments for the rapid relief of symptoms of depression, especially in patients with treatment-resistant depression (TRD)[1,2]
- Esketamine (S-ketamine, the S enantiomer of ketamine) nasal spray (ESK), a novel glutamate modulator, is currently under development for the treatment of TRD[3-5]
- Given the unique safety profile of ESK, clinicians and patients are interested in knowing what to expect following administration on dosing days
  - We sought to examine the incidence of adverse events (AES) occurring after ESK treatment and their outcome, particularly those considered "outliers" (ie, treatment-emergent acute hypertension, severe dissociation, and severe sedation)
- Comparison of results from specific scales used in clinical trials with those of spontaneous AE reporting may better characterize key aspects of the safety profile of ESK

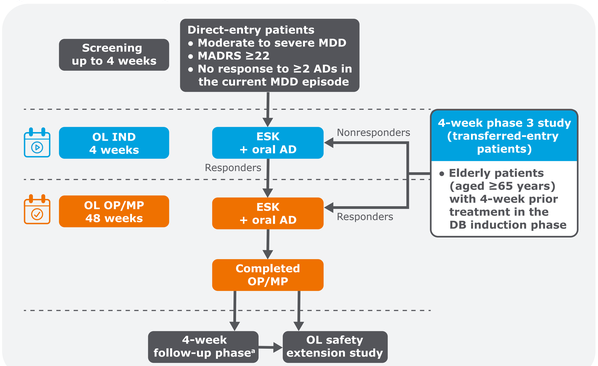
OBJECTIVE

- To determine whether spontaneously reported AEs track with those identified with specific scales or vital signs data for identified safety parameters during long-term treatment with ESK in patients with TRD

METHODS

- SUSTAIN-2 (NCT02497287) is an open-label, long-term, multicenter, phase 3 study that evaluated the safety and tolerability of ESK plus a newly initiated oral antidepressant for up to 1 year in patients with TRD[6] (**Figure 1**)

Figure 1. Study Design



AD, antidepressant; DB, double-blind; ESK, esketamine nasal spray; IND, induction phase; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, major depressive disorder; OL, open-label; OP/MP, optimization phase/maintenance phase.
[a]Nonresponders from the IND, discontinued patients from both treatment phases, or patients who completed the OP/MP entered the follow-up phase.

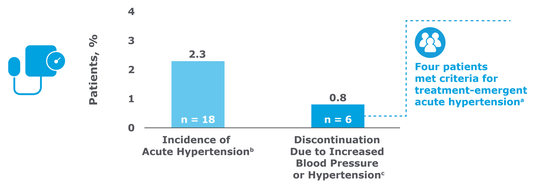
- This post hoc analysis assessed specific safety parameters that were evaluated on dosing days in patients over the initial 4-week induction phase (twice-weekly ESK dosing) as well as during the subsequent (up to 48-week) optimization phase/maintenance phase (OP/MP; once-weekly or every-other-week ESK dosing)
- Clinically significant treatment-emergent events of interest were
  - Acute hypertension (systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥110 mm Hg was identified by vital signs data) and discontinuations due to AEs of increased blood pressure or hypertension
  - Severe dissociative symptoms (identified by AE data/Clinician-Administered Assessment of Dissociative States Scale [CADSS])
  - Severe sedation (identified using the Modified Observer's Assessment of Alertness/Sedation [MOAA/S] scores 0 or 1 and/or AE data)
- The CADSS was administered on each intranasal dosing day predose and at 40 minutes and 1.5 hours postdose. The scale consists of 23 subjective items (total score range, 0-92)[7]
- The association of these events reported as AEs versus those identified by scales/vital signs data are presented descriptively
- Associated discontinuation status, incidence of serious AEs (SAEs), cardiac treatment-emergent AEs (TEAEs) and SAEs, and use of concomitant medications during both the induction and the OP/MP phases of the study are also presented descriptively

RESULTS

Induction Phase (n = 779)

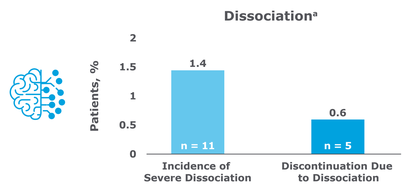
- During the induction phase, the incidence of treatment-emergent acute hypertension (study defined), severe dissociation, and severe sedation was relatively low. Few discontinuations occurred, and no patients were hospitalized for these events
- For the SAEs of dissociation in the induction phase, the CADSS total score ranged from 12 to 47
- There was no evidence of associated respiratory depression in any of the cases of severe sedation

Treatment-Emergent Blood Pressure Changes[a]



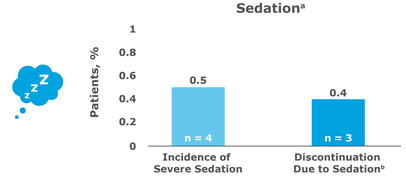
[a]Systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥110 mm Hg. Per protocol, prior to intranasal dosing, patients aged <65 years were required to have a blood pressure measurement of ≤140/90 mm Hg; those aged ≥65 years were required to have a blood pressure measurement of ≤150/90 mm Hg. Individuals with controlled hypertension were permitted to participate in the study.
[b]Based on vital signs data.
[c]Based on adverse event data.

Dissociation[a]



[a]Based on adverse event data.

Sedation[a]

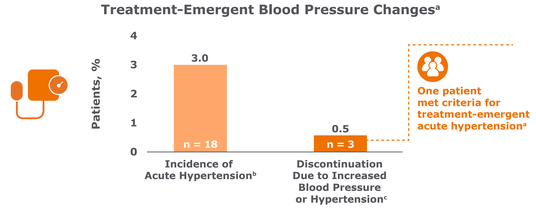


[a]Severe sedation was defined as an MOAA/S score of 0 or 1. Scores on the MOAA/S correlate with the levels of sedation defined by the American Society of Anesthesiologists (ASA) continuum. MOAA/S scores range from 0 = no response to painful stimulus (corresponding to ASA continuum for general anesthesia) to 5 = readily responds to name spoken in normal tone (awake; corresponding to ASA continuum for minimal sedation).
[b]Treatment-emergent adverse event leading to discontinuation; sedation, 2 patients (0.3%); depressed consciousness, 1 patient (0.1%).

Optimization Phase/Maintenance Phase (n = 603)

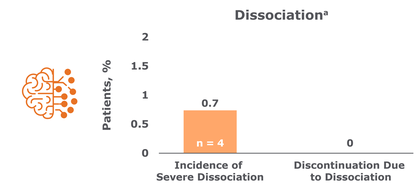
- During the OP/MP, the incidence of treatment-emergent acute hypertension, severe dissociation, and severe sedation was relatively low and there were few discontinuations
- One participant had an SAE of delirium 35 minutes after ESK (56 mg) dosing that led to discontinuation. The patient had involuntary movements lasting a few minutes, was nonresponsive to pain/light for about 10 minutes, and then had a 30-second period of apnea, **which did not require resuscitation**. The patient was hospitalized; MOAA/S was not completed
- For the SAEs of dissociation, the CADSS total score ranged from 16 to 24
- No cases of respiratory depression occurred

Treatment-Emergent Blood Pressure Changes[a]



[a]Systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥110 mm Hg.
[b]Based on vital signs data.
[c]Based on adverse event data.

Dissociation[a]

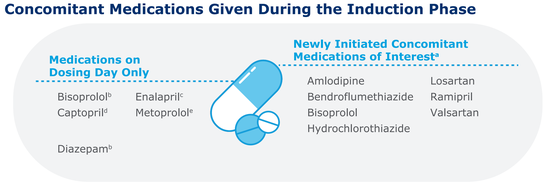


[a]Based on adverse event data.

Sedation[a]

[a]Severe sedation was defined as an MOAA/S score of 0 or 1. Scores on the MOAA/S correlate with the levels of sedation defined by the American Society of Anesthesiologists (ASA) continuum. MOAA/S scores range from 0 = no response to painful stimulus (corresponding to ASA continuum for general anesthesia) to 5 = readily responds to name spoken in normal tone (awake; corresponding to ASA continuum for minimal sedation).

Concomitant Medications Given During the Induction Phase



[a]Each administered to a single patient, with the exception of hydroclorothiazide and amlodipine, which were given to the same patient; bendroflumethiazine was given to 2 patients.
[b]Given to 1 patient, one time.
[c]Given to 2 patients, one time each.
[d]Given to 4 patients (2 patients, 3 times each; 2 patients, one time).
[e]Given to 1 patient, 3 times.

Summary of Cardiovascular TEAEs and SAEs

TEAE (n = 3)

- **Events**
  Angina pectoris, coronary artery disease, ventricular arrhythmia, arrhythmia
- **Description**
  - All 4 events were considered related to ESK
  - The participants with angina pectoris, coronary artery disease, and arrhythmia discontinued the study but recovered from the events
  - All 3 patients had a prior history of hypertension, but otherwise none had a prior medical history of cardiovascular disease
  - One participant with ventricular arrhythmia (moderate intensity) had multiple premature ventricular complexes observed in the echocardiography conducted after ESK administration
    - Received therapy with amiodarone, but continued to have the arrhythmia after subsequent ESK doses, and discontinued
    - Had no prior cardiovascular history
    - Had obstructive sleep apnea that was controlled with continuous positive airway pressure

SAE (n = 1)

- **Event**
  Acute cardiac failure
- **Description**
  - 60-year-old man with a medical history of hypertension, right lower limb vein surgery
    - Did not report prior cardiac AEs
    - Tolerated ESK treatment (56 mg) and sertraline (150 mg) well
    - Had normal BP during the study
  - Treated with candesartan cilexetil; died on study day 113, 5 days after his last dose
  - Death was due to acute cardiac and respiratory failure; both considered doubtfully related to ESK treatment

BP, blood pressure; ESK, esketamine nasal spray; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- **In SUSTAIN-2, clinically significant increased blood pressure, severe dissociation, and severe sedation were relatively uncommon and very few patients discontinued treatment because of these events**
- **Use of scales or observed vital signs data in addition to spontaneous AE reporting helps better identify outliers and safety parameters and evaluate the tolerability of long-term intermittent esketamine nasal spray dosing in patients with treatment-resistant depression**

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