Long-Term Safety of Esketamine Nasal Spray in Patients With Treatment-Resistant Depression: Interim Results of the SUSTAIN-3 Study

Session I, No. 27

Naim Zaki, MD[1*], Abigail I. Nash, MD, PhD[2], Nancy Chen, PhD[1], Rosanne Lane, MAS[1], Qiaoyi Zhang, MD, PhD[3], Randall L. Morrison, PhD[1], Tricia J. Lopena, PharmD[2], Gerard Sanacora, MD, PhD[4], Maju Mathews, MD[1], Jaskaran B. Singh, MD[1†], Vanina Popova, MD[5]

Janssen Research & Development, LLC, Titusville, NJ, US[1]; Janssen Scientific Affairs, LLC, Titusville, NJ, US[2]; Janssen Research & Development, LLC, Pennington, NJ, US[3]; Yale University School of Medicine, New Haven, CT, US[4]; Janssen Research & Development, Beerse, Belgium[5]

*Presenting Author
†Currently employed by Neurocrine Biosciences, San Diego, CA US

INTRODUCTION

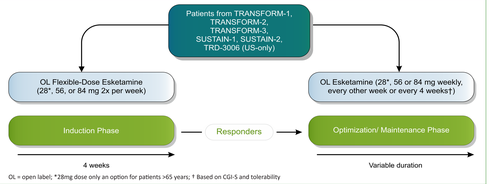
- Esketamine nasal spray, in conjunction with a newly-initiated oral antidepressant, is approved for treatment-resistant depression (TRD),[1,2] largely based on results of 5 phase 3 studies – TRANSFORM-1, TRANSFORM-2, TRANSFORM-3, SUSTAIN-1, and SUSTAIN-2.
- TRD is a chronic condition that is associated with higher rates of relapse even after initial improvement compared to non-treatment-resistant major depressive disorder (MDD).[3]
- SUSTAIN-3 is being conducted to confirm the long-term safety (and efficacy) of individualized, intermittently-dosed esketamine in conjunction with an oral antidepressant in patients with TRD.

METHODS

Study Design

- SUSTAIN-3 is an ongoing, phase 3, open-label study into which adults (≥18 years) who previously participated in 1 of 6 phase 3, "parent" studies of esketamine are enrolled (Figure 1). Each parent study enrolled patients with recurrent or single-episode (≥2 years) MDD (per DSM-5 criteria) without psychotic features and who met the definition of TRD.
- Patients enter into either the 4-week induction phase or the long-term optimization/maintenance phase of SUSTAIN-3 based on their status at the end of the parent study (Figure 1).
- In the induction phase, patients self-administer (under supervision) esketamine (28 mg [starting dose age ≥65 years], 56 mg, or 84 mg) as a flexible dose, twice-weekly for 4 weeks. In the optimization/maintenance phase, patients receive interval dosing of esketamine individualized to the severity of their depression.

Figure 1. SUSTAIN-3 Study Design



OL = open label; *28mg dose only an option for patients >65 years; † Based on CGI-S and tolerability

Evaluations of Safety

- Adverse events, including adverse events of clinical interest (i.e., dissociation, sedation, increased blood pressure, interstitial cystitis), are being monitored throughout the study.
- Cognition was assessed using the Cogstate computerized test battery and the Hopkins Verbal Learning Test-Revised (HVLT-R). Assessments were made at baseline and day 28 during the induction phase, and week 3, week 16 and subsequently every 12 weeks during the optimization/maintenance phase.

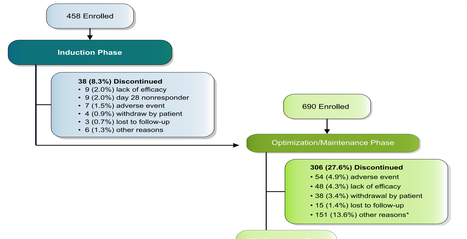
Statistical Methods

- The number (percentage) of subjects with adverse events (AEs), including treatment-emergent adverse events (TEAEs) of clinical interest, serious AEs (SAEs), and TEAEs that led to nasal spray study drug withdrawal are summarized by preferred term.
- Descriptive statistics for values and changes from baseline were provided at each scheduled time point for cognitive testing.

RESULTS

- As of the interim data cutoff (20 May 2020; ~4 years from study initiation), SUSTAIN-3 has enrolled 1,148 adult patients with TRD. Overall, 458 patients were enrolled into the induction phase, 38 of whom discontinued and 420 continued to the optimization/maintenance phase. In addition, 690 other patients were enrolled directly into the optimization/maintenance phase (Figure 2).
- Of 1,110 patients who participated in the optimization/maintenance phase, 306 (27.6%) discontinued the study, primarily due to AEs (n=54), lack of efficacy (n=48), and other reasons (n=135; e.g., symptom improvement, scheduling/logistical conflicts, etc.).
- At the time of interim data cutoff, ~4 years from study initiation, 804 patients were ongoing in the study.

Figure 2. SUSTAIN-3 Patient Disposition



*e.g. Symptom improvement, scheduling/logistical conflicts, moving to another state, starting new job, patient's choice, protocol violation, pregnancy, death, noncompliance with study drug.

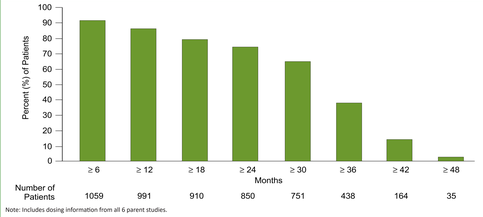
- Demographic characteristics of the study sample are shown in Table 1.

Table 1. Demographic and Clinical Characteristics

	Esketamine Nasal Spray N=1148
Age (years)	
N	1148
Mean (SD)	49.6 (12.28)
Sex, n (%)	
N	1148
Male	384 (33.4%)
Female	764 (66.6%)
Race, n (%)	
N	1147
Asian	45 (3.9%)
Black or African American	45 (3.9%)
White	996 (86.8%)
Other	61 (5.3%)
Employment status, n (%)	
N	1148
Any type of employment	693 (60.4%)
Any type of unemployment	281 (24.5%)
Other	174 (15.2%)
Hypertension status, n (%)	
N	1148
Yes	271 (23.6%)
No	877 (76.4%)
Region, n (%)	
N	1148
Europe	486 (42.3%)
North America	343 (29.9%)
Other	319 (27.8%)

- Median exposure to esketamine nasal spray in SUSTAIN-3 was 31.7 months (35.8 months including exposure in the preceding parent study). The distribution of exposure is shown in Figure 3.

Figure 3. Duration of Exposure



Note: Includes dosing information from all 6 parent studies.

Treatment-Emergent Adverse Events

- The 5 most common TEAEs were dissociation, dizziness, nausea, vertigo, and dysgeusia during the induction phase and headache, dizziness, nausea, dissociation, and somnolence in the optimization/maintenance phase (Table 2).

Table 2. Most Frequently Reported Adverse Events[a]

	Esketamine Nasal Spray
Induction Phase (N=458)	
dissociation	97 (21.2%)
dizziness	94 (20.5%)
nausea	81 (17.7%)
vertigo	77 (16.8%)
dysgeusia (bad/altered taste)	76 (16.6%)
headache	69 (15.1%)
Optimization/Maintenance Phase (N=1110)	
headache	346 (31.2%)
dizziness	331 (29.8%)
nausea	312 (28.1%)
dissociation	248 (22.3%)
somnolence	242 (21.8%)
nasopharyngitis	239 (21.5%)
dysgeusia	206 (18.6%)
vertigo	186 (16.8%)
anxiety	160 (14.4%)
back pain	159 (14.3%)
vomiting	151 (13.6%)
diarrhea	137 (12.3%)
increased blood pressure	134 (12.1%)
urinary tract infection	134 (12.1%)
upper respiratory tract infection	125 (11.3%)
blurred vision	112 (10.1%)

a. ≥10% of patients.

Dissociation

- Dissociation included reports of feeling disconnected from oneself and/or one's thoughts, feelings, space and time.
- Overall, dissociation was reported in 23.4% of patients; 21.2% in the induction phase and 22.3% in the optimization/maintenance phase.
- Few patients (0.6%) required treatment with concomitant medication(s) for dissociation.
- There were no SAEs of dissociation.
- Almost all (99.5%) TEAEs of dissociation occurred and resolved on the day of dosing. Very few patients (0.3%) experienced an TEAE of dissociation that led to withdrawal of study drug.

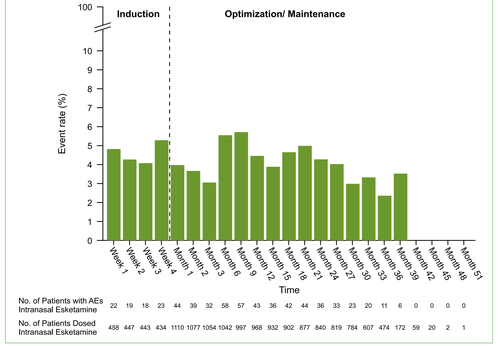
Sedation

- Overall, sedation was reported in 7.7% of patients; 5.5% in the induction phase and 7.0% in the optimization/maintenance phase.
- The majority (99.4%) of sedation events occurred on a dosing day and resolved the same day.
- There were no SAEs of sedation, or TEAEs of sedation that led to withdrawal of study drug.

Increased Blood Pressure

- Overall, 16.6% of patients experienced a TEAE(s) related to increased BP.

Figure 4. Treatment-Emergent Increased Blood Pressure Events Over Time



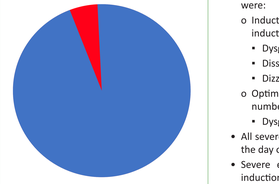
- Most (>95%) BP events occurred and resolved on the day of dosing.
- One (0.1%) patient experienced a "hypertensive emergency", which occurred and resolved on the day of dosing.

Interstitial Cystitis

- There have been no cases of treatment-related interstitial/ulcerative cystitis.
- TEAEs of cystitis were mostly of mild severity, transient and self-limiting, and considered to be of infectious etiology (i.e., urinary tract infection).
- Urinary tract infections were reported in 139 (12.1%) patients.
  - For context, in a health claims database we found 14.4% of patients with TRD were diagnosed with urinary tract infections in the year prior to the diagnosis of TRD.

Severity of TEAEs

Figure 5. Severity of Treatment-Emergent Adverse Events



- Most (95.4%) TEAEs were mild or moderate in severity (Figure 5).
- Among patients having severe events, the most common were:
  - Induction Phase (n=458 total number of patients induction phase)
    - Dysgeusia – 2.6%
    - Dissociation – 2.0%
    - Dizziness – 2.0%
  - Optimization/Maintenance Phase (n=1,110 total number of patients optimization/maintenance phase)
    - Dysgeusia – 2.3%
- All severe TEAEs of dysgeusia occurred and resolved on the day of dosing.
- Severe events of dissociation occurred only in the induction phase and generally resolved within 90 minutes, and rarely required medication.

Serious Adverse Events

- SAEs were reported for 13.7% of patients.
- The only SAE reported in >1% of patients was depression (1.2% of patients).
- Investigators considered the majority (98.8%) of SAEs to be doubtfully or not related to esketamine.
- There were 4 (0.3%) deaths, none considered by the investigator as related to esketamine:
  - Suicide: 48 yo male, day 26 of induction phase, 4 days after last dose of esketamine
  - Multiple injuries (bike accident): 59 yo male, day 364 of optimization/maintenance phase, 6 days after last dose of esketamine
  - Myocardial infarction: 73 yo female, day 321 of optimization/maintenance phase, 6 days after last dose of esketamine
  - COVID-19 pneumonia: 66 yo male, day 927 of optimization/maintenance phase, 13 days after last dose of esketamine

TEAEs Leading to Discontinuation of Esketamine

- Of the 1,148 patients who began the study, with some in treatment for long as 48 months, 61 (5.3%,) discontinued study drug due to ≥1 adverse event.
- The most common adverse events leading to discontinuation of esketamine in SUSTAIN-3 are summarized in Table 3.

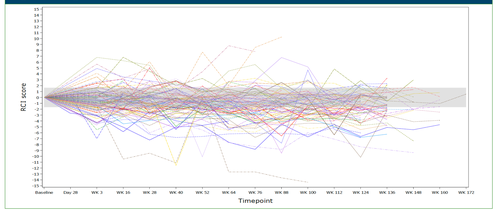
Table 3. Treatment-Emergent Adverse Events Leading to Discontinuation of ≥2 Esketamine-Treated Patients (Induction Plus Optimization/Maintenance Phases)

	Esketamine Nasal Spray N=1148
blood pressure increased	6 (0.5%)
depression	4 (0.3%)
dissociation	4 (0.3%)
anxiety	3 (0.3%)
major depression	3 (0.3%)
mania	3 (0.3%)
fatigue	2 (0.2%)
suicidal ideation	2 (0.2%)

Cognition

- Group mean performance on each of the cognitive tests, at visits from baseline (n=1138) to Week 148 (n=130), generally demonstrated either a slight improvement or no change from baseline.
- Results by patient age:
  - Patients <65 years old: no evidence of any negative cognitive effects (baseline n=963, Week 148 n=114)
  - Patients ≥65 years of age (baseline n=119, Week 148 n=16)
    - Slowing of simple and choice Reaction Time (Detection and Identification tests) was observed relative to baseline; however, there was considerable intraindividual variability (IIV) over time as assessed by reaction time (RT) trajectories (e.g., Figure 6).
    - Performance on all tests of higher cognitive function (visual learning, working memory, executive function, verbal learning, delayed verbal memory, and recognition memory) remained stable or slightly improved.

Figure 6. Spaghetti Plots by Patient for Simple Reaction Time in Patients Aged ≥65 Years



DISCUSSION AND LIMITATIONS

- The clinical meaningfulness of RT slowing, or whether slowing is associated with esketamine treatment, cannot be determined. However, both slowing of RT/processing speed and increased IIV of RT/processing speed have been observed in other longitudinal trials in patients aged ≥65, including a maintenance treatment trial in patients with MDD.[4]
- This is an open-label study with no comparator group.
- The generalizability of the study findings may be limited by potential bias related to which patients chose to continue (or not continue) from the parent study into this study and the exclusion of participants with significant psychiatric or medical co-morbidities or substance dependence.
- Sample size decreases at later time points in the trial may have implications for representativeness and/or generalizability of findings.

CONCLUSIONS

- The safety profile of esketamine with continued intermittent dosing of up to 48 months was consistent with the established safety profile in patients exposed to esketamine for up to one year.[1,2]
- Most clinically relevant safety findings, including TEAEs, involved the psychiatric and CNS body systems, were mild or moderate in intensity, and were transient.
- Cognition remained stable or showed a trend for small averaged improvement among patients during the induction and optimization/maintenance phases, with the exception of a slight slowing of RT in patients aged ≥65 years. However, these patients also exhibited considerable IIV in RT trajectories.
- Long-term exposure to esketamine (~3 years) showed no new or unexpected safety signals.

References: 1. Spravato™ (esketamine) nasal spray Prescribing Information. © 2020 Janssen Pharmaceutical Companies; 2. Spravato (esketamine) Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/spravato-epar-product-information_en.pdf. Accessed 29 March 2021; 3. APA. Practice Guideline for the Treatment of Patients With Major Depressive Disorder, Third Edition. https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf; 4. Reynolds CF, et al. Arch Gen Psychiatry. 2011;68(1):51-60.

Trial Registrations: NCT02417064, NCT02418585, NCT02493868, NCT02497287, NCT02422186, NCT03434041

Acknowledgements: Dr. Sandra Norris (Norris Communications Group, LLC) provided writing assistance and Dr. Ellen Baum (Janssen Research & Development, LLC) provided editorial support for this poster. Authors also thank the study participants, without whom this study would never have been accomplished and all the investigators for their participation in this study.

Disclosures: Drs. Zaki, Nash, Chen, Zhang, Morrison, Lopena, Mathews, and Popova and Ms. Lane are employees of Janssen Research & Development, LLC or Janssen Scientific Affairs, as was Dr. Singh at the time this work was conducted (currently employed by Neurocrine Biosciences, San Diego, CA), and all are stockholders of Johnson & Johnson. In the last 12 months Dr. Sanacora has provided consulting services to Allergan, Axsome Therapeutics, Biohaven Pharmaceuticals, Bristol-Myers Squibb, Clexio Biosciences, Denovo Biopharma, EMA Wellness, Engrail, Gilgamesh, Intra-Cellular Therapies, Janssen, Lundbeck, Merck, Navitor Pharmaceuticals, Neurocrine, Novartis, Noven Pharmaceuticals, Perception Neuroscience, Praxis, Sage Pharmaceuticals, Seelos Pharmaceuticals, and XW Labs. He has received funds for contracted research from Janssen Pharmaceuticals, Merck, and Usona Institute. He is holds equity in Biohaven Pharmaceuticals and has received royalties paid from patent licenses with Biohaven Pharmaceuticals. His employer, Yale University, has a financial relationship with Janssen Pharmaceuticals and may receive financial benefits from this relationship.

Supported by funding from Janssen Research & Development, LLC, Titusville, NJ, USA

Presented at 2021 Annual Meeting of the American Society of Clinical Psychopharmacology (ASCP), June 2, 2021, Virtual