Esketamine Nasal Spray Plus Oral Antidepressant in Patients With Treatment-Resistant Depression:

Assessment of Long-Term Safety in a Phase 3, Open-Label Study (SUSTAIN-2)

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ABSTRACT

Objective: To evaluate long-term safety and efficacy of esketamine nasal spray plus a new oral antidepressant (OAD) in patients with treatment-resistant depression (TRD).

Methods: This phase 3, open-label, multicenter, long-term (up to 1 year) study was conducted between October 2015 and October 2017. Patients (≥ 18 years) with TRD (*DSM-5* diagnosis of major depressive disorder and nonresponse to ≥ 2 OAD treatments) were enrolled directly or transferred from a short-term study (patients aged ≥ 65 years). Esketamine nasal spray (28-mg, 56-mg, or 84-mg) plus new OAD was administered twice a week in a 4-week induction (IND) phase and weekly or every-other-week for patients who were responders and entered a 48-week optimization/maintenance (OP/MAINT) phase.

Results: Of 802 enrolled patients, 86.2% were direct-entry and 13.8% were transferred-entry; 580 (74.5%) of 779 patients who entered the IND phase completed the phase, and 150 (24.9%) of 603 who entered the OP/MAINT phase completed the phase. Common treatment-emergent adverse events (TEAEs) were dizziness (32.9%), dissociation (27.6%), nausea (25.1%), and headache (24.9%). Seventy-six patients (9.5%) discontinued esketamine due to TEAEs. Fifty-five patients (6.9%) experienced serious TEAEs. Most TEAEs occurred on dosing days, were mild or moderate in severity, and resolved on the same day. Two deaths were reported; neither was considered related to esketamine. Cognitive performance generally either improved or remained stable postbaseline. There was no case of interstitial cystitis or respiratory depression. Treatment-emergent dissociative symptoms were transient and generally resolved within 1.5 hours postdose. Montgomery-Åsberg Depression Rating Scale total score decreased during the IND phase, and this reduction persisted during the OP/MAINT phase (mean [SD] change from baseline of respective phase to endpoint: IND, −16.4 [8.76]; OP/MAINT, 0.3 [8.12]).

Conclusions: Long-term esketamine nasal spray plus new OAD therapy had a manageable safety profile, and improvements in depression appeared to be sustained in patients with TRD.

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Esketamine, the *S*-enantiomer of ketamine racemate and an *N*-methyl-ᴅ-aspartate receptor antagonist, has been recently approved as a nasal spray administration for the treatment of treatment-resistant depression (TRD).[1–4] Rapid and robust reductions in symptoms of TRD along with manageable tolerability have been observed following intravenous and intranasal administration of esketamine adjunctive to oral antidepressant (OAD) therapy in short-term studies[1,3–5]; however, long-term safety has remained to be elucidated.

Potentially serious safety concerns of long-term, ketamine/esketamine use have been posited following observations of cognitive deficits (spatial memory and pattern recognition), bladder toxicity with interstitial/ulcerative cystitis, hepatotoxicity, and dependence with prolonged, or frequent, recreational long-term use of ketamine 3 times a week or daily.[6–9]

As TRD is a chronic, recurrent condition with an escalating demand for pharmacotherapies that provide sustained benefit, this study aimed to assess the safety, tolerability, and efficacy of esketamine nasal spray plus a new OAD to empirically validate its long-term use in patients with TRD.

Clinical Points
■ Esketamine has shown favorable efficacy and tolerability in short-term studies of patients with treatment-resistant depression (TRD); however, data on its long-term safety have been lacking prior to the current study.
■ Long-term (up to 1 year) treatment with esketamine nasal spray demonstrated acceptable tolerability and an adverse event profile comparable with that of the short-term studies in patients with TRD.

METHODS

Study Design

This open-label (OL), multicenter study was conducted between October 2015 and October 2017 at 114 sites in 21 countries. The study had a 4-week screening phase (direct-entry patients only), a 4-week induction (IND) phase (direct-entry patients and transferred-entry nonresponder patients), an up to 48-week optimization/maintenance (OP/MAINT) phase (all responders from the OL IND phase of the current study and the transferred-entry responders), and a 4-week follow-up phase (for all patients). By design, the study closure was set at the timepoint when the pre-specified esketamine exposure criteria were met (ie, ≥300 patients exposed for 6 months and ≥100 patients exposed for 1 year).

The appropriate ethics body at each site approved the study protocol. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. All patients provided written informed consent before enrollment (SUSTAIN-2; NCT02497287).

Patients

Details of patient eligibility criteria appear at https://clinicaltrials.gov/ct2/show/NCT02497287. Patients entered the study either directly ("direct-entry patients," aged ≥18 years) or after completing the double-blind IND phase of a randomized, 4-week, efficacy study[10] ("short-term study") in patients aged ≥65 years with TRD ("transferred-entry patients"). Transferred-entry patients who were responders (≥50% reduction in Montgomery-Åsberg Depression Rating Scale [MADRS][11] total score) in the short-term study joined the current study in the OP/MAINT phase, while nonresponders joined the IND phase. Eligible patients had DSM-5 diagnosis of recurrent major depressive disorder (MDD) or single episode (≥2 years) MDD without psychotic features, nonresponse to ≥2 OADs (as assessed retrospectively using the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire [ATRQ][12]) in the current depressive episode, and MADRS total score ≥22 at screening (Supplementary Appendix 1).

Treatment

Induction phase. Patients self-administered esketamine nasal spray (200 μL solution [14 mg esketamine/100 μL spray]) twice a week for 4 weeks as a flexible-dose regimen starting at 28 mg (≥65-years) or 56 mg (<65-years) under supervision of a health care provider. Adjustments for subsequent doses (<65-years: 56 or 84 mg; ≥65-years: 28, 56, or 84 mg) were allowed based on efficacy and tolerability per the investigator's clinical judgment. Direct-entry patients simultaneously initiated a new OAD, and transferred nonresponder patients continued the OAD initiated in the short-term study (either duloxetine, escitalopram, sertraline, or venlafaxine extended-release).

Optimization/maintenance phase. During weeks 5–8, responders from the IND phase were administered esketamine once-weekly at the same dose and continued the OAD treatment. Transferred-entry responder patients started a flexible dosing regimen at 28 mg (week 5) with possible dose up-titration (56 mg or 84 mg) allowed through week 8 and continued the OAD initiated in the short-term study. Subsequently, esketamine dosing frequency was driven by an algorithm; treatment regimens were either weekly (if MADRS total score was >12) or every-other-week (if MADRS total score was ≤12), with reevaluation at 4-week intervals.

Esketamine treatment was discontinued in the follow-up phase, and patients were encouraged to continue treatment with OADs if clinically appropriate (see Supplementary Appendix 1).

Safety Assessments

Treatment-emergent adverse events (TEAEs) were monitored throughout the study. Cogstate Computerized Test Battery (Cogstate, Inc; New Haven, Connecticut) included the measures of processing speed (simple reaction time—detection, DET) and choice reaction time (identification, IDN), visual learning and recall (one card learning, OCL), working memory (one back, ONB), and executive function/visuospatial memory and sequencing (Groton Maze Learning Test, GMLT). In addition, episodic memory was evaluated (Hopkins Verbal Learning Test–Revised, HVLT-R[13]). Cognitive assessments were performed at predose. Suicidal ideation and behavior (Columbia–Suicide Severity Rating Scale [C-SSRS][14]), dissociative symptoms (Clinician Administered Dissociative States Scale [CADSS][15]), psychotic and affective symptoms (positive symptom subscale of the Brief Psychiatric Rating Scale [BPRS+][16]), and sedation (Modified Observer's Assessment of Alertness/Sedation [MOAA/S][17]) were assessed longitudinally. Bladder symptoms were monitored using Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS).[18] The 20-item Physician Withdrawal Checklist (PWC-20)[19] was used to assess potential withdrawal symptoms following cessation of esketamine at IND- or OP/MAINT-endpoint and at weeks 1, 2, and 4 of the follow-up phase. Clinical laboratory tests, vital signs assessment, electrocardiogram (ECG), nasal examination, and nasal symptom questionnaire were performed at prespecified timepoints. Respiratory rate and pulse oximetry were monitored with a Masimo Radical-7 Pulse CO-oximeter (Masimo Corporation; Irvine, California) at each dosing session. Per protocol

Figure 1. Study Design and Patient Disposition for the SUSTAIN-2 Study
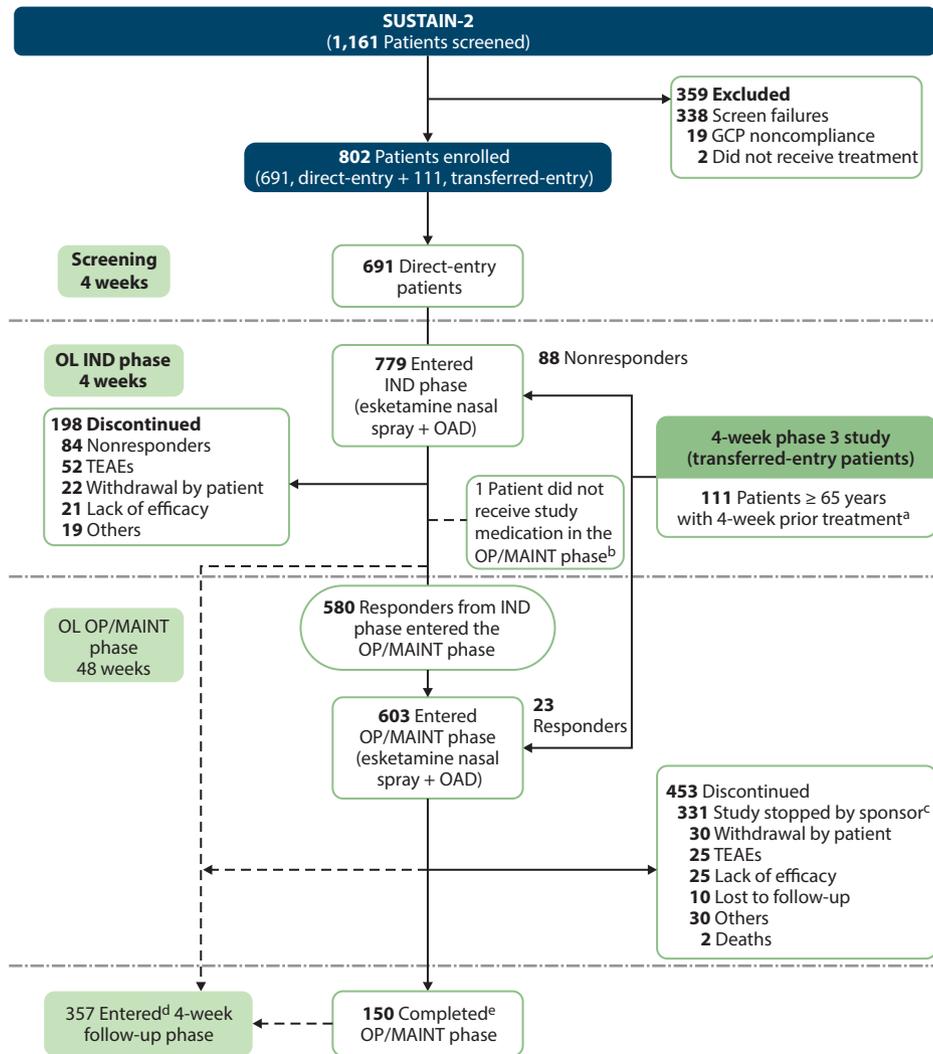
aResponders and nonresponders from prior study irrespective of treatment group (esketamine nasal spray/placebo + OAD).
bOne patient who was dispensed study medication in the OP/MAINT phase never received the study medication and was not counted as continuing into the OP/MAINT phase; this patient was considered discontinued from this phase.
cOn the basis of predefined total patient exposure criteria, ≥ 300 patients reached 6 months of exposure and ≥ 100 patients reached 12 months of exposure to esketamine nasal spray.
dNonresponders from the IND phase, discontinued patients from both treatment phases, and patients who completed the OP/MAINT phase were eligible to enter the follow-up phase.
eA patient was considered a completer if he or she completed safety assessments at week 52 of the OP/MAINT phase.
Abbreviations: GCP = Good Clinical Practice, IND = induction, OAD = oral antidepressant, OL = open-label, OP/MAINT = optimization/maintenance, TEAEs = treatment-emergent adverse events.

guidance, administration of esketamine nasal spray was not recommended if the patient's blood pressure (BP) was repeatedly > 140/90 (< 65 years) or > 150/90 (≥ 65 years) mm Hg. If the BP was ≥ 200/120 (< 65 years) or ≥ 190/110 (≥ 65 years) mm Hg, treatment with esketamine nasal spray was discontinued.

Efficacy Assessments

Changes in MADRS total score from IND and OP/MAINT baseline to respective endpoints were assessed. Response (≥ 50% reduction in MADRS total score) and remission (MADRS total score ≤ 12 and ≤ 10)[20–22] rates over time were assessed from baseline to endpoint and over

time in the IND and OP/MAINT phases. Symptom status was also assessed by Patient Health Questionnaire–9-Item Depression Module (PHQ-9),[23] and functional disability was evaluated using Sheehan Disability Scale (SDS).[24,25] Clinician-determined global severity of the patient's illness was assessed by Clinical Global Impressions–Severity of Illness Scale (CGI-S).[26]

Statistical Methods

No formal sample size calculation was performed. The projected sample size of 750 direct-entry plus transferred-entry patients was considered adequate to obtain ≥ 300 patients who had received treatment with esketamine for

Table 1. Participant Demographic and Clinical Characteristics at Baseline[a]

Characteristic	Esketamine Nasal Spray + OAD (N = 802)
Age, y, mean (SD)	52.2 (13.69)
Age, y, n (%)	
18–44	225 (28.1)
45–64	399 (49.8)
65–74	159 (19.8)
≥75	19 (2.4)
Women, n (%)	502 (62.6)
Race, n (%)	
White	686 (85.5)
Asian	81 (10.1)
Black or African American	15 (1.9)
Other	8 (1.0)
Multiple	8 (1.0)
Not reported	4 (0.5)
Ethnicity, n (%)	
Not Hispanic or Latino	640 (79.8)
Hispanic or Latino	149 (18.6)
Not reported	10 (1.2)
Unknown	3 (0.4)
Baseline BMI, kg/m^2, mean (SD)	27.9 (5.68)
OAD, n (%)[b]	
Duloxetine	251 (31.3)
Escitalopram	237 (29.6)
Sertraline	157 (19.6)
Venlafaxine XR	156 (19.5)
Baseline MADRS total score,[c] mean (SD)	31.4 (5.39)
Baseline CGI-S score,[c] mean (SD)	4.8 (0.77)
History of suicidal ideation in the past 6 months, n (%)	215 (26.9)
Number of prior OAD with nonresponse in the current depressive episode, n (%)[d]	
1	17 (2.1)
2	465 (58.0)
3	187 (23.3)
≥4	133 (16.6)
Family history of psychiatric illness, n (%)	
Depression	346 (43.1)
Anxiety disorder	61 (7.6)
Bipolar disorder	35 (4.4)
Schizophrenia	38 (4.7)

[a]IND phase for all enrolled analysis set.
[b]N = 801 (1 patient did not receive OAD).
[c]For direct-entry and transferred-entry nonresponder patients, baseline is the last observation prior to or on the start date of IND phase. For the transferred-entry responder patients, baseline is upon transfer from the short-term, phase 3 study in elderly patients.
[d]On the basis of the study inclusion criterion, transferred-entry patients reported nonresponse to 1 OAD when they entered the 4-week, phase 3 study. Nonresponse to a second OAD was demonstrated during the 4-week screening period.
Abbreviations: BMI = body mass index, CGI-S = Clinical Global Impressions–Severity of Illness scale, IND = induction, MADRS = Montgomery-Åsberg Depression Rating Scale, OAD = oral antidepressant, PHQ-9 = Patient Health Questionnaire–9-Item Depression Module, XR = extended release.

6 months and ≥100 patients for 12 months and to include ≥100 patients aged ≥65 years.

Safety and efficacy outcomes were summarized descriptively based on the full analysis sets (all patients who received ≥1 dose of esketamine or 1 dose of OAD) for both treatment phases. Selected safety analyses were summarized for the entire treatment period based on the all enrolled analysis set (all patients who were not screen failures and received ≥1 dose of esketamine or 1 dose of OAD). Efficacy was analyzed using last-observation-carried-forward data and observed data.

RESULTS

Patients and Disposition

In total, 1,161 patients were screened, and 802 patients were enrolled (Figure 1). At study closure, 364 patients were dosed for 6 months, and 136 were dosed for 12 months. A total of 357 patients entered the follow-up phase, and 463 patients continued esketamine treatment in a separate OL extension safety study (NCT02782104). The mean age at IND baseline was 52.2 years, 62.6% of patients were women, and 85.5% were white (Table 1).

Extent of Exposure

Median exposure to esketamine was 22.9 weeks. Greater proportions of patients received a final dose of 56-mg (IND: 45.8%; OP/MAINT: 45.6%) and 84-mg (IND: 48.8%; OP/MAINT: 50.2%) esketamine as compared with 28-mg esketamine (IND: 5.3%; OP/MAINT: 4.0%). During the OP/MAINT phase, 24.0% of patients received weekly dosing, 38.1% were maintained on every-other-week dosing, and 37.8% switched more than once between weekly and every-other-week dosing based on the algorithm (see Methods).

Safety

Treatment-emergent adverse events and related rating scale measures. TEAEs were reported in 723/802 patients (90.1%; Table 2). Dizziness (32.9%), dissociation (27.6%), nausea (25.1%), and headache (24.9%) were reported frequently (≥20% patients) during the IND and OP/MAINT phases (percentages shown are the overall combined values for the 2 study phases). Dissociative symptoms presented in a variety of ways including perceptual changes and as being described as feeling disconnected from oneself, one's thoughts, feelings, space, and time. Overall, the types and frequencies of TEAEs were similar in the IND and OP/MAINT phases. Most esketamine-related TEAEs were mild or moderate in intensity, occurred shortly after esketamine nasal spray administration, and resolved the same day. Seventy-six patients (9.5%) had TEAEs that led to discontinuation of esketamine. Serious TEAEs were reported in 55/802 patients (6.9%), of which 5 events in 4 patients were considered to be esketamine-related by the investigator: suicidal ideation (n = 1), suicide attempt (n = 1), anxiety and delusions (both in 1 patient), and delirium (n = 1). Two deaths, assessed as doubtful or unrelated to esketamine by the investigator, were reported, both occurring in the OP/MAINT phase; 1 event due to acute cardiac and respiratory failure and the other due to suicide (see "Serious TEAEs" in Supplementary Appendix 2). Dizziness, dissociation, and somnolence were frequent (≥10% of patients), occurred on the day of esketamine administration, and were considered related to its mechanism of action. There were no reports of drug seeking, overdose, or abuse of esketamine (or ketamine), and there were no requests from patients to increase the frequency of dosing intervals (other than those specified in the protocol) or to increase the esketamine dose (>84 mg). Urine drug screen tests for other drugs of abuse were conducted every 2 weeks

Table 2. Treatment-Emergent Adverse Events[a]

Adverse Event	4-Wk IND Phase (n=779), n (%)	48-Wk OP/MAINT Phase (n=603), n (%)	IND and OP/MAINT Phases (N=802), n (%)
Patients with ≥ 1 TEAE	653 (83.8)	516 (85.6)	723 (90.1)
Patients with ≥ 1 serious TEAE	17 (2.2)	38 (6.3)	55 (6.9)
TEAEs leading to discontinuation of nasal spray medication	53 (6.8)	23 (3.8)	76 (9.5)
TEAEs leading to discontinuation of OAD	20 (2.6)	14 (2.3)	33 (4.1)
TEAEs leading to death	0	2 (0.3)	2 (0.2)
Most common TEAEs (≥ 10% patients) for combined phases			
Dizziness	228 (29.3)	135 (22.4)	264 (32.9)
Dissociation	182 (23.4)	113 (18.7)	221 (27.6)
Nausea	157 (20.2)	84 (13.9)	201 (25.1)
Headache	137 (17.6)	114 (18.9)	200 (24.9)
Somnolence	94 (12.1)	85 (14.1)	134 (16.7)
Dysgeusia	77 (9.9)	54 (9.0)	95 (11.8)
Hypoesthesia	79 (10.1)	40 (6.6)	95 (11.8)
Vertigo	68 (8.7)	43 (7.1)	88 (11.0)
Vomiting	56 (7.2)	45 (7.5)	87 (10.8)
Viral upper respiratory tract infection	19 (2.4)	70 (11.6)	82 (10.2)
Increased blood pressure–related TEAEs			
Increased blood pressure	53 (6.8)	46 (7.6)	75 (9.4)
Increased systolic blood pressure	7 (0.9)	8 (1.3)	12 (1.5)
Increased diastolic blood pressure	12 (1.5)	15 (2.5)	21 (2.6)
Hypertension	13 (1.7)	13 (2.2)	25 (3.1)
Increased heart rate–related TEAEs			
Tachycardia	6 (0.8)	8 (1.3)	13 (1.6)
Cystitis-related TEAEs			
Cystitis	4 (0.5)	1 (0.2)	5 (0.6)
Bacterial cystitis	0	1 (0.2)	1 (0.1)
Most common serious TEAEs (≥ 2 patients)			
Depression	5 (0.6)	3 (0.5)	8 (1.0)
Suicidal ideation	2 (0.3)	4 (0.7)	6 (0.7)
Suicide attempt	4 (0.5)	2 (0.3)	6 (0.7)
Anxiety	2 (0.3)	0	2 (0.2)
Gastroenteritis	0	2 (0.3)	2 (0.2)
Most common TEAEs[b] (≥ 2 patients) leading to discontinuation of esketamine nasal spray			
Anxiety	9 (1.2)	0	9 (1.1)
Suicidal ideation	3 (0.4)	4 (0.7)	7 (0.9)
Depression	3 (0.4)	3 (0.5)	6 (0.7)
Dizziness	6 (0.8)	0	6 (0.7)
Blood pressure increased	4 (0.5)	2 (0.3)	6 (0.7)
Dissociation	5 (0.6)	0	5 (0.6)
Muscular weakness	4 (0.5)	0	4 (0.5)
Vomiting	3 (0.4)	0	3 (0.4)
Hypertension	2 (0.3)	1 (0.2)	3 (0.4)
Suicide attempt	1 (0.1)	1 (0.2)	2 (0.2)
Headache	2 (0.3)	0	2 (0.2)
Sedation	2 (0.3)	0	2 (0.2)
Somnolence	2 (0.3)	0	2 (0.2)
Nausea	2 (0.3)	0	2 (0.2)
Vertigo	1 (0.1)	1 (0.2)	2 (0.2)

[a]All enrolled analysis set.
[b]A TEAE that started in one phase and resulted in discontinuation in the following phase is counted as treatment-emergent in the phase in which the onset of the adverse event occurred.
Abbreviations: IND = induction, OAD = oral antidepressant, OP/MAINT = optimization/maintenance, TEAE = treatment-emergent adverse event.

There was no case of interstitial/ulcerative cystitis during the study. A total of 136 patients (17.0%) reported TEAEs related to renal and urinary disorders (all preferred terms listed in the Medical Dictionary for Regulatory Activities [MedDRA version 20.0] for renal/urinary disorders and urinary-related preferred terms in infections and infestations). In this group, 4 patients had 6 serious TEAEs (pyelonephritis, acute pyelonephritis, and tubulointerstitial nephritis in 1 patient each, and the fourth patient had urinary tract infection [UTI] and additionally underwent surgery for stress urinary incontinence and vesical fistula), of which none led to discontinuation from the study or was deemed related to the treatment with esketamine. There were 5 adverse events of cystitis, which resolved while continuing esketamine treatment. The TEAE of UTI, diagnosed based on clinical symptoms and urinalysis, was reported in 65 patients (8.1%). Most cases of urinary tract symptoms were mild-to-moderate and resolved within 2 weeks. One patient had a dose interruption due to TEAE of urinary retention, assessed as doubtfully related to esketamine by the investigator; it resolved in 4 days, and treatment was re-started. Another patient had dose reduction (from 84 mg to 56 mg) due to a TEAE of pollakiuria of moderate severity, which was assessed as probably related to esketamine and resolved in 5 days. One patient discontinued due to urinary incontinence. Of a total of 14 patients who had multiple episodes of BPIC-SS scores > 18, 6 patients had the TEAE of UTI/cystitis, 2 had the TEAE of nonspecific urinary symptoms (dysuria, pollakiuria), 1 had a preexisting condition (benign prostate hyperplasia), 3 showed signs of UTI in their urinalysis, and 2 had no adverse events/laboratory changes in urinalysis reported. Overall, BPIC-SS total score over time remained low, suggesting no/minimal bladder symptoms (Supplementary Figure 2).

Vital Signs, Laboratory Tests, and ECG

Overall, mean systolic BP (SBP) and diastolic BP (DBP) increased at 40 minutes postdose, with the greatest mean (SD) change of 9.6 (11.99) mm Hg (SBP) and 5.6 (8.32) mm Hg (DBP) in the IND phase and 9.2 (11.30) mm Hg (SBP) and 5.9 (7.28) mm Hg (DBP) in the OP/MAINT phase.

during the IND phase and every 8 weeks in the OP/MAINT phase; 1 patient was discontinued due to protocol deviation of positive test for amphetamine and cocaine. In addition, there were 6 positive urine drug screens (+UDS; n = 2, phencyclidine; n = 2, opiates; n = 1, barbiturates; and n = 1, cocaine), which were not related to prescription drug use. The rate of positive drug screens among all 802 patients was estimated to be 0.0146 +UDS/person year.[27]

Postdose psychotic-like symptoms, as measured by the BPRS+, were transient and resolved on the same day (Supplementary Figure 1).

The BP values generally returned close to predose values at the 1.5-hour postdose timepoint, and there was no evidence of elevation in the mean predose measures over time. A total of 33/802 patients (4.1%) had treatment-emergent acute hypertension (defined as SBP ≥ 180 or DBP ≥ 110 mm Hg). Incidences of acute hypertension were numerically higher in patients with a medical history of hypertension (16/220 [7.3%]) versus patients without hypertension (17/582 [2.9%]); however, magnitude of difference from predose in mean postdose SBP and DBP levels on dosing days was similar. A new antihypertensive medication was initiated in 25/220 patients (11.4%) with hypertension and 29/582 patients (5.0%) without hypertension during the study. There was no occurrence of respiratory depression (see "Vital signs" in Supplementary Appendix 2) and no clinically relevant change in mean ECG intervals or laboratory parameters (see "Clinical laboratory tests and ECG" in Supplementary Appendix 2). On 7 occasions (in 6 patients) in the IND phase and on 3 occasions (in 3 patients) in the OP/MAINT phase, esketamine nasal spray dose was temporarily interrupted or dose was reduced due to increased BP/hypertension. Four patients met discontinuation criteria due to elevated BP and were withdrawn from the study.

Cognitive Effects

Group mean performance on all tests (Cogstate and HVLT-R), including measures of simple and choice reaction time, visual and verbal learning and memory, working memory, and executive function, either demonstrated improvement from baseline in cognitive function or remained stable through week 44 in all patients (Supplementary Table 1). To investigate whether this pattern of results was consistent across different age groups, patients were classified into subgroups based on age: < 65 years and ≥ 65 years. In patients aged < 65 years, performance on all cognitive tests remained stable or slightly improved from baseline during long-term treatment. In patients ≥ 65 years, the mean performance on all 4 tests of higher cognitive functioning (ie, visual learning and memory, working memory, executive function, and verbal learning and memory) improved or remained stable, while the simple and choice reaction time (DET and IDN on the Cogstate battery) showed slowing that began at week 20 of the OP/MAINT phase (Supplementary Table 2). There was high intraindividual variability in reaction time among patients ≥ 65 years. Among patients with reaction times at baseline that were within age-adjusted norms, 7 showed consistent slowing as the study progressed, and no patient manifested impaired reaction time (z score < −1.5 on detection or identification tasks) at study endpoints and follow-up (Supplementary Tables 3 and 4).

Suicidal Ideation and Behavior

In the C-SSRS assessment, 114/784 patients (14.5%) reported new occurrences of suicidal ideation during the study. A total of 8 patients reported suicidal behavior, 2 of whom had a score of 6 ("preparatory acts or behavior") and 6 a score of 9 ("non-fatal suicide attempt"). One death due to

suicide was reported in a 55-year-old woman on day 188 of the study. The patient had a family history of depression and no prior history of suicidal behavior or intent. The patient was clinically in remission of depressive symptoms (MADRS score of 7 and 9 on the last 2 assessments) prior to the event; however, there were environmental circumstances present.

Dissociative and Perceptual Symptoms

Changes in CADSS total score were observed shortly after administration of esketamine, peaked at 40 minutes postdose, and generally resolved within 1.5 hours on the same dosing day. A post hoc, longitudinal analysis showed that the mean maximum postdose CADSS total score declined over time (see "Longitudinal analysis of maximum post-dose CADSS total score" in Supplementary Appendix 2 and Supplementary Figures 3 and 4).

Sedation

Clinically-relevant sedation, defined by MOAA/S score ≤ 3, occurred in 8.4% of patients in the IND phase and 7.0% of patients in the OP/MAINT phase. Of all patients who completed the scale, 5 had MOAA/S scores of 0 (corresponding to no reaction to painful trapezius squeeze) or 1 (purposeful reflexive withdrawal in response to trapezius squeeze). MOAA/S ≤ 3 was reported in 1.8% and 0.5% of dosing sessions in the IND and OP/MAINT, respectively. The longest period of sedation was 1 hour 30 minutes (starting 45 minutes postdose). Another patient was nonresponsive to pain for a shorter period; however, MOAA/S was not completed. Patients who experienced deep sedation did not require ventilation or resuscitation and woke up spontaneously.

Nasal Examination and Nasal Symptom Questionnaire

Taste disturbance (IND: 10.2%; OP/MAINT: 11.0%), postnasal drip (IND: 9.9%; OP/MAINT: 11.0%), and stuffy nose (IND: 5.9%; OP/MAINT: 9.1%) were the most common moderate or severe symptoms on the nasal symptom questionnaire, and < 1% of patients had findings (epistaxis and nasal crusts, discharge, or erythema) on nasal examination.

Withdrawal Symptoms

The mean (SD) PWC-20 total scores (range 0–60; 0–3-point scale [not present = 0, mild = 1, moderate = 2, severe = 3]) were 8.0 (7.61) (at end of treatment) and 7.9 (6.91) (week 1), 8.0 (7.42) (week 2), and 7.7 (7.07) (week 4) during follow-up. In patients who discontinued from the OP/MAINT phase, the most common (> 20%) new or worsening "withdrawal" symptom reported at week 1 was fatigue-lethargy/lack of energy (25.0%) and at endpoint was insomnia (22.7%) (Supplementary Table 5).

Efficacy

The mean MADRS total score decreased in the IND phase (mean [SD] change from IND baseline to endpoint: −16.4 [8.76], n = 756). The improvement in MADRS total score

appeared to be sustained in patients who were responders (direct and transfer entry) and who continued treatment for up to 1 year of exposure (mean [SD] change from OP/MAINT baseline to endpoint: 0.3 [8.12]) (Table 3 and Figure 2; also see "Efficacy results" in Supplementary Appendix 2 and Supplementary Tables 6 and 7).

In the IND phase, the percentage of responders and remitters increased over time, with 78.4% responders and 47.2% remitters (MADRS ≤ 12) at endpoint. The percentage of responders and remitters at the OP/MAINT phase endpoint was 76.5% and 58.2%, respectively (Table 3).

DISCUSSION

The present study is one of the first to demonstrate the long-term (up to 1 year) safety and tolerability of weekly or every-other-week treatment with esketamine nasal spray plus a new OAD. Previously, only 1 study[28] with a small sample size (n = 54) showed manageable tolerability and low discontinuation rate due to adverse events with long-term (up to 29 months) intravenous ketamine treatment in patients with severe, treatment-resistant mood disorders.

Overall, the nature of TEAEs reported in this study was consistent with the known safety profile of esketamine reported in placebo-controlled, short-term studies[1–5,10] of patients with TRD. The majority of TEAEs were mild or moderate in severity, and the incidence of serious TEAEs was low. Most patients with serious TEAEs either recovered or were recovering at study closure. Two deaths reported during the study were not attributed to esketamine as judged by the study site investigator. Reductions in depressive symptoms were observed during the first 4 weeks of treatment (IND phase) and appeared to be sustained through the 1-year exposure period. In addition, reduction in dosing frequency from weekly to every-other-week regimens was consistently achieved in a considerable proportion (38.1%) of patients. As dosing frequency was based on treatment response together with tolerability, for most patients, the findings suggested consistent benefits and acceptable tolerability of esketamine nasal spray treatment over a period of up to 1 year.

The majority of clinically-relevant esketamine-related TEAEs in this study were transient and resolved on the day of administration. In patients with low cardiovascular risk at baseline, increases in BP observed after esketamine administration were generally transient and led to discontinuation in 0.7% of patients. No case of interstitial/ulcerative cystitis was reported, and TEAEs of cystitis were mostly of mild severity, transient and self-limiting, and considered to be suggestive of an infectious etiology (ie, UTI). UTIs account for nearly a quarter of common

Table 3. Efficacy Outcome Based on MADRS Total Score[a]

MADRS Total Scores	IND Phase, n = 779	OP/MAINT Phase, n = 603
Baseline,[b] mean (SD)	31.2 (5.29)	11.0 (4.52)
Endpoint, mean (SD)	14.8 (8.83)[c]	11.3 (7.87)
Change from baseline to endpoint, mean (SD)	−16.4 (8.76)[c]	0.3 (8.12)
Responders at endpoint, n (%)	593 (78.4)[c]	461 (76.5)
Remitters (MADRS ≤ 12) at endpoint, n (%)	357 (47.2)[c]	351 (58.2)
Remitters (MADRS ≤ 10) at endpoint, n (%)	239 (31.6)[c]	300 (49.8)

[a]All enrolled analysis set; LOCF.
[b]For direct-entry and transferred-entry nonresponder patients, baseline (IND phase) is the last observation prior to or on the start date of IND phase. For the transferred-entry responder patients, the baseline is the start of the IND phase of the short-term phase 3 study from which they were transferred. Baseline (OP/MAINT phase) is the last observation prior to or on the start date of the OP/MAINT phase.
[c]n = 756.
Abbreviations: IND = induction, LOCF = last observation carried forward, MADRS = Montgomery-Åsberg Depression Rating Scale, OP/MAINT = optimization/maintenance, SD = standard deviation.

Figure 2. MADRS Total Score Over Time for Esketamine + OAD[a]

No. of Patients[d]														
Esketamine +OAD	779	688	603	550	530	500	446	405	346	294	284	243	210	170	139
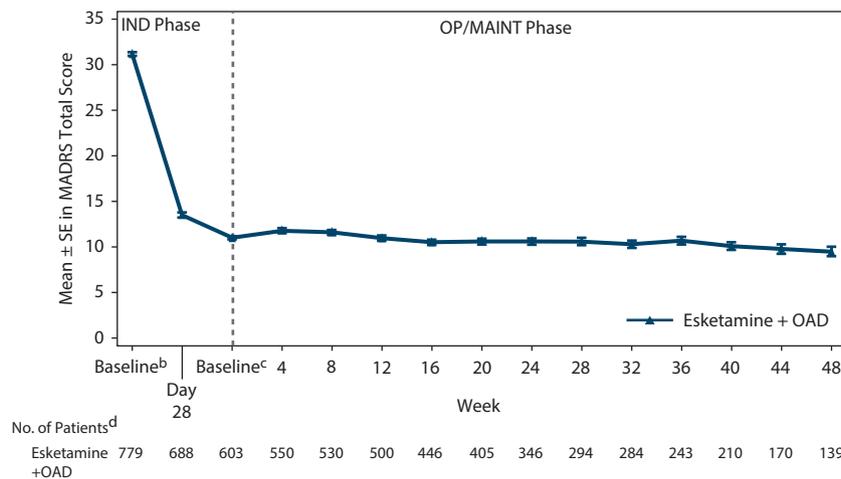
[a]All enrolled analysis set; observed case analysis.
[b]Baseline IND phase.
[c]Baseline OP/MAINT phase.
[d]Number of patients who had a MADRS assessment at a given timepoint of the OP/MAINT phase.
Abbreviations: IND = induction, MADRS = Montgomery-Åsberg Depression Rating Scale, OAD = oral antidepressant, OP/MAINT = optimization/maintenance, SE = standard error.

infections and are expected events in a long-term study of a predominantly middle- to older-age study sample with a preponderance of female patients.[29,30] The incidence of UTI (8.1%) in the present study was analogous to rates observed in a general adult female population (over 10%) over a 1-year period.[31] The serious TEAEs related to renal and urinary tract disorders were assessed as not related to esketamine and resolved while the treatment was ongoing.

Suicidal ideation and behavior are associated with TRD with estimated incidence rates of 0.47 completed and 4.66 attempted suicides per 100 patient years. These rates are substantially higher than those in the general MDD population and similar to those found before and after treatments such as electroconvulsive therapy.[32] Another study[33] reported that in TRD patients, the life-time risk of suicide attempts is assessed to be close to 30%. In the present study, 14.5% of patients who did not have suicidal ideation at baseline reported new suicidal ideation, 6 patients (0.7%) attempted suicide (1.571 per 100 patient years), and 1 patient completed suicide (0.262 per 100 patient years).

Cognitive deficits, impairments in working memory, and decrements in episodic memory have been documented following acute and repeated recreational abuse of ketamine.[8] Although a single subanesthetic dose (0.2 and 0.5-mg/kg) of ketamine showed no cognitive impairment (working memory and go/no-go tasks on days 3 and 14 postketamine infusion) in patients with TRD, effects on cognitive performance with repeated use of ketamine over longer periods remains elusive.[34] In the present study, preservation or improvement in all clinically significant cognitive domains on the Cogstate and HLVT-R was observed, except in patients aged ≥65 years, who had slowing of performance only on simple (DET) and choice reaction-time (IDN) tests of the Cogstate. The interpretation of this effect was limited by the substantial intraindividual variability in reaction time among patients ≥65 years across successive study visits, the lack of a control group, small sample size, and the absence of impaired reaction times on day 28 of the IND phase, at the OP/MAINT phase endpoint, and at follow-up. In addition, there was no significant change in the more complex cognitive domains (verbal, visual, working memory, and executive function), suggesting that the slowing in reaction times may be an isolated observation, not implicating attentional deficit.[35] Further investigation in specially designed, controlled, long-term studies in ≥65-year-old patients is warranted to understand and interpret the effect of esketamine on reaction time in this population. Finally, alternate forms (HVLT-R: Forms 1–6; Cogstate: playing-cards–based tests [DET, IDN, OCL, and ONB tasks] and 18 parallel maze forms for the GMLT) were used for all cognitive tests to attenuate practice effects.[36] Nonetheless, it cannot be known whether practice effects occurred that might have obscured some decline in cognitive performance. Although, in a longitudinal, randomized withdrawal trial[37] in which patients with TRD who had responded to 28-day induction treatment with esketamine plus OAD were randomized to esketamine plus OAD or OAD plus placebo, performance of patients aged 18–64 years on the Cogstate and HVLT-R was similar across treatment arms through week 44 of maintenance treatment, and on some tests (eg, HVLT-R), performance of patients who continued on esketamine and OAD appeared to show improvement over patients in the placebo group. Further methodological research should be considered to enable better understanding and quantification of practice effects and optimal control strategies in longitudinal trials involving repeat cognitive assessments.

In this study, there was no indication of abuse of esketamine, and the duration of TEAEs of dizziness, dissociation, and somnolence was generally limited to the day of esketamine administration. The mean (SD) PWC-20 total score 2 weeks after discontinuation of esketamine (8.0 [7.42]) was similar to that observed at end of treatment (8.0 [7.61]) and was approximately 2- to 3-times lower than the total scores reported in patients after successful (17.2 [11.6]) and unsuccessful (24.6 [12.6]) tapering-off of their benzodiazepines.[19] Collectively, these findings and discontinuation-related symptoms from the PWC-20 assessment suggest that withdrawal symptoms were infrequent, mild, and in quality appeared generally indistinguishable from early return in MDD symptoms.

Notably, the rapid clearance from plasma, short half-life, and low frequency of dosing (weekly or every-other-week) did not allow esketamine to reach steady-state in patients dosed in this study. Consistent with the rapid plasma clearance, dissociative symptoms and dizziness were transient and mostly resolved within 1.5 hours after dosing. Similar to that in earlier reports of esketamine,[1–5,10] severity of dissociative symptoms in this study attenuated over time in most cases, although in rare instances transient reemergence of higher intensity dissociative symptoms at a later dosing session was observed.

This study had several limitations including its open-label study design, the simultaneous initiation of a new OAD, and the absence of a control group; however, the high response and remission rates suggest that long-term (up to 1 year) esketamine treatment appears to provide sustained symptom improvement. Remission rate observed in this treatment-resistant population at end of the OP/MAINT phase was 58.2% using MADRS ≤12 criteria and 49.8% using MADRS ≤10 cutoff. The definition of remission as a MADRS score ≤12 was selected taking into account that the patients manifested TRD prior to entry and thus had higher MADRS scores at baseline than those typically included for studies assessing the efficacy of new treatments in the general MDD population. Nevertheless, the same definition has also been used previously in clinical studies[20,21] of patients with MDD who were selected irrespective of response to previous treatment. In the landmark Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study,[38] remission rates assessed by a different instrument and more strict criteria (Quick Inventory of Depressive Symptomatology–Self-Report [QIDS-SR] ≤5) were 30.6% after 2, 13.7% after 3, and 13.0% after 4 failed AD trials.

In this study, improvements in patient-reported measures of depressive symptoms (PHQ-9; Supplementary Table 6), functionality, and associated disability (SDS; Supplementary Table 7) appear to further support the long-term efficacy of esketamine.

This study involved difficult-to-treat patients with a long-term history of TRD, moderate to severe depression at baseline, and a mean duration of the current depressive episode of about 3 years, and approximately a quarter of the sample had a prior history of suicidal ideation.[39] Furthermore, the high retention rates (75% of patients from the IND phase entered the OP/MAINT phase) and attainment of adequate exposure requirements (as outlined in the International Council for Harmonisation [ICH] E1 guideline)[40] adds to the comprehensiveness of the data collected during this longitudinal study.[41,42] Exclusion of patients with clinically relevant psychiatric or medical comorbidities or substance dependence may potentially limit the generalizability of study findings. To standardize treatment conditions and reduce variability, the 4 OADs used in this study were among the commonly available standard-of-care treatments in the participating countries.

In summary, esketamine nasal spray plus a new OAD demonstrated favorable long-term safety and manageable tolerability in long-term (up to 1 year) intermittent treatment in patients with TRD. The adverse event profile of weekly or every-other-week dosing of esketamine was consistent with findings from earlier short-term studies.

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See supplementary material for this article at PSYCHIATRIST.COM.

Supplementary Material

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List of Supplementary Material for the article

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This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

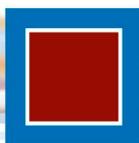**Supplementary material for Esketamine Nasal Spray Plus Oral Antidepressant in Patients with Treatment-Resistant Depression: Assessment of Long-term Safety in a Phase 3, Open-label Study (SUSTAIN-2)**

APPENDIX 1

SUPPLEMENTARY METHODS

Inclusion criteria

Direct-entry patients

- Adult (≥18 years of age) man or woman
- DSM-5 diagnosis of recurrent MDD or single-episode MDD (if single episode MDD, the duration was to be ≥2 years), without psychotic features, based on clinical assessment and confirmed by the MINI
- Non-response to ≥2 oral antidepressant treatments in the current episode of depression, as assessed retrospectively using the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH-ATRQ) and confirmed by documented records (e.g., medical/pharmacy/prescription records or a letter from treating a physician, etc.)
- MADRS total score of ≥22 at screening

Transferred-entry patients

- All patients who completed the DB IND phase of short-term phase 3 study, regardless of their response status, were eligible to participate in this study
- All aforementioned criteria for direct-entry patients

Exclusion criteria

- History of previous non-response to all four oral antidepressants (i.e., duloxetine, escitalopram, sertraline, and venlafaxine XR) or esketamine or ketamine in the current depressive episode

- Current or prior DSM-5 diagnosis of a psychotic disorder or MDD with psychotic features, bipolar or related disorders (confirmed by the MINI), obsessive compulsive disorder (current only), intellectual disability, autism spectrum disorder, borderline personality disorder, antisocial personality disorder, histrionic personality disorder, or narcissistic personality disorder

- Homicidal ideation/intent, or suicidal ideation with some intent to act within 6 months prior to the start of the screening phase, per the investigator's clinical judgment or based on the C-SSRS

- History of moderate or severe substance or alcohol use disorder (DSM-5 criteria), except nicotine or caffeine, within 6 months before screening

- Presence of clinically significant cardiovascular disease or history of uncontrolled hypertension (despite diet, exercise or a stable dose of an allowed anti-hypertensive treatment at screening) or history of hypertensive crisis

Concomitant medications

Benzodiazepines were prohibited for 12 hours before esketamine dosing and the use was permitted at dosages ≤ equivalent of 6 mg/day of lorazepam. Permitted medications included: rescue medications for anxiety or agitation (e.g. midazolam or short-acting benzodiazepine) and nausea (ondansetron, metoclopramide or dimenhydrinate). Treatment with antidepressants (other than the specific antidepressant started in the IND phase), antipsychotics and other psychotropic medications were prohibited with few exceptions, as prespecified in the protocol.

SUPPLEMENTARY RESULTS

Serious TEAEs

Of the two deaths reported, one patient, a 60-year-old man, with a medical history of hypertension and right lower limb vein surgery, died on day 113 of the study (last dose of esketamine: day 108) due to acute cardiac and respiratory failure that were assessed as doubtfully related to esketamine treatment by the investigator. The other patient, a 55-year-old woman, died due to suicide on day 188 of the study (last dose of esketamine: day 176) during her first depressive episode as reported. The patient had a family history of depression and no prior history of suicidal behavior or intent. The patient had a MADRS total score of 27 at study entry, was a responder in the IND phase, and was clinically in remission of depressive symptoms (MADRS score of 7 and 9 on the last 2 assessments) prior to the event. The event was not considered related to esketamine treatment by the investigator.

Of the 55 serious TEAEs, 5 events were assessed as related to the treatment with esketamine by the investigator: [suicidal ideation, suicide attempt, anxiety and delusions (both in 1 patient) and delirium]. Delirium occurred 35 minutes after esketamine dosing on day 127 in a patient with prior history of alcohol use. After a period of agitation, the patient had 30 seconds of apnea and 10 minutes stupor unconsciousness without reaction to pain or light reflex, and subsequently became conscious and alert. No alcohol/drug tests were performed on the day of event, although prior such tests were negative. The events of anxiety and delusions were reported together with the serious TEAE of alcohol abuse (not esketamine-related), 5 days after administration of the first dose of esketamine.

Supplementary figure 1: Mean (SE) changes in BPRS+ total scores over time (All enrolled analysis set)
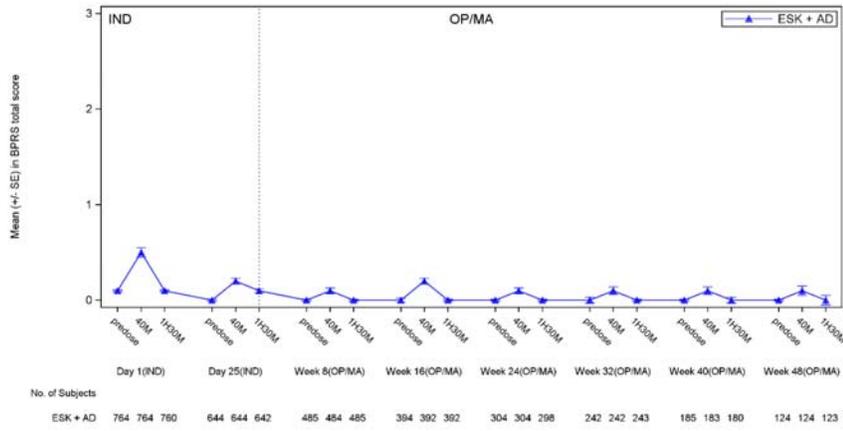
BPRS, Brief Psychiatric Rating Scale; IND, induction phase; OP/MA, optimization/maintenance phase; SE, standard error

Supplementary figure 2: Bladder pain/interstitial cystitis symptom score (BPIC-SS) total score over time (Induction and optimization/maintenance phases; All enrolled analysis set)
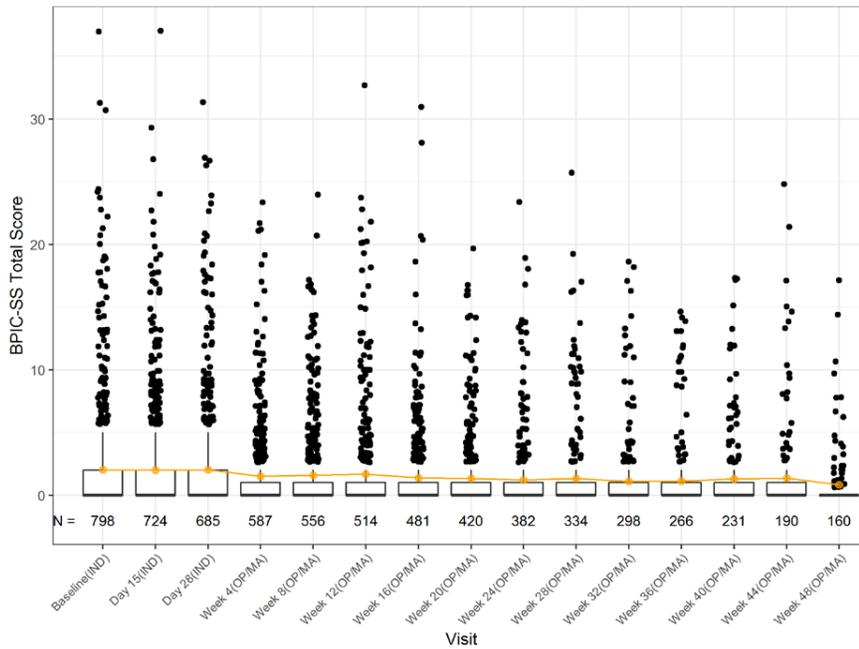
The BPIC-SS is a patient-reported outcome measure to identify an appropriate bladder pain syndrome/interstitial cystitis population for clinical studies evaluating new treatments for bladder pain syndrome. Patients responded to 7 questions using a 5-point scale (0=never, 1=rarely, 2=sometimes, 3=most of the time, 4=always for frequency-based questions, and 0=not at all, 1=a little, 2=somewhat, 3=moderately, and 4=a great deal for items related to bother associated with symptoms). Question 8 recorded the worst bladder pain in the last 7 days using a 0-10 numerical rating scale. A total score was calculated by adding up the numbers beside the response options chosen by the patient. The range of scores for the scale is 0 to 38 and score >18 is regarded as the threshold for cystitis.

Orange dots represent mean scores and boxes show the interquartile range.

BPIC-SS, Bladder Pain/Interstitial Cystitis Symptom Score IND, Induction phase; OP/MA,

Optimization/Maintenance phase

Vital signs

There were few patients who experienced peak increase in blood pressure after the 40 min post-dose timepoint. During the IND phase one patient each had maximum change (68 mm Hg) in SBP occurred at 1.5-h post-dose timepoint (day 4) and maximum change (44 mm Hg) in DBP at the 1 h post-dose timepoint (day 4). During the OP/MAINT phase one patient each had a maximum change (70 mm Hg) in SBP at the 40-min post-dose (week 3) and 1.5-h post-dose timepoint (week 27) and maximum change (47 mm Hg) in DBP at 40 min and 1.5-h post-dose timepoint (week 11).

Generally, oxygen saturation remained stable after esketamine dosing. Total 14 patients had asymptomatic and transient decreases in oxygen saturation level (<93%), with the lowest value of 73% which did not require intervention and spontaneously returned to baseline values. The patient who had the serious TEAE of delirium, experienced a 30 second period of apnea which resolved spontaneously.

Cognitive effects

Supplementary Table 1: Cognitive domains- change from baseline (IND) over time (All enrolled analysis set)

	Mean (SD) change from baseline[a]											
	Baseline (mean [SD])		IND phase (day 28)		Week 20 (OP/MAINT phase)		Week 32 (OP/MAINT phase)		Week 44 (OP/MAINT phase)		OP/MAINT phase endpoint	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
DET-Attention (simple reaction time)[b]	784	2.5983 (0.15633)	623	0.0143 (0.12199)	426	0.0062 (0.12501)	295	0.0033 (0.14260)	197	−0.0178 (0.13807)	561	−0.0028 (0.12744)
IDN-Attention (choice reaction time)[b]	784	2.7505 (0.10904)	630	0.0101 (0.08679)	430	−0.0001 (0.08808)	297	0.0020 (0.10754)	197	−0.0054 (0.10953)	561	−0.0083 (0.09656)
Visual learning[c]	787	0.9506 (0.12726)	635	0.0290 (0.10694)	430	0.0374 (0.11983)	298	0.0495 (0.12947)	197	0.0598 (0.13105)	561	0.0502 (0.13149)
Working memory[b]	787	2.9348 (0.11641)	635	0.0177 (0.08707)	431	0.0151 (0.08707)	297	0.0146 (0.09349)	197	0.0127 (0.08343)	563	0.0177 (0.10026)
Executive function[d]	715	59.9 (25.85)	569	4.8 (22.03)	394	6.8 (24.81)	270	7.6 (22.85)	185	7.8 (30.81)	506	6.9 (25.36)

[a] Higher change from baseline is better performance
[b] Speed of performance (log10 ms), lower score= better performance
[c] Accuracy of performance, higher score= better performance
[d] Number of errors, lower score = better performance
Abbreviations: DET, detection; IDN, identification**;** IND, induction phase; OP/MAINT, optimization/maintenance phase

Supplementary Table 2: Cognitive domains- change from baseline (IND) over time in patients

≥65 years (All enrolled analysis set)

	Baseline		IND phase (day 28)		Week 20 (OP/MAINT phase)		Week 32 (OP/MAINT phase)		Week 44 (OP/MAINT phase)		OP/MAINT phase endpoint	
	n	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**
DET-Attention (simple reaction time)[b]	168	2.6133 (0.15955)	120	0.0076 (0.13876)	72	−0.0258 (0.14292)	45	−0.0427 (0.17679)	28	−0.1032 (0.16230)	119	−0.0313 (0.12889)
IDN-Attention (choice reaction time)[b]	168	2.7498 (0.09465)	121	−0.0001 (0.08175)	72	−0.0136 (0.07794)	46	−0.0210 (0.10060)	28	−0.0587 (0.10346)	119	−0.0203 (0.07206)
Visual learning[c]	168	0.9259 (0.13319)	123	0.0189 (0.10182)	73	0.0321 (0.11613)	46	0.0280 (0.12054)	28	0.0446 (0.11956)	119	0.0242 (0.12663)
Working memory[b]	168	2.9562 (0.11487)	123	0.0151 (0.08792)	73	0.0023 (0.08214)	45	−0.0106 (0.07330)	28	−0.0350 (0.08199)	119	0.0079 (0.08977)
Executive function[d]	137	63.1 (23.93)	97	2.8 (17.78)	54	3.7 (17.62)	35	2.1 (19.58)	23	−5.7 (46.33)	94	2.2 (22.25)

[a] Higher change from baseline is better performance

[b] Speed of performance (log10 ms), lower score= better performance

[c] Accuracy of performance, higher score= better performance

[d] Number of errors, lower score = better performance

Abbreviations: DET, detection; IDN, identification IND, induction phase; OP/MAINT, optimization/maintenance phase

Supplementary Table 3: Z-scores by patient across study timepoints in patients ≥65 years for simple reaction time (Detection- Attention)

Patient No.	Age	Baseline (IND)	Day 28 (IND)	Week 20 (OP/MAINT	Week 32 (OP/MAINT)	Week 44 (OP/MAINT)	Endpoint (OP/MAINT)	Week 4 (F/U)
1	72			-3.71	-1.26	-2.35	-0.91	
2	68	0.23	0.45	-1.29	-1.57	0.38	0.45	-0.19
3	75	0.67	0.62	0.63	-0.40	-1.64	-0.72	-1.26
4	70	0.38	-0.82	-2.14	-0.21	-1.32	-1.38	-0.26
5	71	0.18	0.23	1.16			-2.51	0.38
6	70	1.15	0.89	1.03		0.30	-0.72	-0.94
7	67	-0.16	-0.05	-0.18	-0.08		-1.75	-0.44
8	72	0.40	1.13	1.42	0.70	-0.19	-0.10	-0.68
9	65	1.37	0.81	-2.03	0.91	-1.89	1.12	0.39
10	69	-0.25		-1.93	-2.87	-1.83	-0.32	-2.53
11	66	1.19	0.84	1.34	-1.78	-1.31	-0.23	0.30
12	78	-2.64	0.20	-1.03	-0.50	-2.62	-2.57	
13	65	-2.02	-1.75	-2.13	-3.12	-1.62	-1.91	-2.30
14	65	-1.43	-3.04	-2.81	-1.83	-3.44	-3.44	-3.03
15	71	0.52	-2.01	-1.38	-1.59	-0.43	-2.68	-0.83
16	65	-0.17	0.16	-2.75	0.49	0.05	-0.56	-0.07
17	65	-2.66	-0.94	-2.77	-3.08	-2.06	-2.17	-1.19
18	73	-0.64	0.01	-1.87	-3.09	-3.30	-1.33	-1.75
19	65	-4.62	-0.70	-0.11	-0.54	-4.48	-4.80	-2.20
20	65	0.24	-1.03	-1.76	-1.27	-0.58	-0.30	-0.70
21	67	0.01	-1.53	-0.23	-4.79	-4.93	-0.10	-3.71
22	73	1.44	0.58		-0.71	-1.54	-1.54	
23	68	-1.38	-0.91	0.36	-1.56	-0.35	0.36	
24	68	0.23		-2.19	1.54	1.40	1.40	
25	71	-0.51	-0.14	-0.47	-1.75	-2.18	-0.66	-1.79

Supplementary Table 4: Z-scores by patient across study timepoints in patients ≥65 years for choice reaction time (Identification- Attention)

Patient No.	Age	Baseline (IND)	Day 28 (IND)	Week 20 (OP/MAINT	Week 32 (OP/MAINT)	Week 44 (OP/MAINT)	Endpoint (OP/MAINT)	Week 4 (F/U)
1	72			-1.83	-1.86	-2.33	-1.95	
2	68	0.98	1.37	0.58	0.29	0.92	0.78	0.33
3	75	2.37	1.26	1.12	1.60	-0.48	0.44	0.52
4	70	0.36	-0.25	1.09	0.42	-0.40	0.33	0.80
5	71	-1.10	0.70	-0.45	-0.19		-0.86	-0.80
6	70	0.70	1.22	1.22		0.76	0.34	0.64
7	67	-0.73	-0.02	-0.12	0.43		-2.88	-0.91
8	72	0.77	0.98	1.62	1.18	0.30	0.90	0.72
9	65	1.70	0.54	0.19	1.16	0.29	0.98	1.60
10	69	-0.23		0.04	-1.16	-0.53	-0.40	-1.98
11	66	-1.09	-0.52	-1.01	-1.26	-1.44	-0.83	-1.15
12	78	-0.11	1.15	1.14	-0.73	-3.40	-1.79	
13	65	-1.60	-0.80	-1.58	-2.72	-1.75	-2.42	-1.42
14	65	-1.71	-1.83	-1.77	-0.86	-2.77	-2.77	-1.91
15	71	0.58	-1.53	-0.52	-0.47	2.32	-0.97	-0.15
16	65	1.25	1.12	-2.94	0.68	0.42	0.67	0.08
17	65	-1.97	-0.48	-2.65	-3.46	-1.74	-2.73	-1.54
18	73	0.24	-0.48	-0.02	-1.30	-0.94	-0.69	-0.84
19	65	-2.85	0.64	0.75	0.68	-4.90	-4.27	-3.51
20	65	1.23	0.61	1.11	1.02	0.58	0.79	0.22
21	67	0.06	-3.51	-1.44	-5.87	-6.16	0.59	-3.85
22	73	0.72	0.99		0.69	-0.29	-0.29	
23	68	-0.30	-0.53	-0.20	-0.45	0.24	0.45	
24	68	0.06		-0.92	0.02	0.55	0.55	
25	71	-0.40	-1.43	-1.42	-1.86	-2.19	-0.66	-1.16

Clinical laboratory tests and ECG

During the IND and OP/MAINT phases, 13 (1.7%) patients had elevations of alanine
aminotransferase (ALT) >3 times the upper limit of normal; in 11 patients these elevations
returned to baseline or near baseline levels while treatment with esketamine was ongoing.
One patient with marked ALT and bilirubin elevations was discontinued due to hepatitis B
and ovarian cancer. One patient discontinued from the treatment due to the TEAE of
ventricular arrhythmia with ventricular extrasystolia in the ECG.

Changes in CADSS total scores

**Supplementary Figure 3: Mean (SE) changes in CADSS total scores over time (All
enrolled analysis set)**
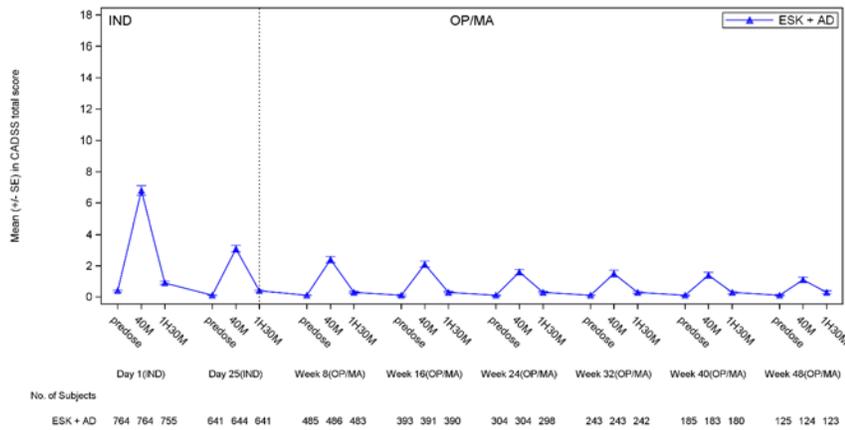
CADSS, Clinician-administered Dissociative States Scale; IND, induction phase; OP/MAINT,
optimization/maintenance phase; SE, standard error

Longitudinal analysis of maximum post-dose CADSS total score

Patients in the all-enrolled analysis set who entered the IND phase were included in the
longitudinal analysis. The transferred-entry responders were not included (n = 23); these

patients entered the study in the OP/MAINT phase. For each patient, the maximum post-dose CADSS total score for each visit was identified. This value was analyzed using a mixed effects model for repeated measures (MMRM) with visit, class of oral antidepressant (SNRI or SSRI), and country as factors; baseline CADSS total score (day 1 pre-dose) as a covariate; and patient as a random effect. The model did not converge with an unstructured covariance matrix but did with a Toeplitz covariance matrix.

Maximum post-dose CADSS total scores generally declined over time, with the steepest decline in the 4-week induction phase. The visit effect in the MMRM was statistically significant (two-sided p < 0.001). Least squares means estimated from the MMRM were plotted by visit (Supplementary Figure 4).

Supplementary Figure 4: Least squares means of maximum post-dose CADSS total score by visit (all enrolled analysis set, excluding transferred responders)
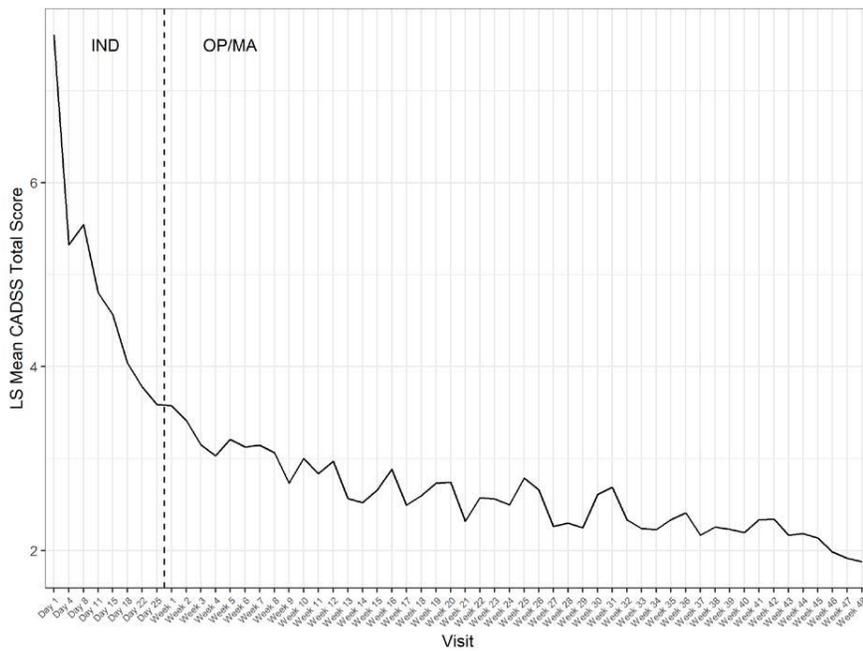
Graph shows least squares means estimated from the MMRM

Supplementary Table 5: Physician Withdrawal Checklist (PWC-20) for patients who discontinued study during OP/MAINT phase: Frequency of withdrawal symptom Status Relative to OP/MAINT phase endpoint over time in the follow-up phase (follow-up analysis Set, n=110)

New or worsened symptom, n (%)	Timepoints in the follow-up phase			
	Week 1	Week 2	Week 4	Endpoint
Loss of appetite	7 (13.5)	9 (12.0)	8 (14.3)	10 (11.4)
Nausea-vomiting	1 (1.9)	4 (5.3)	1 (1.8)	3 (3.4)
Diarrhea	3 (5.8)	4 (5.3)	4 (7.1)	5 (5.7)
Anxiety-nervousness	9 (17.3)	17 (22.7)	10 (17.9)	17 (19.3)
Irritability	6 (11.5)	15 (20.0)	9 (16.1)	15 (17.0)
Dysphoric mood-depression	7 (13.5)	17 (22.7)	13 (23.2)	16 (18.2)
Insomnia	8 (15.4)	22 (29.3)	15 (26.8)	20 (22.7)
Fatigue-lethargy-lack of energy	13 (25.0)	17 (22.7)	9 (16.1)	17 (19.3)
Poor coordination	3 (5.8)	7 (9.3)	3 (5.4)	6 (6.8)
Restlessness-agitation	5 (9.6)	9 (12.0)	3 (5.4)	7 (8.0)
Diaphoresis	6 (11.5)	7 (9.3)	5 (8.9)	7 (8.0)
Tremor-tremulousness	4 (7.7)	8 (10.7)	4 (7.1)	7 (8.0)
Dizziness-lightheadedness	3 (5.8)	4 (5.3)	5 (8.9)	7 (8.0)
Headaches	2 (3.8)	4 (5.3)	6 (10.7)	7 (8.0)
Muscle aches and stiffness	4 (7.7)	7 (9.3)	5 (8.9)	6 (6.8)
Weakness	4 (7.7)	9 (12.0)	3 (5.4)	8 (9.1)
Increased acuity sound smell touch	1 (1.9)	6 (8.0)	2 (3.6)	3 (3.4)
Paresthesias	2 (3.8)	2 (2.7)	3 (5.4)	4 (4.5)
Difficulty concentrating, remember	7 (13.5)	17 (22.7)	10 (17.9)	17 (19.3)
Depersonalization-derealization	2 (3.8)	3 (4.0)	1(1.8)	2 (2.3)

Abbreviations: OP/MAINT, optimization/maintenance phase

Efficacy results

The mean (SD) PHQ-9 total scores decreased from IND baseline to endpoint and this

improvement appeared to be maintained from OP/MAINT baseline to endpoint

(Supplementary table: 6). The percentage of responders (≥50% improvement in PHQ-9) and

remitters (PHQ-9 total score ≤4) also increased over time through the IND phase and was

consistent throughout the OP/MAINT phase.

Supplementary Table 6: Efficacy outcome based on PHQ-9 total score (All enrolled

analysis set; LOCF)

PHQ-9 total scores	IND phase N=779	OP/MAINT phase N=603
Baseline[a], mean (SD)	17.3 (5.00)	6.5 (4.23)
Endpoint, mean (SD)	8.4 (5.80)[b]	6.3 (5.33)
Mean (SD) change from baseline to endpoint	−8.9 (6.67)[b]	−0.2 (5.65)
Responders[c] at endpoint, n (%)	461 (62.0)[d]	449 (74.6)[e]
Remitters[f] at endpoint, n (%)	201 (26.9)[b]	286 (47.4)

[a] Baseline (IND phase) is the last observation prior to or on the start date of IND phase for direct-entry and transferred-entry non-responder patients and is baseline (IND) from the 4-week phase 3 study in elderly patients for the transferred-entry responder patients. Baseline (OP/MAINT phase) is the last observation prior to or on the start date of the OP/MAINT phase
[b] n=746; [c] A patient is defined as a responder at a given time point if the percent improvement from baseline (IND) in PHQ-9 total score is at least 50%; [d] n=744; [e] n=602; [f] A patient is in remission at a given time point if the PHQ-9 total score is ≤4
Abbreviations: IND, induction phase; LOCF, last observation carried forward; OP/MAINT, optimization/maintenance phase; SD, standard deviation

The mean (SD) changes in SDS scores through the IND phase were also suggestive of

improvements in functionality that appeared to be sustained through the OP/MAINT

(Supplementary table 7). The percentage of responders (SDS total score ≤12 and individual

item scores each ≤4) and remitters (SDS total score ≤6 and individual item scores each ≤2)

also showed a similar trend of increase through the IND phase that was maintained in the

OP/MAINT phase.

Supplementary Table 7: Efficacy outcome based on SDS total score (All enrolled

analysis set; LOCF)

SDS total scores[a]	IND phase N=779	OP/MAINT phase N=603
Baseline[b], mean (SD)	22.2 (5.45)[c]	11.3 (7.27)[f]
Endpoint, mean (SD)	12.8 (7.89)[d]	9.5 (7.89)[g]
Mean (SD) change from baseline to endpoint	−9.3 (7.86)[e]	−1.6 (8.25)[h]
Responders[i] at endpoint, n (%)	310 (47.8)[d]	351 (63.0)[g]
Remitters[j] at endpoint, n (%)	137 (21.1)[d]	220 (39.5)[g]

[a] SDS total score ranges from 0 to 30; a higher score indicates greater impairment
[b] Baseline (IND phase) is the last observation prior to or on the start date of IND phase for direct-entry and transferred-entry non-responder patients and is baseline (IND) from the 4-week phase 3 study in elderly patients for the transferred-entry responder patients. Baseline (OP/MAINT phase) is the last observation prior to or on the start date of the OP/MAINT phase
[c] n= 709; [d] n= 648; [e] n=626; [f] n=564; [g] n=557; [h] n=541; [i] A patient is a responder at a given time point if the SDS total score ≤12 and individual item scores each ≤4; [j]A patient is in remission at a given time point if SDS total score ≤6 and individual item scores each ≤2.
Abbreviations: IND, induction phase; LOCF, last observation carried forward; OP/MAINT, optimization/maintenance phase; SD, standard deviation; SDS, Sheehan Disability Scale