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Supplementary Material

Article Title: 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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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.

APPENDIX 2

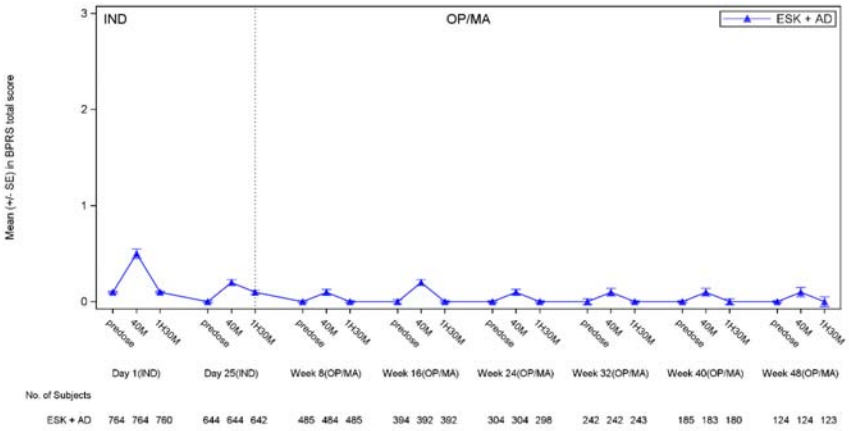
SUPPLEMENTARY RESULTS

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.

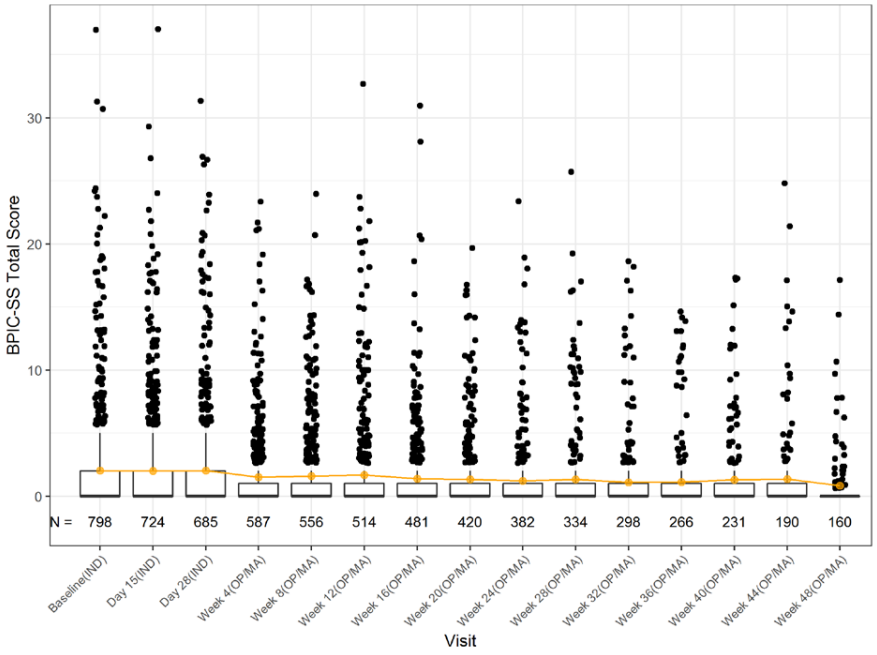
Of the 55 serious TEAEs, 5 events were assessed as related to the treatment with esketamine by the investigator: [suicidal ideation, suicide attempt, anxiety and delusions (both in 1 patient) and delirium]. Delirium occurred 35 minutes after esketamine dosing on day 127 in a patient with prior history 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)

	Mean (SD) change from baseline[a]											
	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)

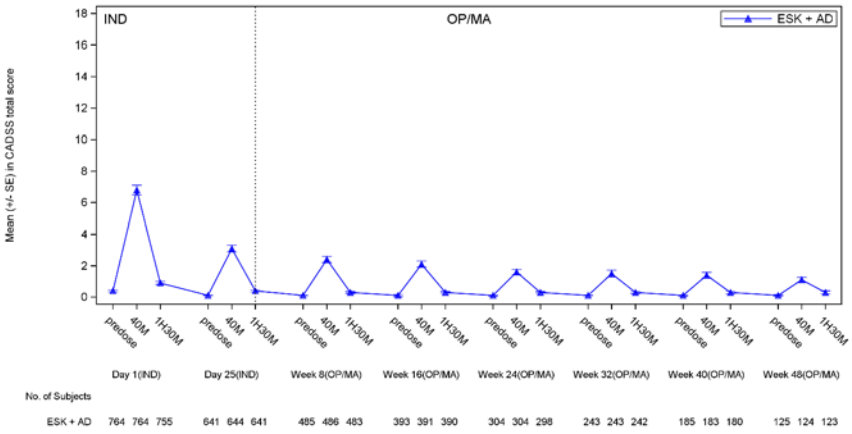
Patient No.	Age	Baseline (IND)	Day 28 (IND)	Week 20 (OP/MAINT	Week 32 (OP/MAINT)	Week 44 (OP/MAINT)	Endpoint (OP/MAINT)	Week 4 (F/U)
1	72			-1.83	-1.86	-2.33	-1.95	
2	68	0.98	1.37	0.58	0.29	0.92	0.78	0.33
3	75	2.37	1.26	1.12	1.60	-0.48	0.44	0.52
4	70	0.36	-0.25	1.09	0.42	-0.40	0.33	0.80
5	71	-1.10	0.70	-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

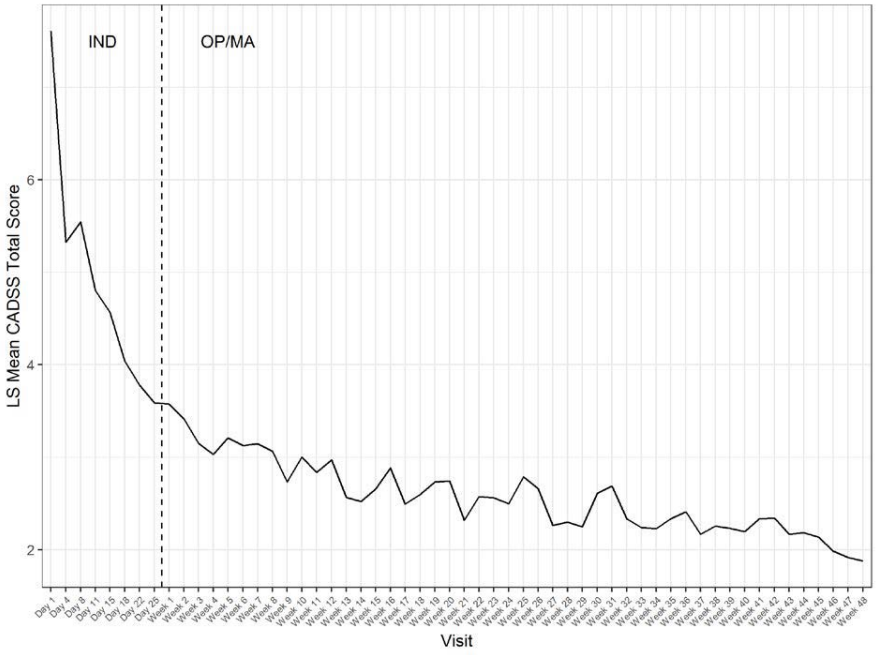
Longitudinal analysis of maximum post-dose CADSS total score

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)

	Timepoints in the follow-up phase			
New or worsened symptom, n (%)	**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