Long-Term Safety and Efficacy of Initial and Repeat Treatment Courses With Zuranolone in Adult Patients With Major Depressive Disorder:

Interim Results From the Open-Label, Phase 3 SHORELINE Study

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Abstract

Objective: Zuranolone is a positive allosteric modulator of both synaptic and extrasynaptic γ-aminobutyric acid (GABA) type A receptors and a neuroactive steroid approved in the United States as an oral, once-daily, 14-day treatment course for adults with postpartum depression and under investigation for adults with major depressive disorder (MDD). Interim results from the open-label, longitudinal, phase 3 SHORELINE Study (NCT03864614) that evaluated the long-term safety and efficacy of zuranolone in adults with MDD are reported.

Methods: This interim report includes patients who were enrolled and had the opportunity to be on study for up to 1 year between February 2019 and September 2021. Adults aged 18–75 years with MDD diagnosed per *DSM-5* criteria and a 17-item Hamilton Rating Scale for Depression (HAMD-17) total score ≥20 received an initial 30-mg or 50-mg 14-day zuranolone course. HAMD-17 responders (≥50% reduction from baseline) at Day (D)15 of the initial treatment period were allowed to continue in the study beyond D28 and were followed up for≤1 year, during which repeat treatment courses were permitted. The primary endpoint was safety and tolerability of the initial and repeat treatment courses through 1 year. Secondary endpoints included change from baseline (CFB) in HAMD-17 total score and need for repeat treatment course(s).

Results: As of September 2021, among patients in the 30-mg (n=725) and 50-mg (n=199) Cohorts who received a zuranolone dose, 493 (68.0%) and 137 (68.8%), respectively, reported a treatment-emergent adverse event (TEAE); most patients who experienced TEAEs reported mild/moderate events (30-mg Cohort, 90.9% [448/493]; 50-mg Cohort, 85.4% [117/137]). Mean (standard deviation) CFB HAMD-17 total score at D15 of the initial treatment period was −15.2 (7.1) and −16.0 (6.0) for the 30-mg and 50-mg Cohorts, respectively; similar improvements were observed after repeat treatment courses. The proportion of patients who received only 1 treatment course during their time on study was 42.9% (210/489) in the 30-mg Cohort and 54.8% (80/146) in the 50-mg Cohort; 57.1% (279/489) and 45.2% (66/146) patients, respectively, received 2–5 total treatment courses. The majority of patients who initially responded to zuranolone received≤2 total treatment courses (30-mg Cohort, 68.5% [335/489]; 50-mg Cohort, 79.5% [116/146]).

Conclusions: Of patients who experienced TEAEs, most reported mild or moderately severe events, and responders to zuranolone experienced improvements in depressive symptoms with initial and repeat treatment courses.

Trial Registration: ClinicalTrials.gov identifier: NCT03864614

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Major depressive disorder (MDD) is a serious mental health disorder associated with major depressive episodes that affected over 21 million US adults in 2021.[1–8] Current standard-of-care (SOC) antidepressant therapies (ADTs) may take weeks to take effect and may be associated with treatment-limiting adverse events (AEs), such as sexual dysfunction, weight gain, fatigue, and insomnia.[9–14] These factors commonly lead to nonadherence and relapse.[15,16] Despite treatment, some patients experience suboptimal or no response, requiring use of adjunctive therapies or frequent medication changes.[17] Even with treatment, many patients with MDD

Clinical Points

- This study provides the first evidence of the long-term safety of 14-day treatment course(s) with zuranolone. The side effects of zuranolone in this study were consistent with those observed in previous clinical studies and were not notably different among patients who later relapsed and received repeat treatment courses, suggesting that the 14-day treatment course of zuranolone can potentially be repeated, if needed.
- Most patients achieved treatment response following a 14-day treatment course with zuranolone. Importantly, for patients who responded to their first treatment, the time to first repeat treatment was over 4 months in both dose groups, and they were likely to respond again if they later relapsed and needed additional treatment course(s).

may experience impaired functioning and diminished quality of life (QoL).[15,16,18,19] Therefore, newer therapies with novel mechanisms of action that may address concerns leading to nonadherence are needed for patients with MDD.

Zuranolone is a neuroactive steroid (NAS) and a positive allosteric modulator (PAM) of synaptic and extrasynaptic γ-aminobutyric acid (GABA) type A receptors ($GABA_AR$) approved in the United States as an oral, once-daily, 14-day treatment course for adults with postpartum depression (PPD) and under investigation for patients with MDD.[20–24] Zuranolone is hypothesized to rapidly restore network balance in brain networks dysregulated in depression by up-regulating $GABA_AR$ expression and enhancing GABAergic signaling.[21] In a preclinical study, oral zuranolone led to rapid increases in beta-band electroencephalogram power, a biomarker of $GABA_AR$ PAM activity, in less than 1 hour.[21] Three completed placebo-controlled clinical studies in MDD (the phase 2 MDD-201b [NCT03000530], phase 3 WATERFALL [NCT04442490], and phase 3 CORAL [NCT04476030] Studies) demonstrated significantly greater improvements with zuranolone vs placebo as assessed by the change from baseline (CFB) in 17-item Hamilton Rating Scale for Depression (HAMD-17) total score at Day 3 or Day 15.[25–27] Self-reported improvements in QoL were observed in post hoc analyses of the WATERFALL Study, and across studies, the safety profile of zuranolone was consistent, with predominantly mild or moderate severity treatment-emergent AEs (TEAEs).[25–30] One phase 3 study (MOUNTAIN [NCT03672175]) evaluating zuranolone 20 and 30 mg did not demonstrate significantly greater improvements in depressive symptoms vs placebo at either dose, as assessed by CFB in HAMD-17 total score at Day 15, but post hoc analyses of patients with measurable plasma levels of zuranolone and/or severe depression (HAMD-17 total score ≥ 24) showed nominally significant improvements with zuranolone 30 mg vs placebo at Day 15.[25] Notably, zuranolone 20 mg did not separate from placebo at any time point, suggesting that zuranolone 30 mg may be the minimum dose required to elicit significant improvements in depressive symptoms.[25] Thus, subsequent studies shifted to include a higher dose of zuranolone 50 mg.

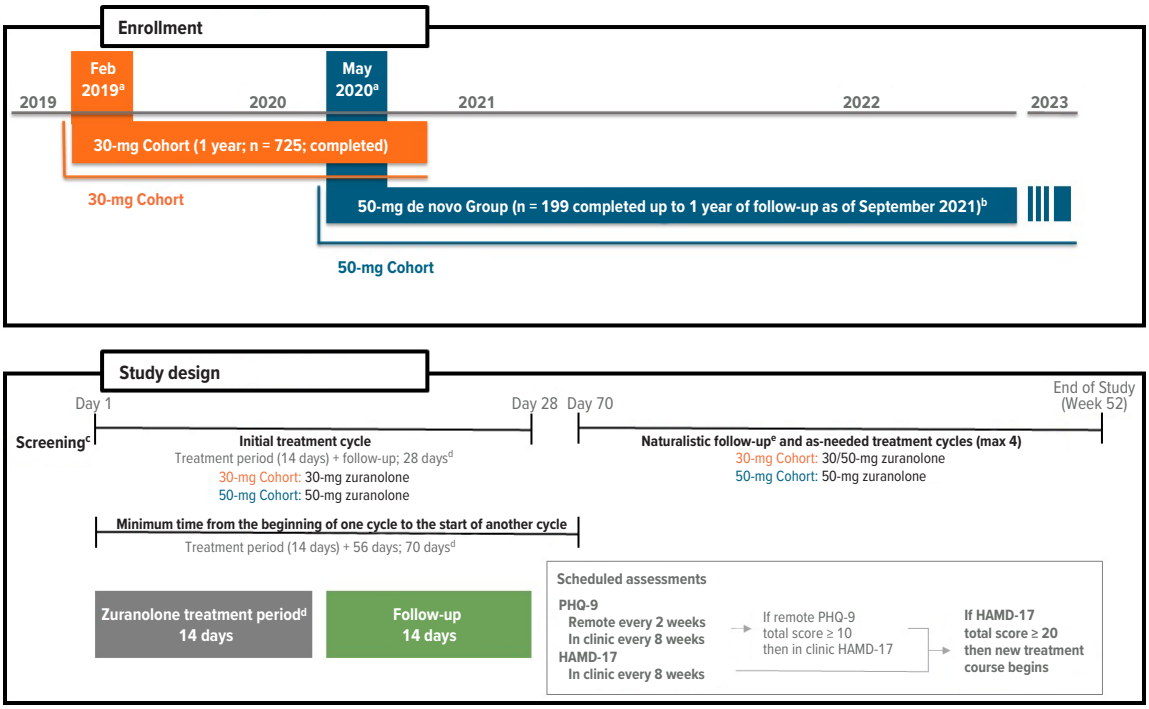
All completed clinical studies of zuranolone evaluated efficacy and safety of a single 14-day treatment course at 30 mg or 50 mg; however, the long-term safety and efficacy of repeat treatment courses of zuranolone (if needed) have not been assessed. The open-label SHORELINE Study was designed to evaluate the long-term safety of and need for repeat treatment course(s) with zuranolone 30 or 50 mg in adults with MDD over ≤ 1 year. Interim results are reported here.

METHODS

Study Design and Participants

SHORELINE (NCT03864614) was an open-label, phase 3, observational study. The study had institutional review board approval and was conducted in accordance with the Declaration of Helsinki and consistent with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use and Good Clinical Practice guidelines. The study started enrolling patients in February 2019, and a second cohort of patients began enrollment in May 2020 (Figure 1). Included in this analysis are data collected from de novo patients who completed or had the opportunity to complete 1 year of follow-up as of September 2021. Eligible patients were 18–75 years old with a diagnosis of MDD per *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition, criteria for ≥ 4 weeks, HAMD-17 total score ≥ 20, and Montgomery-Asberg Depression Rating Scale total score ≥ 28 at screening and before dosing at Day 1.[30,31] Determination of having MDD with elevated anxiety was based on HAMD-17 anxiety subscale standardized score ≥ 39 (raw score ≥ 7). Patients could take SOC ADTs if they were on a stable dose for ≥ 60 days before their first zuranolone dose and intended to continue the ADT through Day 28. Exclusion criteria included a history of bipolar disorder, schizophrenia, active psychosis, attempted suicide or significant risk of suicide in the current episode, or treatment-resistant depression, defined as persistent depressive symptoms despite treatment with adequate doses of antidepressants within the current major depressive episode (excluding antipsychotics) from 2 different classes for at least 4 weeks of treatment. Additionally, regular use of benzodiazepines, barbiturates, or other $GABA_AR$ modulators within 28 days prior to enrollment and dosing on Day 1 was exclusionary. Women with PPD were excluded due to specific parturition-related pathology and because use of NASs for PPD is considered complete after a single treatment course.[32–34] Full eligibility criteria are available in Supplementary Appendix 1. All patients provided written informed consent.

Figure 1.
Study Design



[a]Date when first patient in each cohort started their initial treatment course of zuranolone. The 30-mg Cohort and 50-mg Cohort were enrolled as distinct populations, with the cohort named based on the dose received in the initial treatment course.
[b]The 50-mg de novo group (all treatments with 50 mg) was expanded to include additional patients in July 2021; data are expected in late 2023.
[c]Screening on Day −28 to Day −1 refers to timing relative to first day of treatment with zuranolone.
[d]Only responders (≥ 50% reduction in HAMD-17 total score from baseline) at Day 15 of the initial treatment period can continue in the SHORELINE Study. Need for repeat treatment courses is first assessed remotely by PHQ-9 every 2 weeks. If PHQ-9 score is ≥ 10, an in-person HAMD-17 assessment is performed within 1 week. If HAMD-17 total score is ≥ 20, a repeat treatment course may be initiated. There is a minimum of 56 days (8 weeks) between consecutive zuranolone 14-day treatment periods, allowing for a maximum of 5 treatment courses in 1 year; a new repeat treatment course cannot start after week 48. The time between the first dose in any given treatment cycle and the start of the next treatment cycle was defined as a study period.
[e]At least 6 weeks; maximum of 48 weeks. Per a protocol amendment, all patients were switched from zuranolone 30 mg to zuranolone 50 mg for subsequent repeat treatments.
Abbreviations: HAMD-17 = 17-item Hamilton Rating Scale for Depression, PHQ-9 = 9-item Patient Health Questionnaire.

Patients were screened for ≤ 4 weeks, followed by a 14-day treatment period and 14-day follow-up (Figure 1). A treatment cycle was defined as the 14-day treatment period and 14-day follow-up (Day 28). Only patients who achieved HAMD-17 response (≥ 50% reduction in HAMD-17 total score from baseline) at Day 15 of the initial treatment course (responders) were eligible to continue in the study. Responders who remained in the study through Day 28 could enter an observational period of ≤ 48 weeks.

Initially, SHORELINE included a single zuranolone 30-mg Cohort. After a protocol amendment, the starting dose was changed to 50 mg. For patients in the 30-mg Cohort still in the study, any future repeat courses were to be administered at 50 mg. Thus, a subset of patients in the 30-mg Cohort received the initial treatment course with zuranolone 30 mg and future treatment courses (if needed) with zuranolone 50 mg. A minimum of 56 days was required between consecutive treatment courses, allowing for a maximum of 5 treatment cycles in a 1-year period. This made Day 70 the earliest eligible date for a repeat treatment course (14-day treatment course + 56 days). The terminal date on study (end of study visit) was defined as the week 52 visit.

Need for repeat treatment courses after the initial treatment cycle was determined by remote assessment of 9-item Patient Health Questionnaire (PHQ-9) every 2 weeks and in-clinic HAMD-17 every 8 weeks.[35] If the PHQ-9 score was ≥ 10, the patient returned to the clinic within 1 week for the clinician-administered HAMD-17. If the follow-up HAMD-17 total score was ≥ 20 and the minimum 56 days had elapsed since the last dose of zuranolone, the patient was considered qualified to receive a repeat treatment course. Patients who relapsed prior to Day 70 could receive a dose adjustment of an existing ADT or start

a new ADT at the investigator's discretion. Supplementary Appendices 1 and 2 include additional detail.

Procedures

Patients were instructed to take zuranolone once daily at night within 1 hour of consuming fat-containing food for 14 days. If a patient missed a dose, they were to skip that dose and take the next scheduled dose. Dose reduction from 30 mg to 20 mg or 50 mg to 40 mg was permitted based on tolerability. Safety, tolerability, and efficacy assessments occurred at screening; on Day 1, Day 8, Day 15, and Day 28 of each treatment cycle; and Day 70, Day 126, Day 182, Day 238, Day 294, Day 350, and Day 364 of each observational period (visit days reset to Day 1 if patients entered an additional treatment course). Clinically significant postbaseline physical examination abnormalities were reported as treatment-emergent AEs (TEAEs).

Endpoints

The primary endpoint was safety and tolerability of the initial and repeat zuranolone treatment courses through 1 year, assessed by incidence of AEs; CFB in clinical laboratory measures, vital signs, and electrocardiograms (ECGs); and changes in suicidal ideation/behavior using the Columbia-Suicide Severity Rating Scale.[36] Secondary endpoints included need for repeat treatment courses and efficacy at the end of each treatment period. Need for repeat treatment courses was evaluated as time to first repeat treatment course, number of patients qualifying for repeat treatment, and number of total treatment courses received. Efficacy was assessed by CFB in HAMD-17 total score and Clinical Global Impressions-Severity (CGI-S) score, percentages of patients experiencing HAMD-17 response, HAMD-17 remission (HAMD-17 total score ≤ 7), and CGI-Improvement (CGI-I) response ("much improved" or "very much improved").[30,37] Patient-reported depressive symptoms measured by CFB in PHQ-9 score were an exploratory endpoint. Time to relapse among those who responded at Day 15 was defined as the time after Day 15 of any given treatment cycle when HAMD-17 total score was ≥ 20 within 10 days of a PHQ-9 score ≥ 10. Depressive symptom severity by study visit was categorized by PHQ-9 score (minimal, 0–4; mild, 5–9; moderate, 10–14; moderately severe, 15–19; severe, 20–27. A post hoc analysis of categorical CGI-S score (minimal/mild, ≤ 3; moderate, 4; severe, 5; very severe, 6; extreme, 7) and PHQ-9 score also assessed depressive symptom severity at study exit.

Statistical Analysis

Data for continuous endpoints were reported with summary statistics unless otherwise specified. Categorical data were summarized with counts and percentages. Times to events were evaluated by Kaplan-Meier (KM) estimates. No formal sample size calculation was performed; the target sample size of 1,200 de novo patients was chosen to have ≥ 675 patients complete 24 weeks and 235 patients complete 56 weeks. The safety set included all patients who received ≥ 1 dose of zuranolone. The full analysis set (FAS) included all dosed patients who achieved a HAMD-17 response at Day 15 in the initial treatment cycle and continued in the study beyond Day 28. The mean number of repeat treatment courses was calculated based on the FAS. Patients who remained in the study for the minimum 56 days between potential treatment courses but did not need any additional treatment courses (based on the HAMD-17 ≥ 20 threshold) were counted as 0 in the calculation of mean repeat treatment courses.

RESULTS

Patient Disposition, Demographics, and Baseline Characteristics

As of September 2021, 924 patients (30-mg Cohort [n = 725]; 50-mg Cohort [n = 199]) received ≥ 1 dose of zuranolone (Supplementary Figure 1). At Day 15 of the initial treatment cycle, 73.5% (505/687) and 80.5% (149/185) of patients who had nonmissing HAMD-17 scores in the 30-mg and 50-mg Cohorts, respectively, achieved a HAMD-17 response, with 23.9% (173/725) and 17.6% (35/199), respectively, withdrawing due to a lack of response. Most patients in the FAS completed 1 full year in the study (30-mg Cohort, 63.6% [311/489]; 50-mg Cohort, 65.1% [95/146]).

Most patients in both cohorts were White, were female, and had MDD with elevated anxiety at baseline (Table 1). Baseline mean (standard deviation [SD]) HAMD-17 total score was 25.3 (4.1) and 25.1 (3.3) in the 30-mg and 50-mg Cohorts, respectively. The median (range) time since initial MDD diagnosis was 9.8 (0–53.1) years (30-mg Cohort) and 12.5 (0–60.6) years (50-mg Cohort), with 11.0% (80/725) and 6.5% (13/199) of patients, respectively, reporting this as their first depressive episode. Approximately 10% of patients were > 65 years of age. The median (range) number of depressive episodes was 4 (1–99) and 4 (1–50) in the 30-mg and 50-mg Cohorts, respectively; 41.9% (304/725) and 41.2% (82/199) of patients were receiving an ADT at baseline, respectively.

Safety and Tolerability

In the safety set, ≥ 1 TEAE was reported by 68.0% (493/725) and 68.8% (137/199) of patients in the 30-mg and 50-mg Cohorts, respectively (Table 2). Most patients who experienced TEAEs reported events that were mild or moderate in severity (30-mg Cohort, 90.9% [448/493]; 50-mg Cohort, 85.4% [117/137]). Sixty-five patients reported severe TEAEs (30-mg Cohort, 6.2% [45/725]; 50-mg Cohort, 10.1% [20/199]). Of these patients with severe TEAEs, 25 reported a total of 32 severe TEAEs that were assessed by the investigator as related to zuranolone, and all were reported while on treatment. Overall, the

Table 1.
Baseline Demographics and Patient Characteristics (Safety Set)[a]

	30-mg Cohort[b] (n = 725)	50-mg Cohort (n = 199)
Age, mean (SD), y	45 (14.2)	45 (14.1)
Age, median (range), y	45 (18–75)	48 (18–73)
Sex, female, n (%)	489 (67.4)	138 (69.3)
Race, n (%)		
White	571 (78.8)	175 (87.9)
Black/African American	115 (15.9)	10 (5.0)
Asian	23 (3.2)	8 (4.0)
Multiracial	11 (1.5)	4 (2.0)
American Indian or Alaska Native	1 (0.1)	2 (1.0)
Native Hawaiian or other Pacific Islander	1 (0.1)	0
Other	3 (0.4)	0
Ethnicity, n (%)		
Hispanic or Latino	176 (24.3)	44 (22.1)
Not Hispanic or Latino	549 (75.7)	155 (77.9)
BMI, mean (SD), kg/m²	30.2 (6.7)	29.3 (5.7)
Years since initial diagnosis, median (range)	9.8 (0–53.1)	12.5 (0–60.6)
Depression with elevated anxiety,[c] n (%)	569 (78.5)	149 (74.9)
HAMD-17 total score, mean (SD)	25.3 (4.1)	25.1 (3.3)
Number of depressive episodes experienced, median (range)	4 (1–99)	4 (1–50)
Length of current episode, median (range), d[d]	225.0 (22–8627)	232.0 (48–7995)
ADT use at baseline, n (%)	304 (41.9)	82 (41.2)
History of psychotropic medication use, n (%)	424 (58.5)	102 (51.3)

[a]The safety set included all patients who received ≥ 1 dose of zuranolone.
[b]The 30-mg Cohort included 645 patients who received zuranolone 30 mg for all treatment courses, and following a protocol amendment, 80 patients who received zuranolone 30 mg in the initial treatment course received zuranolone 50 mg in repeat treatment courses.
[c]Determination of elevated anxiety was based on patient HAMD-17 anxiety subscale standardized score ≥ 39 (raw score ≥ 7).
[d]Length of current episode was calculated as the time between the date of the first dose and start date of the current depressive episode.
Abbreviations: ADT = antidepressant therapy, BMI = body mass index, HAMD-17 = 17-item Hamilton Rating Scale for Depression, SD = standard deviation.

TEAEs reported by ≥ 10% of patients were headache (14.2% [103/725]) and somnolence (11.9% [86/725]) in the 30-mg Cohort and somnolence (16.1% [32/199]), dizziness (15.1% [30/199]), headache (12.6% [25/199]), and sedation (10.1% [20/199]) in the 50-mg Cohort. The proportion of patients with TEAEs leading to dose reduction was 6.1% (44/725, 30-mg Cohort) and 18.6% (37/199, 50-mg Cohort). The TEAEs leading to dose reduction (occurring in ≥ 2 patients) were somnolence, fatigue, dizziness, anxiety, lethargy, nausea, sedation, tremor, headache, and attention disturbance in the 30-mg Cohort and dizziness, somnolence, sedation, headache, nausea, tremor, fatigue, asthenia, gait disturbance, agitation, and blurred vision in the 50-mg Cohort. The proportion of patients with TEAEs leading to study withdrawal was 4.4% (32/725; 30-mg Cohort) and 8.0% (16/199; 50-mg Cohort). The TEAEs leading to study withdrawal (occurring in ≥ 2 patients) were anxiety, depression, suicidal ideation, dizziness, confusional state, insomnia, nausea, and pulmonary embolism.

Patients reported TEAEs primarily while on treatment in treatment cycles 1 and 2, and no new or unexpected safety findings were identified with repeat treatment courses (Table 2; Supplementary Table 1). Among patients in the 30-mg Cohort, the most common TEAEs (reported by ≥ 5% of patients) during the first 28-day treatment cycle (ie, treatment cycle TEAEs) were somnolence (9.7% [70/725]), headache (8.8% [64/725]), and dizziness (5.9% [43/725]); 25 patients (3.4%) had their dose reduced and 19 (2.6%) withdrew from the study due to treatment cycle TEAEs. Among patients who received a second treatment course, the most common treatment cycle TEAE was headache (6.3% [18/286]); the rate of dose reduction due to TEAEs was 4.2% (12/286), and 4 patients (1.4%) withdrew due to treatment cycle TEAEs. There were ≤ 6 patients with dose reduction or study withdrawal due to treatment cycle TEAEs in study periods 3, 4, or 5. Headache and somnolence were the most frequently reported treatment cycle TEAEs among patients who received a third treatment course (somnolence, 3.8% [6/157]; headache, 2.5% [4/157]) and a fourth treatment course (somnolence, 4.2% [4/96]; headache, 4.2% [4/96]). Of 43 patients in the 30-mg Cohort who received a fifth treatment course, the most common treatment cycle TEAE was fatigue (7.0% [n = 3]).

Among the 199 patients in the 50-mg Cohort, the most common TEAEs during the initial 28-day treatment cycle were dizziness (15.1% [30/199]), somnolence (13.6% [27/199]), sedation (8.5% [17/199]), headache (8.0% [16/199]), and nausea (5.0% [10/199]); 33 patients (16.6%) had their dose reduced and 12 (6.0%) withdrew due to treatment cycle TEAEs (Table 2). Of these 199 patients, 66 later qualified for and received a second treatment course. The most common treatment cycle TEAEs in treatment cycle 2 were somnolence (6.1% [n = 4]) and sedation (6.1% [n = 4]). The rate of dose reduction due to TEAEs in the second treatment cycle was 4.5% (3/66), and no patients withdrew due to treatment cycle TEAEs. There was ≤ 1 patient with dose reduction or study withdrawal due to TEAEs in treatment cycles 3, 4, or 5. In treatment cycle 3, the most common TEAEs were somnolence (10.0% [3/30]), anxiety (6.7% [2/30]), and tremor (6.7% [2/30]). Fifteen patients in the 50-mg Cohort received a fourth treatment course, and 5 reported treatment cycle TEAEs, which included headache, dry mouth, and dyspepsia (6.7% [n = 1 each]). Of 5 patients who received a fifth treatment course, 1 each reported nausea, nasal congestion, and urinary tract infection during the treatment cycle. Overall, the incidence and timing of TEAEs were not notably different between patients who received zuranolone

Table 2.

TEAEs Overall and by Treatment Cycle (Safety Set)[a]

	Overall[b]	Cycle 1[c]	Cycle 2[c]	Cycle 3[c]	Cycle 4[c]	Cycle 5[c]
30-mg Cohort	**n = 725**	**n = 725**	**n = 286**	**n = 157**	**n = 96**	**n = 43**
TEAE	493 (68.0)	368 (50.8)	120 (42.0)	45 (28.7)	28 (29.2)	12 (27.9)
Mild	200 (27.6)	204 (28.1)	69 (24.1)	22 (14.0)	15 (15.6)	4 (9.3)
Moderate	248 (34.2)	147 (20.3)	46 (16.1)	20 (12.7)	11 (11.5)	5 (11.6)
Severe	45 (6.2)	17 (2.3)	5 (1.7)	3 (1.9)	2 (2.1)	3 (7.0)
SAE	20 (2.8)	6 (0.8)	1 (0.3)	1 (0.6)	0	0
Death	1 (0.1)	0	0	0	0	0
Dose reduction due to TEAE	44 (6.1)	25 (3.4)	12 (4.2)	5 (3.2)	2 (2.1)	6 (14.0)
Treatment discontinuation due to TEAE	20 (2.8)	16 (2.2)	3 (1.0)	0	0	1 (2.3)
Study withdrawal due to TEAE	32 (4.4)	19 (2.6)	4 (1.4)	1 (0.6)	0	1 (2.3)
Most common TEAEs (> 5% at any time)						
Headache	103 (14.2)	64 (8.8)	18 (6.3)	4 (2.5)	4 (4.2)	0
Somnolence	86 (11.9)	70 (9.7)	13 (4.5)	6 (3.8)	4 (4.2)	2 (4.7)
Dizziness	54 (7.4)	43 (5.9)	7 (2.4)	4 (2.5)	2 (2.1)	1 (2.3)
Sedation	40 (5.5)	32 (4.4)	10 (3.5)	2 (1.3)	3 (3.1)	2 (4.7)
Diarrhea	54 (7.4)	27 (3.7)	11 (3.8)	1 (0.6)	1 (1.0)	0
Dry mouth	43 (5.9)	35 (4.8)	7 (2.4)	1 (0.6)	0	1 (2.3)
URTI	57 (7.9)	14 (1.9)	7 (2.4)	3 (1.9)	0	0
Insomnia	36 (5.0)	14 (1.9)	8 (2.8)	2 (1.3)	2 (2.1)	1 (2.3)
Fatigue	35 (4.8)	20 (2.8)	9 (3.1)	4 (2.5)	1 (1.0)	3 (7.0)
50-mg Cohort	**n = 199**	**n = 199**	**n = 66**	**n = 30**	**n = 15**	**n = 5**
TEAE	137 (68.8)	118 (59.3)	22 (33.3)	12 (40.0)	5 (33.3)	2 (40.0)
Mild	44 (22.1)	51 (25.6)	8 (12.1)	4 (13.3)	3 (20.0)	2 (40.0)
Moderate	73 (36.7)	54 (27.1)	12 (18.2)	7 (23.3)	2 (13.3)	0
Severe	20 (10.1)	13 (6.5)	2 (3.0)	1 (3.3)	0	0
SAE	9 (4.5)	5 (2.5)	0	0	0	0
Death	0	0	0	0	0	0
Dose reduction due to TEAE	37 (18.6)	33 (16.6)	3 (4.5)	1 (3.3)	0	0
Treatment discontinuation due to TEAE	13 (6.5)	13 (6.5)	0	0	0	0
Study withdrawal due to TEAE	16 (8.0)	12 (6.0)	0	1 (3.3)	0	0
Most common TEAEs (> 5% at any time)						
Headache	25 (12.6)	16 (8.0)	1 (1.5)	1 (3.3)	1 (6.7)	0
Somnolence	32 (16.1)	27 (13.6)	4 (6.1)	3 (10.0)	0	0
Dizziness	30 (15.1)	30 (15.1)	1 (1.5)	0	0	0
Sedation	20 (10.1)	17 (8.5)	4 (6.1)	1 (3.3)	0	0
Tremor	11 (5.5)	9 (4.5)	2 (3.0)	2 (6.7)	0	0
Dry mouth	8 (4.0)	6 (3.0)	1 (1.5)	0	1 (6.7)	0
Nausea	13 (6.5)	10 (5.0)	1 (1.5)	0	0	1 (20.0)
Dyspepsia	3 (1.5)	2 (1.0)	0	0	1 (6.7)	0
Urinary tract infection	5 (2.5)	0	0	0	0	1 (20.0)
Insomnia	14 (7.0)	10 (5.0)	0	1 (3.3)	0	0
Anxiety	9 (4.5)	5 (2.5)	1 (1.5)	2 (6.7)	1 (6.7)	0
Thrombocytopenia	1 (0.5)	0	0	0	1 (6.7)	0
Muscle strain	5 (2.5)	0	1 (1.5)	0	1 (6.7)	0
Ligament sprain	3 (1.5)	0	0	0	1 (6.7)	0
Nasal congestion	3 (1.5)	0	0	1 (3.3)	0	1 (20.0)

[a]Results presented as n (%); n refers to the number of patients with TEAEs. The safety set included all patients who received ≥1 dose of zuranolone. The 30-mg Cohort includes patients who initially received zuranolone 30 mg in treatment cycle 1 and received zuranolone 50 mg in subsequent treatment cycles.

[b]Overall refers to TEAEs reported at any time throughout the study, including the 28-day treatment cycle or in the observational period up to 48 weeks. The treatment cycle TEAEs include only patients reporting TEAEs within the 28-day treatment cycle (ie, not during the observational period). Thus, the overall number of patients reporting TEAEs may be higher than the sum of patients reporting TEAEs within each treatment cycle.

[c]Cycle refers to the 28-day treatment cycle. These data reflect TEAEs, dose reduction, or study withdrawal that occurred within the 14-day treatment period and 14-day follow-up of the treatment cycle.

Abbreviations: SAE = serious adverse event, TEAE = treatment-emergent adverse event, URTI = upper respiratory tract infection.

alone vs those who received zuranolone and a stable dose of ADTs at baseline (Supplementary Table 2).

The overall incidence of serious AEs was 2.8% (20/725; 30-mg Cohort) and 4.5% (9/199; 50-mg Cohort), and most were observed in the initial study period (ie, during the initial 28-day treatment cycle or ≤ 48-week observational period). One patient in the 30-mg Cohort died due to herpes simplex encephalitis and intracranial hemorrhage; the death occurred > 150 days after the last dose and was determined by the investigator to be unrelated to zuranolone. Findings surrounding patient vital sign parameters, ECGs, withdrawal symptoms, and suicidal ideation/behavior are reported in the Supplementary Material (Supplementary Appendix 2, Supplementary Figure 2).

Efficacy

Most dosed patients responded at Day 15 of the initial treatment cycle and remained in the study beyond Day 28 (FAS; 30-mg Cohort, 67.4% [489/725]; 50-mg Cohort, 73.4% [146/199]). Among responders, 42.9% (210/489) of the 30-mg Cohort and 54.8% (80/146) of the 50-mg Cohort received only the initial 14-day treatment course with zuranolone during their time in the study up to 1 year (Figure 2). The proportion of responders to the initial treatment course who received exactly 2 total treatment courses during their time on study was 25.6% (125/489; 30-mg Cohort) and 24.7% (36/146; 50-mg Cohort). The proportion of responders to the initial treatment course who received 2 to 5 total treatment courses (ie, received at least 1 repeat treatment course during their time in the study) was 57.1% (279/489) in the 30-mg Cohort and 45.2% (66/146) in the 50-mg Cohort. Most patients received 1 or 2 total treatment courses (no repeat treatment course or 1 repeat treatment course) throughout up to 1 year in the study (30-mg Cohort, 68.5% [335/489]; 50-mg Cohort, 79.5% [116/146]). Overall, the mean (SD) number of repeat treatment courses among patients in the FAS was 1.2 (1.3) and 0.8 (1.1) for the 30-mg and 50-mg Cohorts, respectively. The number of total treatment courses was comparable between patients who received zuranolone with and without baseline ADT (Supplementary Figure 3). The median time to first repeat treatment course based on KM estimation was 135 and 249 days for the 30-mg and 50-mg Cohorts, respectively (Figure 3). In the initial study period, the estimated median time to relapse based on the KM method was 109 and 224 days for the 30-mg and 50-mg Cohorts, respectively (Supplementary Figure 4).

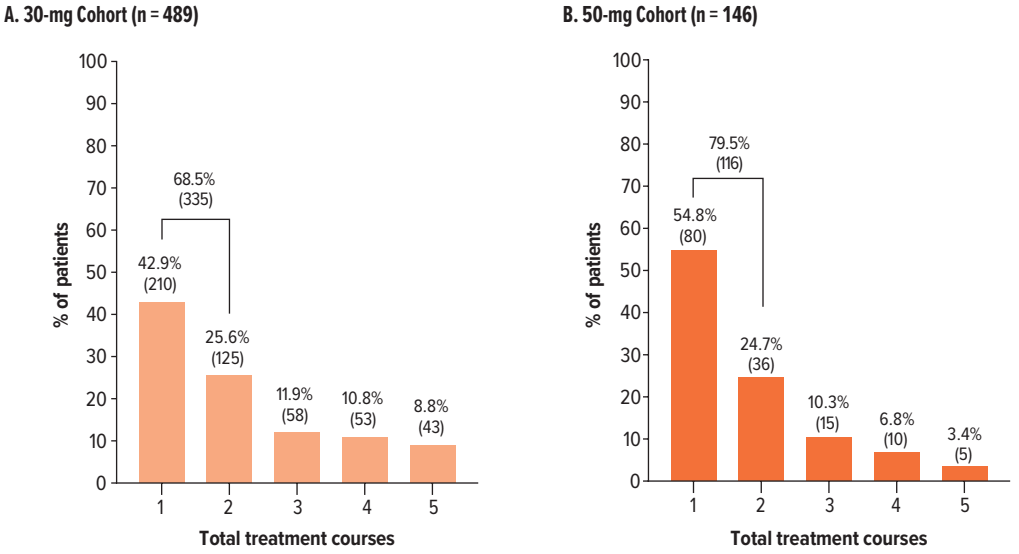
At Day 15 of the initial treatment period, patients experienced improvements from baseline in depressive symptoms across efficacy endpoints (Supplementary Table 3). In the overall population, improvements in depressive symptoms, as assessed by mean (SD) CFB in HAMD-17 total score, were observed at Day 15 of the initial treatment period (safety set; 30-mg Cohort, −15.2 [7.1]; 50-mg Cohort, −16.0 [6.0]). Improvements in HAMD-17 total score at Day 70 in those who remained on study were sustained beyond Day 28 (FAS, mean [SD] CFB; 30-mg Cohort, −12.2 [9.1]; 50-mg Cohort, −14.0 [7.2]). Most patients in both cohorts in the safety set achieved a CGI-I response at Day 8 that was sustained at all study visits through Day 70 in study period 1 in the FAS (Supplementary Figure 5). Patient-reported depressive symptoms as assessed by mean PHQ-9 score were consistent with results from the investigator-reported HAMD-17 (Supplementary Figure 6A). At Day 15 of the initial treatment period, the majority of dosed patients in both cohorts reported minimal or mild depressive symptoms as assessed by PHQ-9 (30-mg Cohort, 71.1% [456/641]; 50-mg Cohort, 76.6% [134/175]).

After the initial treatment course, improvements in depressive symptoms, as assessed by change from period-specific baseline in HAMD-17 total score, mean PHQ-9 score, and categorical depression severity as assessed by PHQ-9, were also observed with repeat treatment courses for patients who received them (Supplementary Table 4; Supplementary Figures 6–8). Of the patients who were eligible for a repeat treatment (ie, patients in the FAS who were on study for the minimum 56 days between treatment courses), the majority in both cohorts reached the threshold for a repeat treatment as defined by a PHQ-9 score ≥ 10 (30-mg Cohort, 69.7% [329/472]; 50-mg Cohort, 58.9% [83/141]). The proportion of patients who reached the threshold defined as a HAMD-17 total score ≥ 20 was similar: 61.4% (290/472) in the 30-mg Cohort and 48.2% (68/141) in the 50-mg Cohort. The proportion of patients in the 30-mg Cohort who received a second treatment course and achieved HAMD-17 response at Day 15 following the repeat treatment course was 64.3% (171/266; Supplementary Table 5). The proportion of patients in the 30-mg Cohort who achieved response at Day 15 following subsequent treatment courses was 63.6% (96/151; treatment cycle 3), 66.7% (62/93; treatment cycle 4), and 71.8% (28/39; treatment cycle 5). In the 50-mg Cohort, the proportion of patients who received a second treatment course and achieved response was 64.6% (42/65). The proportion of patients who achieved response in the 50-mg Cohort at Day 15 following repeat treatment courses was 50.0% (14/28), 40.0% (6/15), and 0/5 patients for treatment cycles 3, 4, and 5, respectively; of note, after the second treatment course, 30 or fewer patients needed and received any additional treatments (Supplementary Table 5).

The proportion of patients in the 30-mg Cohort who achieved remission at Day 15 following the second treatment course was 33.5% (89/266). The rates of remission in treatment cycles 3, 4, and 5, respectively, were 31.1% (47/151), 38.7% (36/93), and 48.7% (19/39; Supplementary Table 5). In the 50-mg Cohort, the proportion of patients who achieved remission at Day 15 following a second treatment course was 33.8% (22/65).

Figure 2.

Number of Total Treatment Courses Received Over 1 Year (FAS)[a]

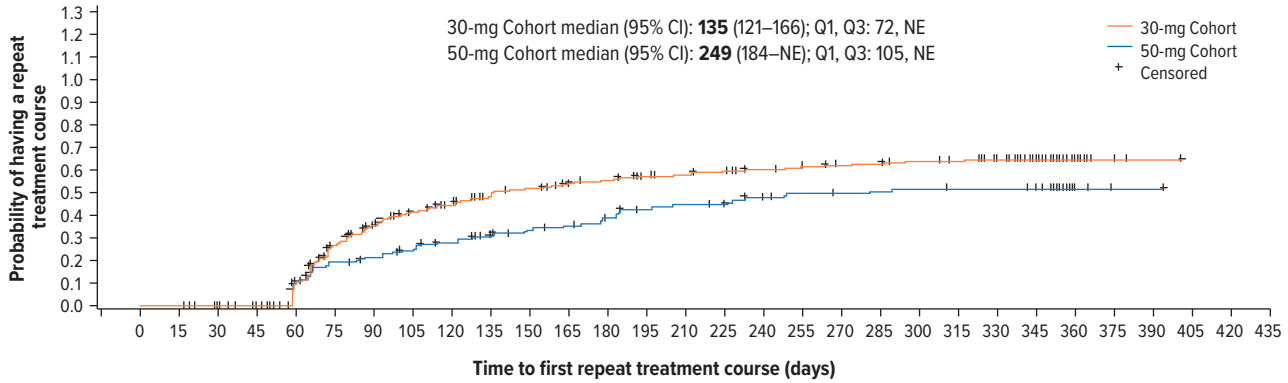


[a]Proportion of patients receiving 1 to 5 total treatment courses in the 30-mg Cohort (A) and 50-mg Cohort (B) in the FAS. The FAS included all safety set patients who achieved a HAMD-17 response at Day 15 and continued in the study beyond Day 28 (ie, completed the initial treatment cycle). Patients who continued in the study for at least 56 days since their last dose were eligible to receive a repeat treatment course. Of 489 patients receiving zuranolone 30 mg in the FAS, 472, 242, 137, and 79 were eligible for repeat treatment in treatment cycles 2, 3, 4, and 5, respectively. Of 146 patients in the FAS receiving zuranolone 50 mg, 141, 62, 24, and 9 patients were eligible for repeat treatment in treatment cycles 2, 3, 4, and 5, respectively.

Abbreviations: FAS = full analysis set, HAMD-17 = 17-item Hamilton Rating Scale for Depression.

Figure 3.

Time to First Repeat Treatment Course (FAS)[a]



No. of patients at risk

30-mg Cohort	489	489	486	480	418	329	284	250	228	204	189	176	168	159	152	146	138	133	127	125	119	117	110	90	12	3	1	0	0	0
50-mg Cohort	146	146	145	142	126	110	105	99	92	86	79	76	70	64	60	59	54	50	49	48	47	46	46	45	4	1	1	0	0	0

No. of patients with a repeat treatment course

30-mg Cohort	0	0	0	0	46	124	162	188	202	218	232	241	247	252	256	261	264	268	271	273	277	277	279	279	279	279	279	0	0
50-mg Cohort	0	0	0	0	15	27	30	34	39	42	45	48	52	56	59	59	62	64	64	65	66	66	66	66	66	66	66	0	0

[a]Time to first repeat treatment course is shown as days since the end of treatment course 1. The safety set included all patients who received ≥1 dose of zuranolone. The FAS included all safety set patients who achieved a HAMD-17 response at Day 15 and continued in the study beyond Day 28 (ie, completed the initial treatment cycle).

Abbreviations: CI = confidence interval, FAS = full analysis set, HAMD-17 = 17-item Hamilton Rating Scale for Depression, NE = not evaluable, No. = number, Q = quartile.

Remission was lower at Day 15 for patients who received a third, fourth, or fifth treatment course in the 50-mg Cohort (treatment cycle 3, 21.4% [6/28]; treatment cycle 4, 26.7% [4/15]; treatment cycle 5, 0/5; Supplementary Table 5). At study exit, most patients in the FAS had minimal/mild depressive symptoms, as assessed by CGI-S score, regardless of whether they completed the study (30-mg Cohort, 84.9% [264/311]; 50-mg Cohort, 88.4% [84/95]) or withdrew prematurely (30-mg Cohort, 71.3% [127/178]; 50-mg Cohort, 74.5% [38/51]). Similar results were observed at study exit as assessed by PHQ-9 score, with most patients reporting minimal or mild depressive symptoms regardless of whether they completed the study (30-mg Cohort, 74.6% [232/311]; 50-mg Cohort, 86.3% [82/95]) or withdrew early (30-mg Cohort, 60.7% [108/178]; 50-mg Cohort, 72.5% [37/51]).

DISCUSSION

In the interim results from SHORELINE, most TEAEs reported by patients receiving a once-daily, 14-day treatment with oral zuranolone 30 mg or 50 mg were mild/moderate in severity, consistent with the safety profile of previous placebo-controlled trials of zuranolone.[32,38–42] The extended follow-up period of this study allowed for the first assessment of long-term safety of zuranolone. The most common TEAEs (somnolence, dizziness, headache, and sedation) were consistent with those reported in previous studies of zuranolone and occurred primarily while on treatment, with no evidence of increased suicidal ideation throughout the study.[32,42] The safety profile of zuranolone was generally consistent in repeat treatment courses, with no notable trends in the frequency of reporting or the types of TEAEs reported by patients who received multiple treatment courses compared with the initial treatment course. Overall, 5.2% (48/924) of patients withdrew from the study due to TEAEs (30-mg Cohort, 4.4% [32/725]; 50-mg Cohort, 8.0% [16/199]), with most withdrawals occurring in treatment cycle 1.

These data may also highlight the potential long-term efficacy of zuranolone in adults with MDD, although the open-label nature of the study must be noted as a limitation. About half of patients in both dose cohorts received only the initial treatment course, while the other half received at least 1 additional treatment course during their time in the study. Notably, while symptoms of elevated anxiety were present at baseline in nearly 80% of patients in SHORELINE, improvements in depressive symptoms were still observed in initial and repeat treatment courses. This is consistent with randomized, double-blinded studies, in which treatment with zuranolone was associated with improvements in depressive symptoms vs placebo in patients with MDD, including those with elevated anxiety (CORAL and integrated data from MDD-201b, MOUNTAIN, and WATERFALL).[27,43] The majority of patients who initially responded to zuranolone reached the threshold for repeat treatment as assessed only by a self-reported PHQ-9 score ≥ 10 in both dose cohorts, and similar results were observed based on the investigator-reported HAMD-17 criterion. KM estimates suggest potentially sustained effects of zuranolone, with a median time to the first repeat treatment course of approximately 4 months in the 30-mg Cohort and 8 months in the 50-mg Cohort. However, while the 50-mg dose was associated with a longer time to first repeat treatment course compared with the 30-mg dose, patients in the 50-mg Cohort were approximately 3 times as likely to require dose reduction due to TEAEs and were twice as likely to withdraw from the study due to TEAEs.

Most responders to the initial treatment course in the 30-mg Cohort regained HAMD-17 response if they received a second treatment course—and a similar trend was observed for subsequent treatment courses—despite the fact that period-specific baseline HAMD-17 total scores were generally lower after treatment cycle 1. Patient-reported PHQ-9 results were consistent with these observations, showing that most patients in the 30-mg Cohort reported minimal or mild symptoms at Day 15 and at later study visits. Response was also regained if initial responders in the 50-mg Cohort received a second treatment course. Response and remission rates decreased with repeat treatment courses among patients in the 50-mg Cohort, although a relatively small number of patients in this cohort (n ≤ 30) received more than 2 total treatment courses with zuranolone 50 mg, which limits the interpretation of these data. In both dose cohorts, those who needed and received 3 or more treatment courses were generally more likely to report moderate/severe depressive symptoms (assessed by PHQ-9) at Day 15 and later study visits compared with those who only needed 1 or 2 total treatment courses, although results varied by study visit, which may be due to the smaller sample size for patients who received 3 or more treatment courses. Regardless of whether responders completed a full year in the study or withdrew early, most exited the study with at most mild depressive symptoms, as assessed both by patient-reported PHQ-9 and by investigator-reported CGI-S score, potentially suggesting that lack of efficacy was not a primary driver in patient dropout.

A limitation of the open-label SHORELINE Study is that it was not designed for comparative safety and efficacy assessments, in part due to the lack of randomization. Additionally, the sample size of the 50-mg Cohort reported here was smaller than that of the 30-mg Cohort, especially in study periods 3 to 5, which limits the interpretation of results. Additional data from the completed 50-mg Cohort will be reported on study completion.

Overall, SHORELINE adds evidence supporting the emergent strategy of targeting GABAergic signaling to treat MDD, which is based on the hypothesis that decreased GABA activity plays a fundamental role in the network dysregulation thought to contribute to the

clinical presentation of depression.[20,44–48] In preclinical models, NASs can lead to rapid and sustained regulation of brain networks implicated in depression, consistent with antidepressant activity.[49] Mechanistically, this is thought to be related to the biochemistry of NASs, which bind to both synaptic and extrasynaptic $GABA_A$Rs and increase surface receptor expression in vitro, consistent with both rapid and sustained signaling.[50,51]

In conclusion, the interim results from SHORELINE show that most TEAEs reported were mild/moderate, and patients who received zuranolone showed improvement in depressive symptoms with initial and repeat treatment courses, with a safety profile that was consistent with previous placebo-controlled studies of zuranolone. In both dose cohorts, improvements in depressive symptoms were potentially sustained for months, with the possibility to recapture response with repeat treatment courses, if needed.

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The Journal of Clinical Psychiatry

Supplementary Material

Article Title: Long-Term Safety and Efficacy of Initial and Repeat Treatment Courses With Zuranolone in Adult Patients With Major Depressive Disorder: Interim Results From the Open-Label, Phase 3 SHORELINE Study

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

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DISCLAIMER

Supplementary materials

Appendix 1

Diagnosis of major depressive disorder (MDD) was determined by the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) Clinical Trials Version. Treatment-resistant depression was assessed by the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire.

If a patient reported a Patient Health Questionnaire (PHQ-9) ≥10, but the HAMD-17-item Hamilton Rating Scale for Depression (HAMD-17) total score was <20, the patient was to complete the PHQ-9 on a weekly basis and return to the site to be assessed by the HAMD-17 each week that the PHQ-9 score remained ≥10. If the PHQ-9 score was <10, the patient took the PHQ-9 every 2 weeks thereafter. Without any trigger by the PHQ-9 score described above, a patient would return to the site every 8 weeks for clinical assessments.

Inclusion criteria

Patients who meet the following criteria are qualified for participation in the study:

1. Patient has signed an informed consent form prior to any study-specific procedures being performed.
2. Patient is a male or female between 18 and 75 years of age, inclusive.
3. Patient is in good physical health and has no clinically significant findings, as determined by the investigator, on physical examination, 12-lead electrocardiogram (ECG), or clinical laboratory tests.
4. Patient agrees to adhere to the study requirements, including not participating in night shift work during any 14-day treatment period.

5. Patient has a diagnosis of MDD as diagnosed by Structured Clinical Interview for DSM-5 Clinical Trials Version, with symptoms that have been present for at least a 4-week period.
6. Patient has a Montgomery-Åsberg Depression Rating Scale total score of ≥28 and a HAMD-17 total score of ≥20 at screening and Day 1 (prior to dosing).
7. Patients taking antidepressants used to treat MDD must have been taking these medications at the same dose for at least 60 days prior to Day 1. Patients who have stopped taking antidepressants must have done so for at least 60 days prior to Day 1. Patients receiving psychotherapy must have been receiving therapy on a regular schedule for at least 60 days prior to Day 1.
8. Female patient agrees to use at least one method of highly effective contraception during participation in the study and for 30 days following the last dose of study drug, unless she is postmenopausal (at least 12 months of spontaneous amenorrhea without an alternative medical cause, with confirmatory follicular stimulation hormone >40 mIU/mL), and/or surgically sterile (hysterectomy, bilateral oophorectomy, and/or bilateral salpingectomy), or does not engage in sexual relations that carry a risk of pregnancy.
9. Male patient agrees to use an acceptable method of effective contraception for the duration of study and for 5 days after receiving the last dose of the study drug, unless the patient does not engage in sexual relations that carry a risk of pregnancy.
10. Male patient is willing to abstain from sperm donation for the duration of the study and for 5 days after receiving the last dose of the study drug.
11. Patient agrees to refrain from misuse of drugs and alcohol for the duration of the study.

Exclusion criteria

Patients who met the following criteria were disqualified from participation in the study:

1. Patient is currently at significant risk of suicide, as judged by the investigator, or has attempted suicide associated with the current episode of MDD.
2. Patient has a recent history or active clinically significant manifestations of metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, dermatological, urogenital, neurological, or eyes, ears, nose, and throat disorders, or any other acute or chronic condition that, in the investigator's opinion, would limit the patient's ability to complete or participate in this clinical study. A body mass index (BMI) ≤18 or ≥45 kg/m^2 at screening is exclusionary; a BMI of 40 to 44.9 kg/m^2, inclusive, at screening is subject to a broader evaluation of medical comorbidities (such as sleep apnea or chronic obstructive pulmonary disease), concomitant medications, and prior tolerability of sedating agents.
3. Patient has treatment-resistant depression, defined as persistent depressive symptoms despite treatment with adequate doses of antidepressants within the current major depressive episode (excluding antipsychotics) from 2 different classes for at least 4 weeks of treatment. Massachusetts General Hospital Antidepressant Treatment Response Questionnaire is used for this purpose.
4. Patient has had vagus nerve stimulation or electroconvulsive therapy or has taken ketamine (including esketamine) within the current major depressive episode.
5. Patient is taking any of the following:
    a. Benzodiazepines, barbiturates, or gamma-aminobutyric acid type A receptor ($GABA_AR$) modulators (e.g., eszopiclone, zopiclone, zaleplon, zolpidem, brexanolone) at Day −28;
    b. Benzodiazepines, barbiturates, or $GABA_AR$ modulators daily or near daily (≥4 days per week) for 1 year, in the year prior to first dose of study drug; or

c. Benzodiazepines or $GABA_AR$ modulators with a half-life of ≥48 hours (e.g., diazepam) from 60 days prior to Day 1.

6. Patient is taking non-GABA anti-insomnia medications (e.g., prescribed therapeutics specifically for insomnia, over-the-counter sleep aids, melatonin), first-generation (typical) antipsychotics (e.g., haloperidol, perphenazine), and/or second-generation (atypical) antipsychotics (e.g., aripiprazole, quetiapine) at Day –14. Note that antihistamines used during the day solely for indication(s) other than insomnia are permitted.
7. Patient has a known allergy to zuranolone, allopregnanolone, or related compounds.
8. Patient has a positive pregnancy test at screening or on Day 1 prior to the start of study drug administration for any treatment cycle.
9. Patient that is breastfeeding at screening or on Day 1 (prior to administration of study drug) does not agree to temporarily cease giving breast milk to her child(ren) from just prior to receiving study drug on Day 1 until 7 days after the last dose of study drug in each treatment cycle.
10. Patient has detectable hepatitis B surface antigen, anti-hepatitis C virus (HCV) antibody and positive HCV viral load, or human immunodeficiency virus antibody at screening.
11. Patient has a clinically significant abnormal 12-lead ECG at the screening or baseline visits. NOTE: mean QT interval calculated using the Fridericia method (QTcF) of >450 msec in males or >470 msec in females is a basis for exclusion from the study.
12. Patient has active psychosis per investigator assessment.
13. Patient has a medical history of seizures.
14. Patient has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
15. Patient has a history of mild, moderate, or severe substance use disorder (including benzodiazepines) diagnosed using DSM-5 criteria in the 12 months prior to screening.

16. Patient had been taking chronic or as-needed psychostimulants (e.g., methylphenidate, amphetamine) or opioids at Day −28.
17. Patient has had exposure to another investigational medication or device within 30 days prior to screening.
18. Patient has previously participated in a zuranolone or a SAGE-547 (brexanolone) clinical trial.
19. Use of any known strong inhibitors of cytochrome P450 (CYP)3A4 within 28 days or 5 half-lives (whichever is longer) or consumption of grapefruit juice, grapefruit, Seville oranges, or products containing these within 14 days prior to the first dose of study drug for any zuranolone treatment cycle.
20. Use of strong CYP3A inducers within 28 days prior to the first dose of study drug for any zuranolone treatment cycle or planned use during any treatment cycle. Examples include rifampin, carbamazepine, enzalutamide, mitotane, phenytoin, and St. John's Wort.
21. Patient has a positive drug and/or alcohol screen at screening or on Day 1 prior to dosing of the initial treatment cycle.
22. Patient plans to undergo elective surgery during the initial treatment and follow-up period.
23. Patient has been diagnosed with and/or treated for any type of cancer (excluding basal cell carcinoma and in situ melanoma) within the past year prior to screening.
24. Patient has a history of sleep apnea.
25. Patient has had gastric bypass surgery, has a gastric sleeve or lap band, or has had any related procedures that interfere with gastrointestinal transit.
26. Patient ≥65 years of age has a history of cognitive impairment, has an increased risk for falls (including but not limited to impaired balance and/or gait), or is already taking ≥2 central nervous system–active drugs, as per the American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults.

Permitted medications

If depressive symptoms worsened after Day 28 but before eligibility for repeat treatment (Day 70), patients could receive supplemental medications, including benzodiazepines, GABA modulators for insomnia (e.g., eszopiclone, zopiclone, zaleplon, zolpidem), and non-GABA treatments for insomnia (e.g., melatonin, over-the-counter sleep aids, trazodone, mirtazapine) for ≤4 days per week. Introduction of a new antidepressant therapy (ADT) or increase in the dose of a current ADT was also permitted at the discretion of the investigator.

Prohibited medications

Benzodiazepines, barbiturates, $GABA_AR$ modulators (e.g., eszopiclone, zopiclone, zaleplon, zolpidem, brexanolone), or GABA-containing, over-the-counter supplements were prohibited from 28 days prior to the first dose of zuranolone in the initial treatment cycle through the 14-day follow-up period (Day 28); thereafter, these medications are prohibited in the 7 days prior to any new zuranolone treatment cycle and through the follow-up period of the cycle. First-generation (typical; e.g., haloperidol, perphenazine) or second-generation (atypical; e.g., aripiprazole, quetiapine) antipsychotics were prohibited from 14 days prior to the initial treatment cycle and throughout the duration of the study. Non-GABA anti-insomnia medications (e.g., prescribed therapeutics specifically for insomnia, over-the-counter sleep aids, melatonin) were prohibited from 14 days prior to the first dose of zuranolone in the initial treatment cycle through the initial 14-day treatment period; thereafter, these medications were prohibited 1 day prior to any new zuranolone treatment cycle and through the follow-up period of the cycle. The use of chronic or as-needed psychostimulants (e.g., methylphenidate, amphetamine) or opioids was prohibited from 28 days prior to the initial treatment cycle and throughout the duration of the study. Exposure to another investigational medication or device was prohibited from 30 days prior to screening and throughout the duration of the study.

Appendix 2

Patient vital sign parameters, ECGs, withdrawal symptoms, and suicidal ideation/behavior

Mean changes from baseline (CFBs) in vital sign parameters and mean ECG results did not differ notably across study periods. The incidence of clinically significant abnormal ECG was low (≤2 patients at any study visit), similar between cohorts, and restricted to study periods 1 and 2. There was no evidence of increased withdrawal symptoms following zuranolone treatment courses. No evidence for increased suicidal ideation/behavior compared with baseline was reported in any study period in either cohort, as measured by Columbia Suicide Severity Rating Scale (C-SSRS; **Supplementary Figure 2**). In study period 5, the postbaseline increase in patients reporting suicidal ideation per C-SSRS was likely due to small sample size.

Supplementary Table 1. Summary of TEAEs on treatment and during follow-up by treatment cycle (safety set).

	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5	
30-mg Cohort	On treatment n=725	Follow-up n=725	On treatment n=286	Follow-up n=286	On treatment n=157	Follow-up n=157	On treatment n=96	Follow-up n=96	On treatment n=43	Follow-up n=43
Any treatment cycle TEAE	348 (48.0)	79 (10.9)	102 (35.7)	40 (14.0)	39 (24.8)	15 (9.6)	25 (26.0)	6 (6.3)	12 (27.9)	0
Somnolence	70 (9.7)	1 (0.1)	13 (4.5)	0	6 (3.8)	0	4 (4.2)	0	2 (4.7)	0
Dizziness	42 (5.8)	1 (0.1)	7 (2.4)	0	4 (2.5)	0	2 (2.1)	0	1 (2.3)	0
Headache	59 (8.1)	9 (1.2)	15 (5.2)	3 (1.0)	4 (2.5)	0	2 (2.1)	2 (2.1)	0	0
Tremor	6 (0.8)	0	1 (0.3)	0	3 (1.9)	0	2 (2.1)	0	0	0
Sedation	32 (4.4)	0	10 (3.5)	0	2 (1.3)	0	3 (3.1)	0	2 (4.7)	0
Insomnia	10 (1.4)	5 (0.7)	2 (0.7)	6 (2.1)	2 (1.3)	0	1 (1.0)	1 (1.0)	1 (2.3)	0
URTI	10 (1.4)	4 (0.6)	6 (2.1)	1 (0.3)	3 (1.9)	0	0	0	0	0
Diarrhea	19 (2.6)	8 (1.1)	10 (3.5)	2 (0.7)	1 (0.6)	0	0	1 (1.0)	0	0
Nausea	19 (2.6)	1 (0.1)	2 (0.7)	0	1 (0.6)	0	0	0	0	0
Dry mouth	32 (4.4)	3 (0.4)	7 (2.4)	0	1 (0.6)	0	0	0	1 (2.3)	0
50-mg Cohort	n=199	n=199	n=66	n=66	n=30	n=30	n=15	n=15	n=5	n=5
Any treatment cycle TEAE	108 (54.3)	27 (13.6)	22 (33.3)	0	9 (30.0)	5 (16.7)	4 (26.7)	1 (6.7)	2 (40.0)	0
Somnolence	27 (13.6)	0	4 (6.1)	0	2 (6.7)	1 (3.3)	0	0	0	0
Dizziness	30 (15.1)	1 (0.5)	1 (1.5)	0	0	0	0	0	0	0

Headache	14 (7.0)	3 (1.5)	1 (1.5)	0	1 (3.3)	0	1 (6.7)	0	0	0
Tremor	9 (4.5)	0	2 (3.0)	0	2 (6.7)	0	0	0	0	0
Sedation	17 (8.5)	0	4 (6.1)	0	1 (3.3)	0	0	0	0	0
Insomnia	4 (2.0)	6 (3.0)	0	0	0	1 (3.3)	0	0	0	0
URTI	0	0	0	0	0	0	0	0	0	0
Diarrhea	3 (1.5)	0	0	0	0	0	0	0	0	0
Nausea	9 (4.5)	1 (0.5)	1 (1.5)	0	0	0	0	0	1 (20.0)	0
Dry mouth	6 (3.0)	0	1 (1.5)	0	0	0	1 (6.7)	0	0	0

Data are presented as n (%). The safety set included all patients who received ≥1 dose of zuranolone. The 30-mg Cohort includes patients who initially received zuranolone 30 mg in treatment cycle 1 and received zuranolone 50 mg in subsequent treatment cycles. On treatment = A TEAE during the study period is defined as an adverse event with onset on or after the first dose of zuranolone in the treatment cycle until the first dose of zuranolone in the subsequent study period plus one day; Follow-up = A follow-up period TEAE is defined as an adverse event with onset 24 hours after the last dose of zuranolone in the same study period until Day 28 in the same study period.

Abbreviations: TEAE = treatment-emergent adverse event; URTI = upper respiratory tract infection.

Supplementary Table 2. Summary of TEAEs on treatment and during follow-up by ADT use at baseline (safety set).

	30-mg Cohort (n=725)		50-mg Cohort (n=199)	
	ADT = Yes	ADT = No	ADT = Yes	ADT = No
Study period 1, n	n=304	n=421	n=82	n=117
Treatment cycle 1	143 (47.0)	225 (53.4)	49 (59.8)	69 (59.0)
On treatment	135 (44.4)	213 (50.6)	44 (53.7)	64 (54.7)
Follow-up	32 (10.5)	47 (11.2)	11 (13.4)	16 (13.7)
Study period 2, n	n=128	n=158	n=34	n=32
Treatment cycle 2	47 (36.7)	73 (46.2)	10 (29.4)	12 (37.5)
On treatment	38 (29.7)	64 (40.5)	10 (29.4)	12 (37.5)
Follow-up	15 (11.7)	25 (15.8)	0	0
Study period 3, n	n=84	n=73	n=16	n=14
Treatment cycle 3	21 (25.0)	24 (32.9)	6 (37.5)	6 (42.9)
On treatment	18 (21.4)	21 (28.8)	5 (31.3)	4 (28.6)
Follow-up	7 (8.3)	8 (11.0)	3 (18.8)	2 (14.3)
Study period 4, n	n=47	n=49	n=10	n=5
Treatment cycle 4	9 (19.1)	19 (38.8)	3 (30.0)	2 (40.0)
On treatment	8 (17.0)	17 (34.7)	2 (20.0)	2 (40.0)

Follow-up	1 (2.1)	5 (10.2)	1 (10.0)	0
Study period 5, n	n=25	n=18	n=3	n=2
Treatment cycle 5	8 (32.0)	4 (22.2)	1 (33.3)	1 (50.0)
On treatment	8 (32.0)	4 (22.2)	1 (33.3)	1 (50.0)
Follow-up	0	0	0	0

Results are presented as n (%); n refers to the number of patients with TEAEs. The safety set included all patients who received ≥1 dose of zuranolone. The 30-mg Cohort includes patients who initially received zuranolone 30 mg in treatment cycle 1 and received zuranolone 50 mg in subsequent treatment cycles. A treatment cycle was defined as the 14-day treatment and 14-day follow-up together. A study period was defined as a treatment cycle plus an observational period of up to 48 weeks.

Abbreviations: ADT = antidepressant therapy; TEAE = treatment-emergent adverse event.

Supplementary Table 3. Summary of efficacy endpoints at Day 15 (treatment cycle 1; safety set).

	30-mg Cohort (n=725)	50-mg Cohort (n=199)
CFB in HAMD-17 total score, mean (SD)	−15.2 (7.1)	−16.0 (6.0)
HAMD-17 response,[a] n/N (%)	505/687 (73.5)	149/185 (80.5)
HAMD-17 remission,[a] n/N (%)	276/687 (40.2)	80/185 (43.2)
CFB in CGI-S score, mean (SD)	−2.1 (1.2)	−2.3 (1.2)
CFB in PHQ-9 score, mean (SD)	−10.3 (7.2)	−11.5 (7.1)

HAMD-17 response was defined as a ≥50% reduction in HAMD-17 total score from baseline. HAMD-17 remission was defined as HAMD-17 total score ≤7.

[a]n/N refers to the number of patients with nonmissing HAMD-17 at Day 15. The safety set included all patients who received ≥1 dose of zuranolone.

Abbreviations: CFB = change from baseline; CGI-S = Clinical Global Impressions-Severity; HAMD-17 = 17-item Hamilton Rating Scale for Depression; PHQ-9 = 9-item Patient Health Questionnaire; SD = standard deviation.

Supplementary Table 4. Change from period-specific baseline in HAMD-17 total score at Day 15 of repeat treatment cycles 2–5 (FAS).

	30-mg Cohort			50-mg Cohort		
	n	Baseline mean (SD) HAMD-17 total score	Day 15 CFPB	n	Baseline mean (SD) HAMD-17 total score	Day 15 CFPB
Treatment cycle 2	279	24.0 (3.3)	−13.2 (6.8)	66	23.3 (2.8)	−12.7 (5.4)
Treatment cycle 3	154	24.7 (3.2)	−13.7 (6.4)	30	23.8 (3.4)	−10.5 (9.3)
Treatment cycle 4	96	24.1 (2.6)	−14.1 (7.5)	15	23.7 (2.9)	−10.8 (5.8)
Treatment cycle 5	43	24.3 (2.9)	−14.9 (8.2)	5	26.4 (4.2)	−3.4 (3.9)

n refers to the baseline population.

Abbreviations: CFPB = change from period-specific baseline; FAS = full analysis set; HAMD-17 = 17-item Hamilton Rating Scale for Depression; SD = standard deviation.

Supplementary Table 5. Summary of HAMD-17 response and remission at Day 15 of repeat treatment cycles 2 through 5 (FAS).

HAMD-17 response[a]	30-mg Cohort n/N (%)	50-mg Cohort n/N (%)
Treatment cycle 2	171/266 (64.3)	42/65 (64.6)
Treatment cycle 3	96/151 (63.6)	14/28 (50.0)
Treatment cycle 4	62/93 (66.7)	6/15 (40.0)
Treatment cycle 5	28/39 (71.8)	0/5 (0)
HAMD-17 remission[b]	**30-mg Cohort n/N (%)**	**50-mg Cohort n/N (%)**
Treatment cycle 2	89/266 (33.5)	22/65 (33.8)
Treatment cycle 3	47/151 (31.1)	6/28 (21.4)
Treatment cycle 4	36/93 (38.7)	4/15 (26.7)
Treatment cycle 5	19/39 (48.7)	0/5

HAMD-17 response was defined as a ≥50% reduction in HAMD-17 total score from baseline. HAMD-17 remission was defined as HAMD-17 total score ≤7. The safety set included all patients who received ≥1 dose of zuranolone. The FAS included all safety set patients who achieved a HAMD-17 response at Day 15 and continued in the study beyond Day 28 (i.e., completed the initial treatment

cycle). A study period starts on or after the first dose of zuranolone in any given cycle and goes up to the start of the next cycle. Data are represented as n/N (%). n/N refers to the number of patients meeting response or remission criteria.

[a]n/N refers to the number of patients in the FAS who were dosed in the specific treatment cycle. [b]n/N refers to the number of patients with nonmissing HAMD-17 at study visit in the specific treatment cycle.

Abbreviations: HAMD-17 = 17-item Hamilton Rating Scale for Depression; FAS = full analysis set.

Supplementary Table 6. Proportion of patients reaching the threshold for a repeat treatment course as assessed by PHQ-9 and HAMD-17 (full analysis set).

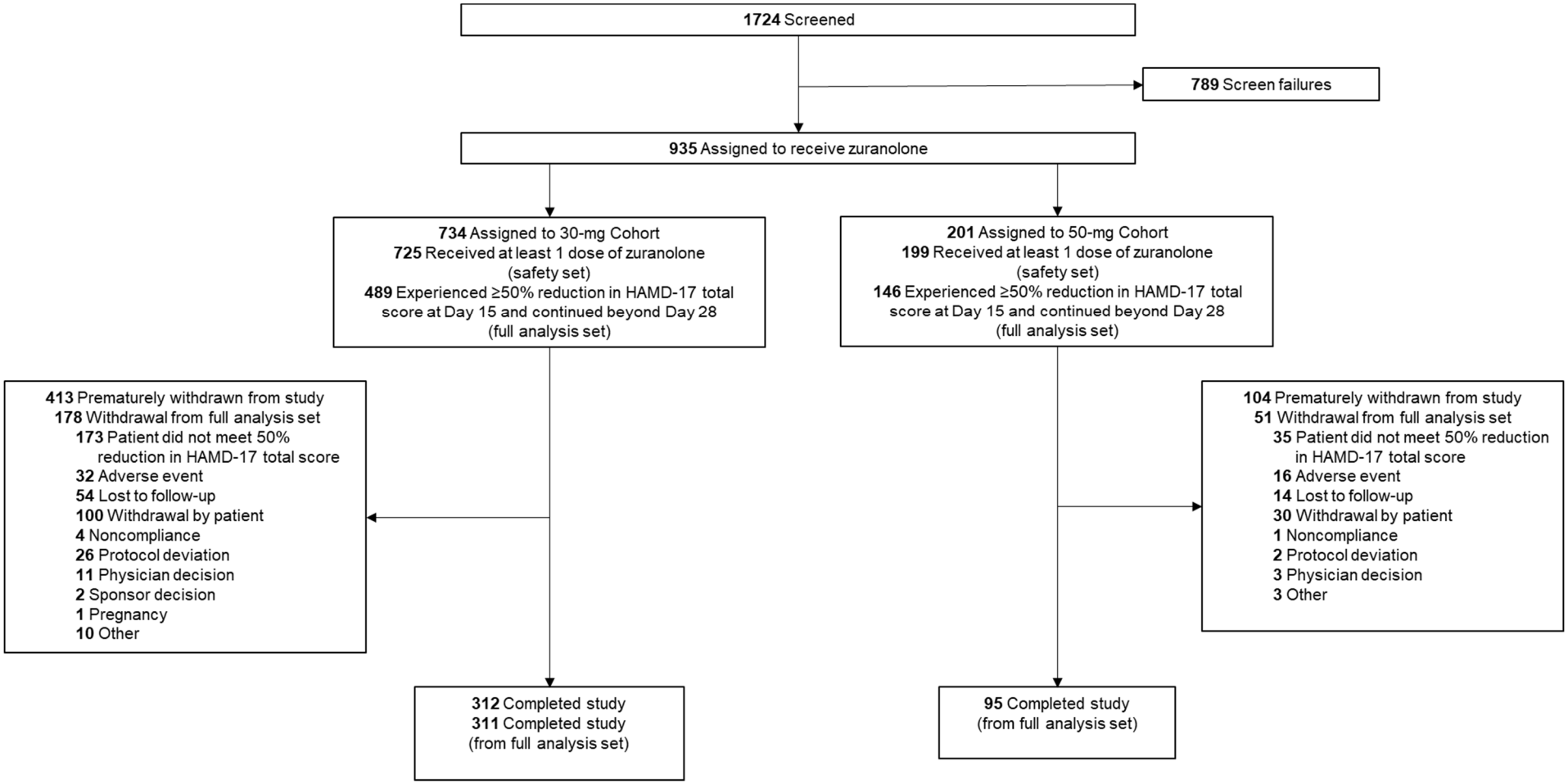
Patients eligible for a repeat treatment course in treatment cycles 2–5[a]	30-mg Cohort N=489	50-mg Cohort N=146
Treatment cycle 2 (first repeat treatment course)	n=472	n=141
Patients reaching the threshold triggered by PHQ-9 ≥10	329 (69.7)	83 (58.9)
Patients reaching the threshold triggered by HAMD-17 ≥20	290 (61.4)	68 (48.2)
Treatment cycle 3 (second repeat treatment course)	n=242	n=62
Patients reaching the threshold triggered by PHQ-9 ≥10	186 (76.9)	37 (59.7)
Patients reaching the threshold triggered by HAMD-17 ≥20	162 (66.9)	34 (54.8)
Treatment cycle 4 (third repeat treatment course)	n=137	n=24
Patients reaching the threshold triggered by PHQ-9 ≥10	110 (80.3)	19 (79.2)
Patients reaching the threshold triggered by HAMD-17 ≥20	100 (73.0)	16 (66.7)
Treatment cycle 5 (fourth repeat treatment course)	n=79	n=9
Patients reaching the threshold triggered by PHQ-9 ≥10	55 (69.6)	8 (88.9)
Patients reaching the threshold triggered by HAMD-17 ≥20	49 (62.0)	7 (77.8)

[a]Patients were eligible for a repeat treatment course if they remained in the study for the minimum 56 days between treatment courses (i.e., Day 70 counting from Day 1 of the treatment course).

n refers to number of patients who discontinued/completed the study, or who were still ongoing in the study at least 56 days since last dose of zuranolone in last treatment cycle.

Abbreviations: HAMD-17 = 17-item Hamilton Rating Scale for Depression; PHQ-9 = 9-item Patient Health Questionnaire.

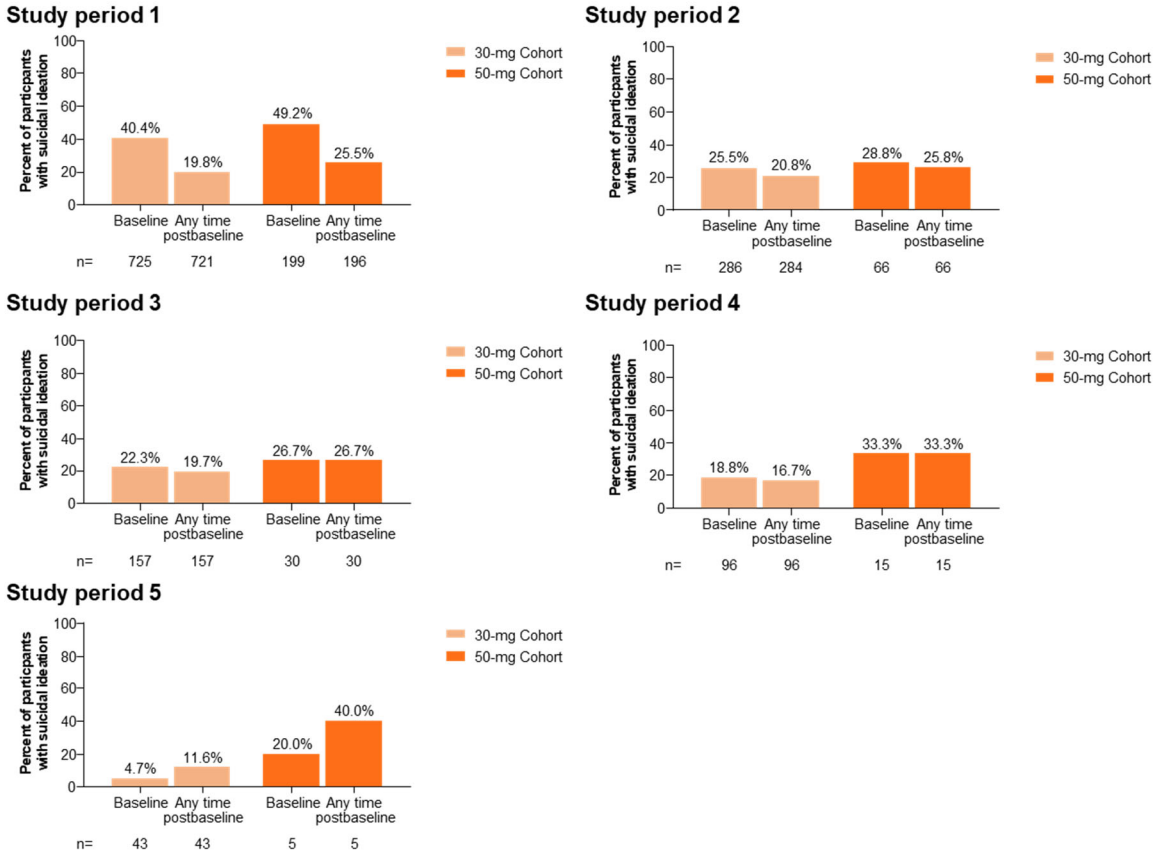
Supplementary Figure 1. Patient disposition.



Patient disposition reflects patients who completed or had the opportunity to complete 1 year of follow-up as of September 2021. The 30-mg Cohort includes patients who initially received zuranolone 30 mg in treatment cycle 1 and received zuranolone 50 mg in subsequent treatment cycles.

Abbreviation: HAMD-17 = 17-item Hamilton Rating Scale for Depression.

Supplementary Figure 2. C-SSRS evaluation at baseline and any time postbaseline by study period (safety set).

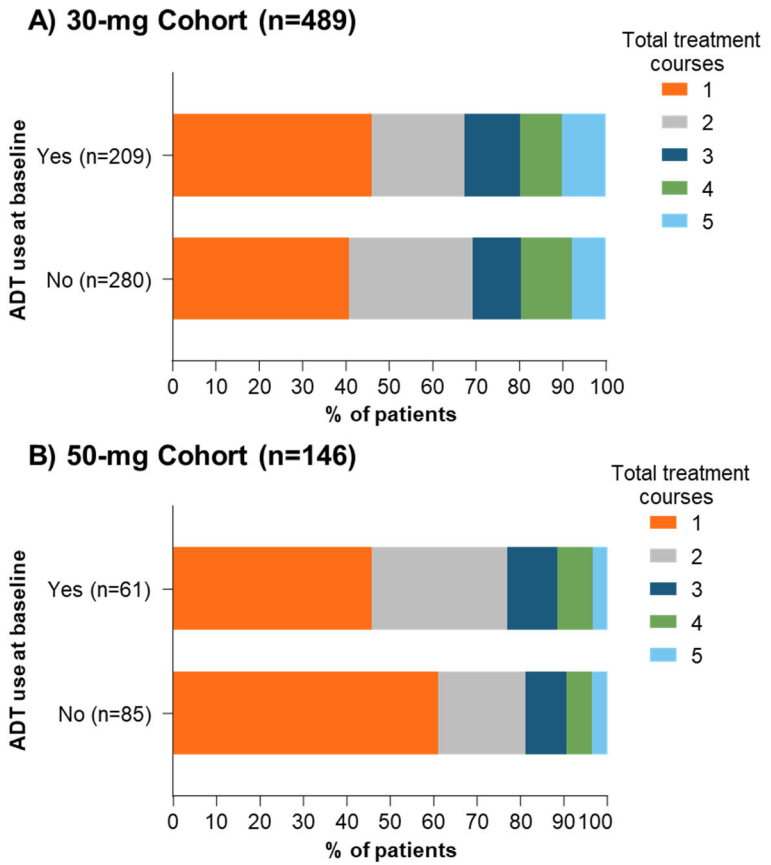


The safety set included all patients who received ≥1 dose of zuranolone. The suicidal ideation at study baseline (treatment period 1) was the worst C-SSRS score in the last 24 months (collected at screening) and since screening (collected at Day 1 before dosing). Period-specific baseline considered all assessments prior to first dose of zuranolone in the specific period, excluding lifetime

assessment. A treatment cycle was defined as the 14-day treatment and 14-day follow-up together. A study period was defined as a treatment cycle plus an observational period of up to 48 weeks.

Abbreviation: C-SSRS = Columbia Suicide Severity Rating Scale.

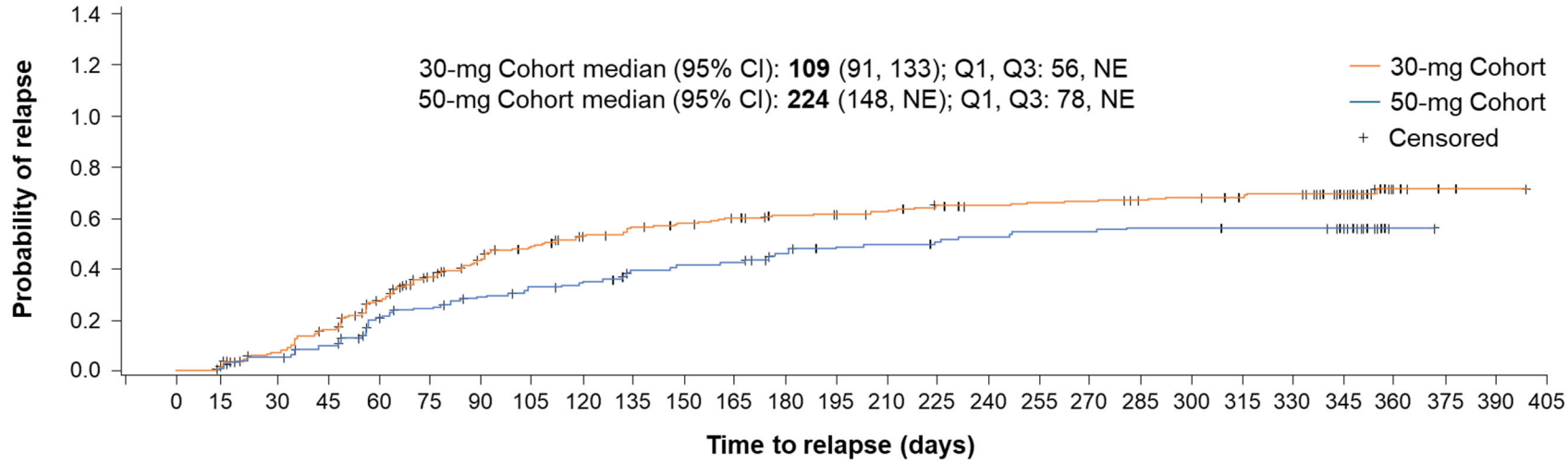
Supplementary Figure 3. Total treatment courses received by ADT use at baseline (FAS).



The FAS included all safety set patients who achieved a HAMD-17 response at Day 15 and continued in the study beyond Day 28 (i.e., completed the initial treatment cycle). Number of total treatment courses received by ADT use at baseline for patients in the 30-mg Cohort (A) and 50-mg Cohort (B).

Abbreviations: ADT = antidepressant therapy; FAS = full analysis set; HAMD-17 = 17-item Hamilton Rating Scale for Depression.

Supplementary Figure 4. Time to relapse in study period 1 (safety set).



No. of patients at risk

30-mg Cohort	495	458	433	391	325	268	234	211	182	167	160	150	141	138	130	121	117	114	112	104	101	98	95	72	6	2	1	0
50-mg Cohort	148	143	137	129	108	101	93	87	83	73	70	69	60	56	54	52	50	48	48	46	46	45	45	40	1	0	0	0

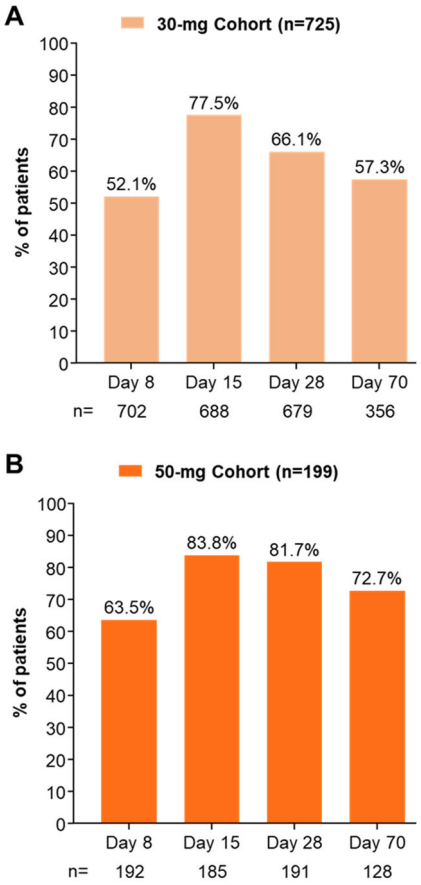
No. of patients with relapse

30-mg Cohort	0	17	36	77	129	169	197	217	236	249	254	262	266	268	272	279	280	283	285	288	291	291	294	294	295	295	295	295
50-mg Cohort	0	4	8	14	29	34	40	45	47	53	56	57	61	63	65	66	68	70	70	72	72	72	72	72	72	72	0	0

The safety set included all patients who received ≥1 dose of zuranolone. Time to relapse for study period 1 was measured among patients in the safety set and defined as the time after Day 15 of any given treatment cycle when HAMD-17 total score was ≥20 within 10 days of a PHQ-9 score ≥10. Time to relapse was calculated only for Day 15 HAMD-17 responders (≥50% reduction from baseline) in study period 1 who have at least one HAMD-17 assessment after the study period 1 Day 15 HAMD-17 date.

Abbreviations: CI = confidence interval; HAMD-17 = 17-item Hamilton Rating Scale for Depression; NE = not evaluable; No. = number; PHQ-9 = 9-item Patient Health Questionnaire; Q = quartile.

Supplementary Figure 5. Percent of patients with a CGI-I response of "very much improved" or "much improved" in the A) 30-mg Cohort and B) 50-mg Cohort (study period 1; safety set).

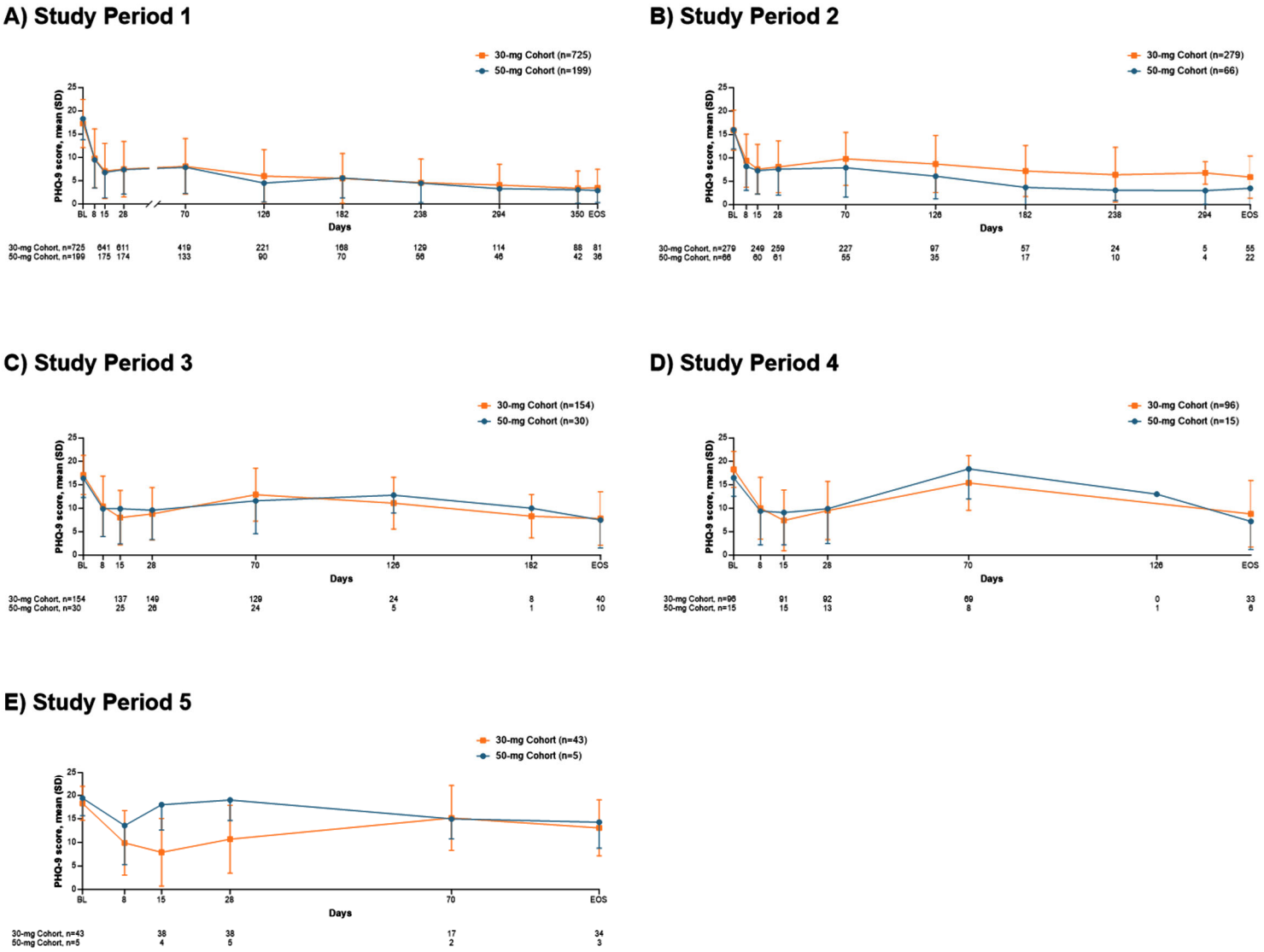


CGI-I response over time in the 30-mg Cohort (A) and 50-mg Cohort (B).

The safety set included all patients who received ≥1 dose of zuranolone.

Abbreviation: CGI-I = Clinical Global Impressions-Improvement.

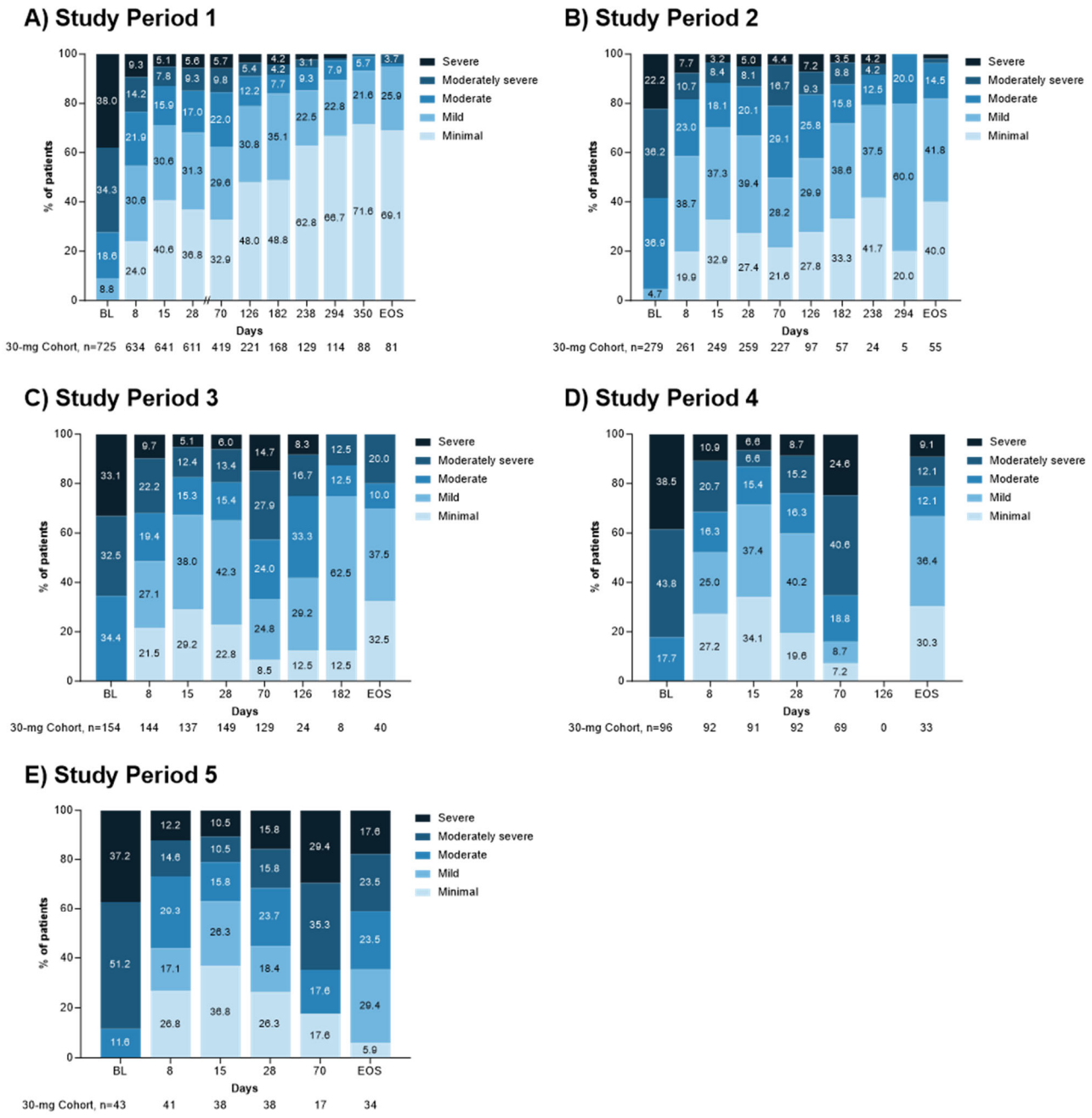
Supplementary Figure 6. Mean PHQ-9 score by study visit and study period.



Data in study period 1 are presented from the safety set through Day 28 and from the full analysis set for Day 70 to EOS.

Abbreviations: BL = baseline; EOS = end of study; PHQ-9 = 9-item Patient Health Questionnaire; SD = standard deviation.

Supplementary Figure 7. Categorical PHQ-9 severity by study visit and study period in the 30-mg Cohort.

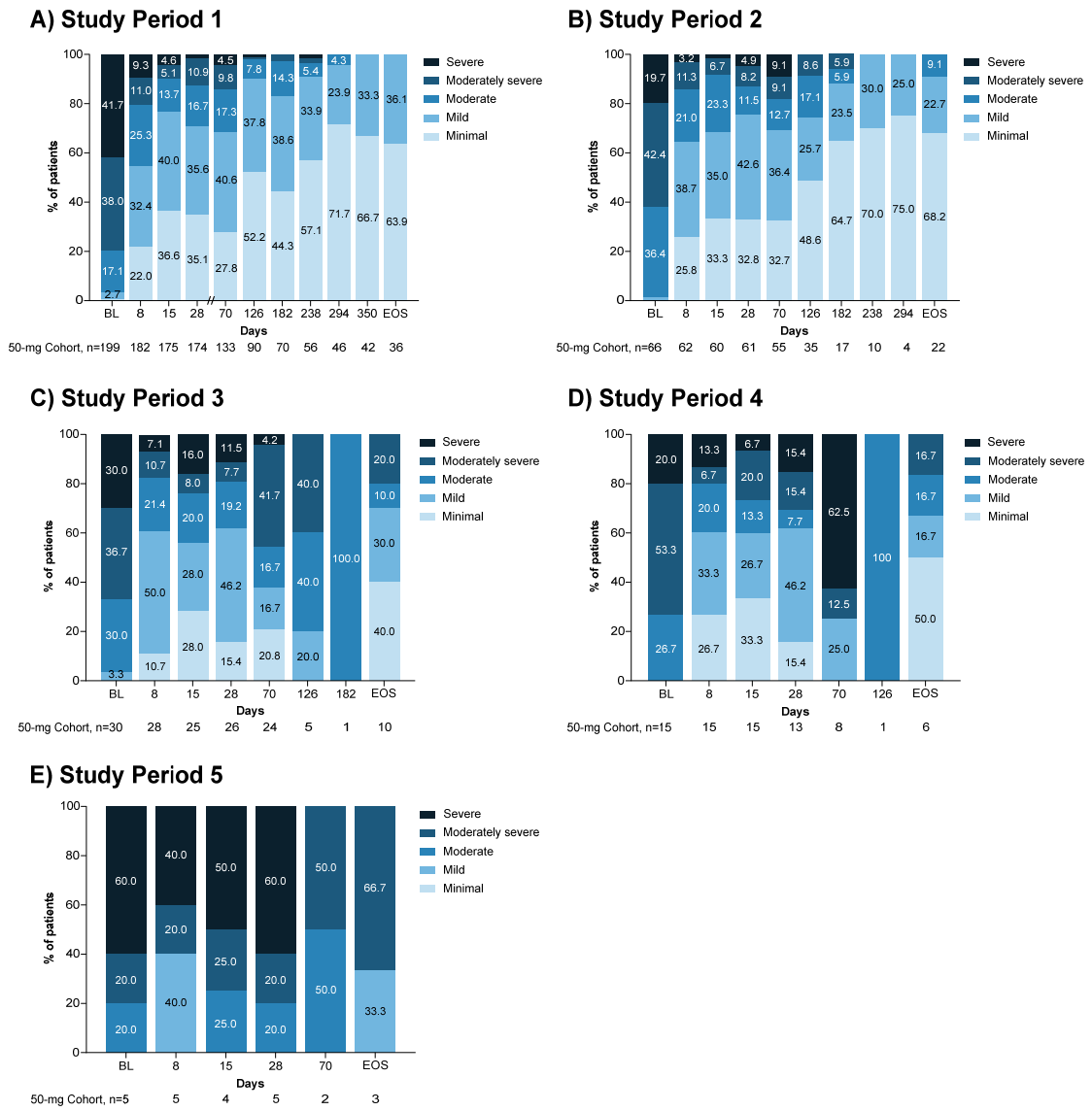


Data in study period 1 are presented from the safety set through D28 and from the full analysis set for Day 70 to EOS.

Depression severity over time was assessed by categorical ranges of PHQ-9 score: minimal, 0–4; mild, 5–9; moderate, 10–14; moderately severe, 15–19; severe, 20–27.

Abbreviations: EOS = end of study; PHQ-9 = 9-item Patient Health Questionnaire.

Supplementary Figure 8. Categorical PHQ-9 severity by study visit and study period in the 50-mg Cohort.



Data in study period 1 are presented from the safety set through D28 and from the full analysis set for D70 to EOS.

Depression severity over time was assessed by categorical ranges of PHQ-9 score: minimal, 0–4; mild, 5–9; moderate, 10–14; moderately severe, 15–19; severe, 20–27.

Abbreviations: EOS = end of study; PHQ-9 = 9-item Patient Health Questionnaire.