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

Authors: Andrew J. Cutler, MD; Gregory W. Mattingly, MD; Susan G. Kornstein, MD; Scott T. Aaronson, MD; Robert Lasser, MD; Hongling Zhang, MSc; Nilanjana Rana, MBBS; Colville Brown, MD; Seth Levin, MD; Catherine Miller, PharmD; Mona Kotecha, MD; Fiona Forrestal, MSc; and James Doherty, PhD

DOI Number: 10.4088/JCP.23m14845

LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

The Journal of Clinical Psychiatry

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).

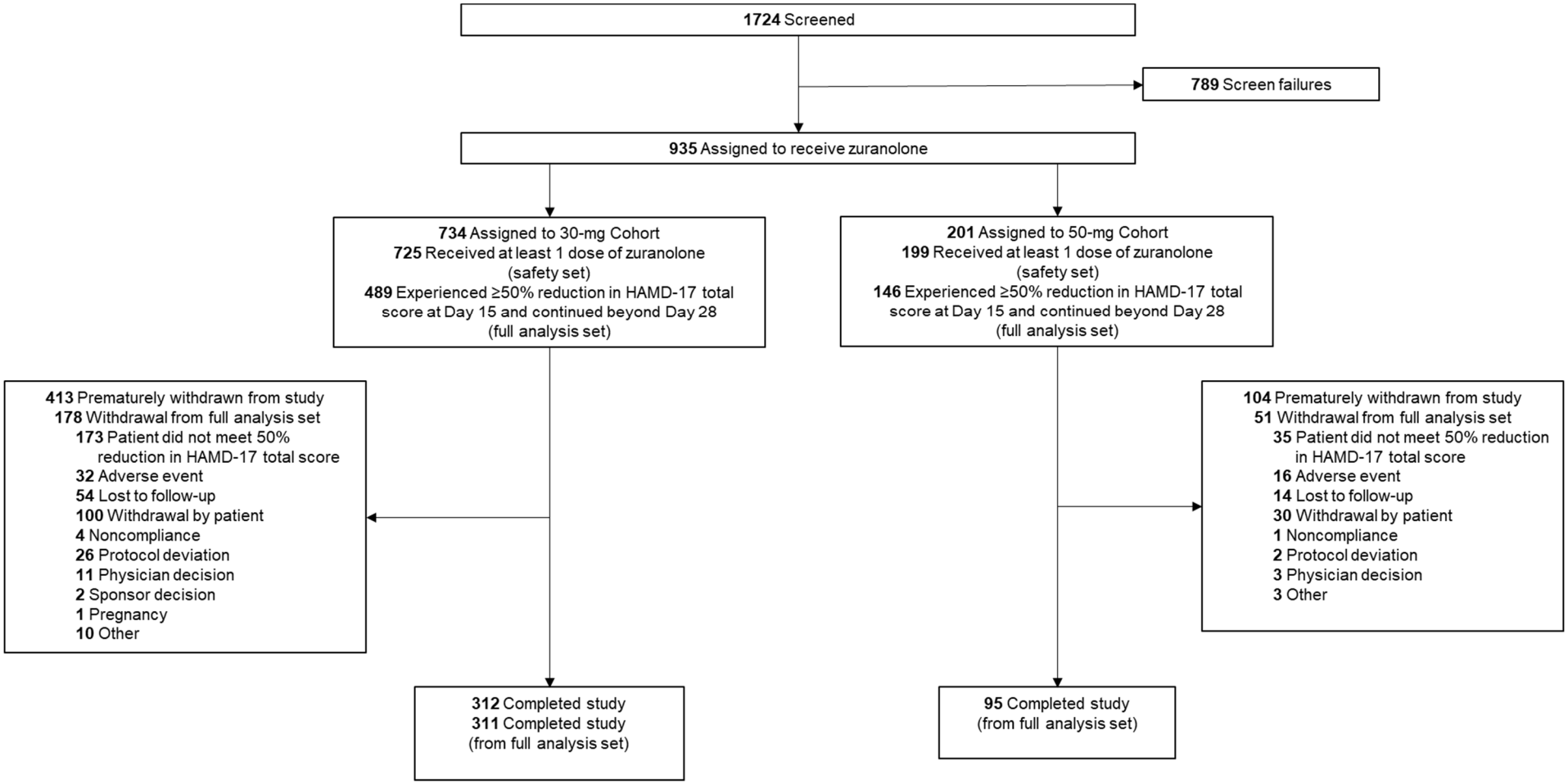
Patients eligible for a repeat treatment course in treatment cycles 2–5[a]	30-mg Cohort N=489	50-mg Cohort N=146
Treatment cycle 2 (first repeat treatment course)	n=472	n=141
Patients reaching the threshold triggered by PHQ-9 ≥10	329 (69.7)	83 (58.9)
Patients reaching the threshold triggered by HAMD-17 ≥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.

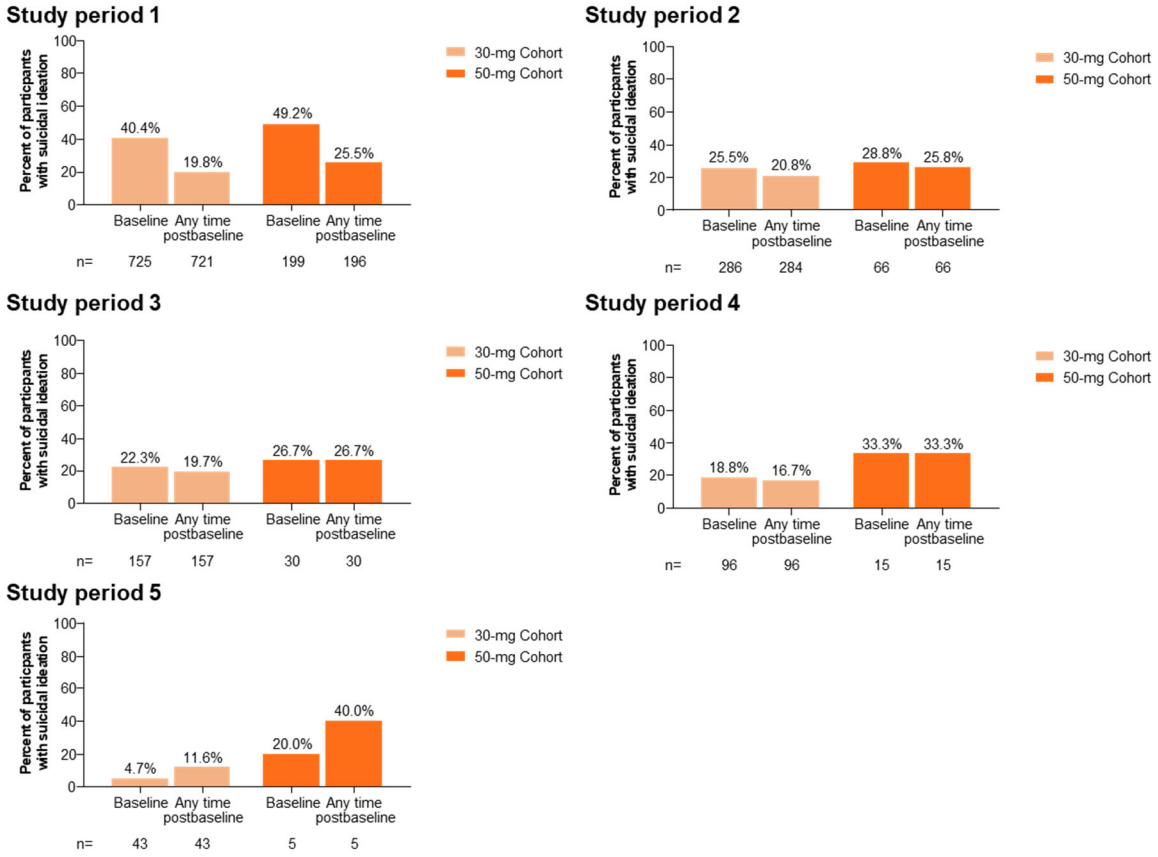
Supplementary Figure 1. Patient disposition.



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).

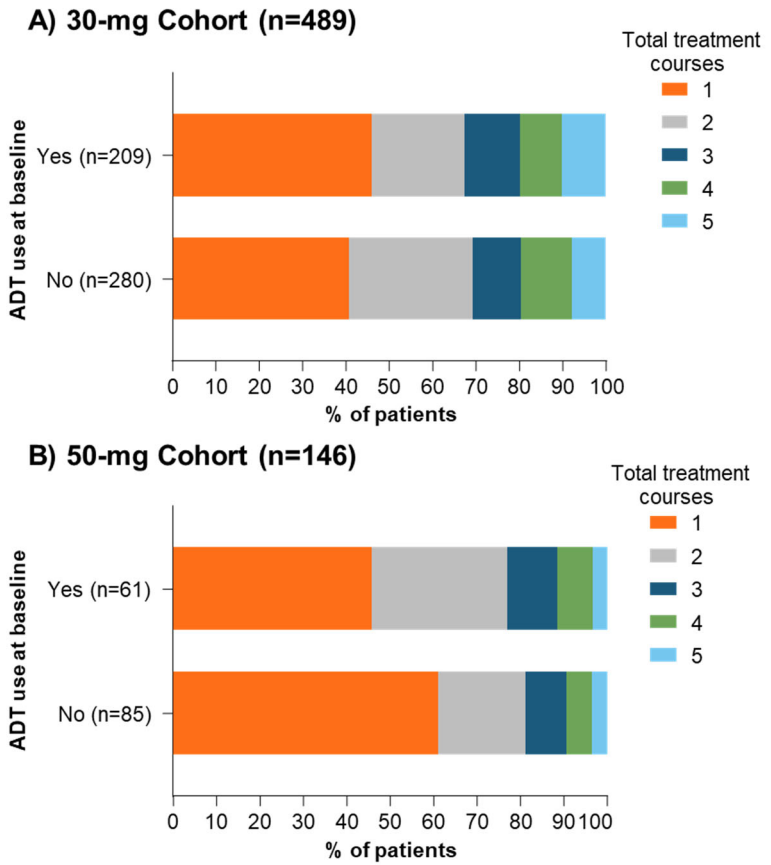


The safety set included all patients who received ≥1 dose of zuranolone. The suicidal ideation at study baseline (treatment period 1) was the worst C-SSRS score in the last 24 months (collected at screening) and since screening (collected at Day 1 before dosing). Period-specific baseline considered all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

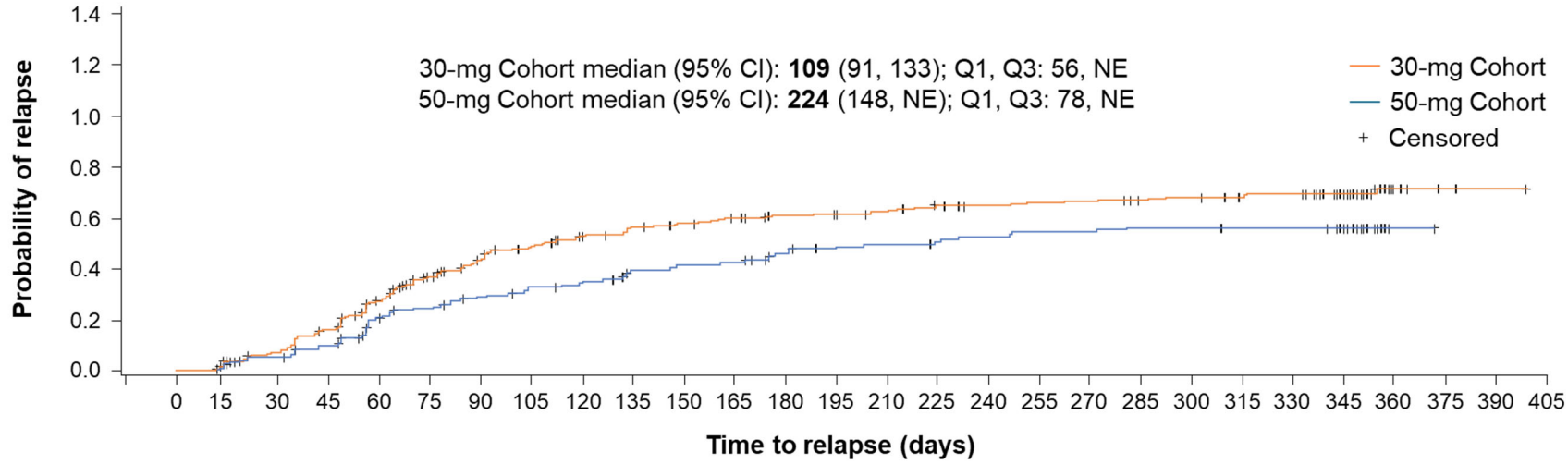
Supplementary Figure 3. Total treatment courses received by ADT use at baseline (FAS).



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

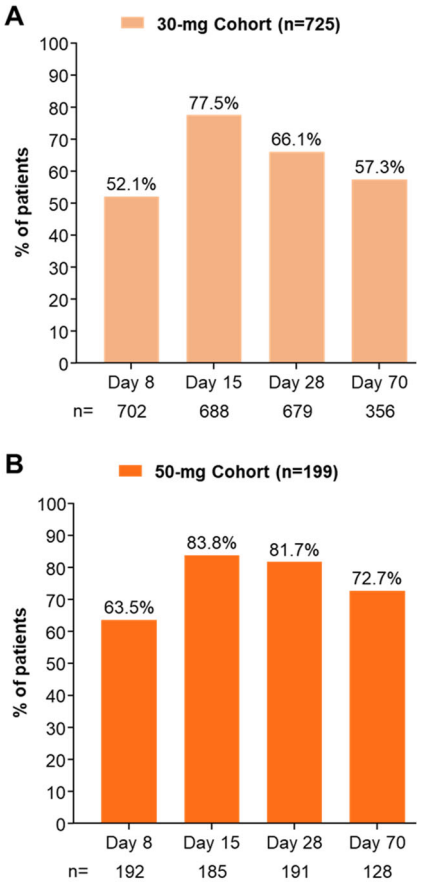
No. of patients with relapse

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).

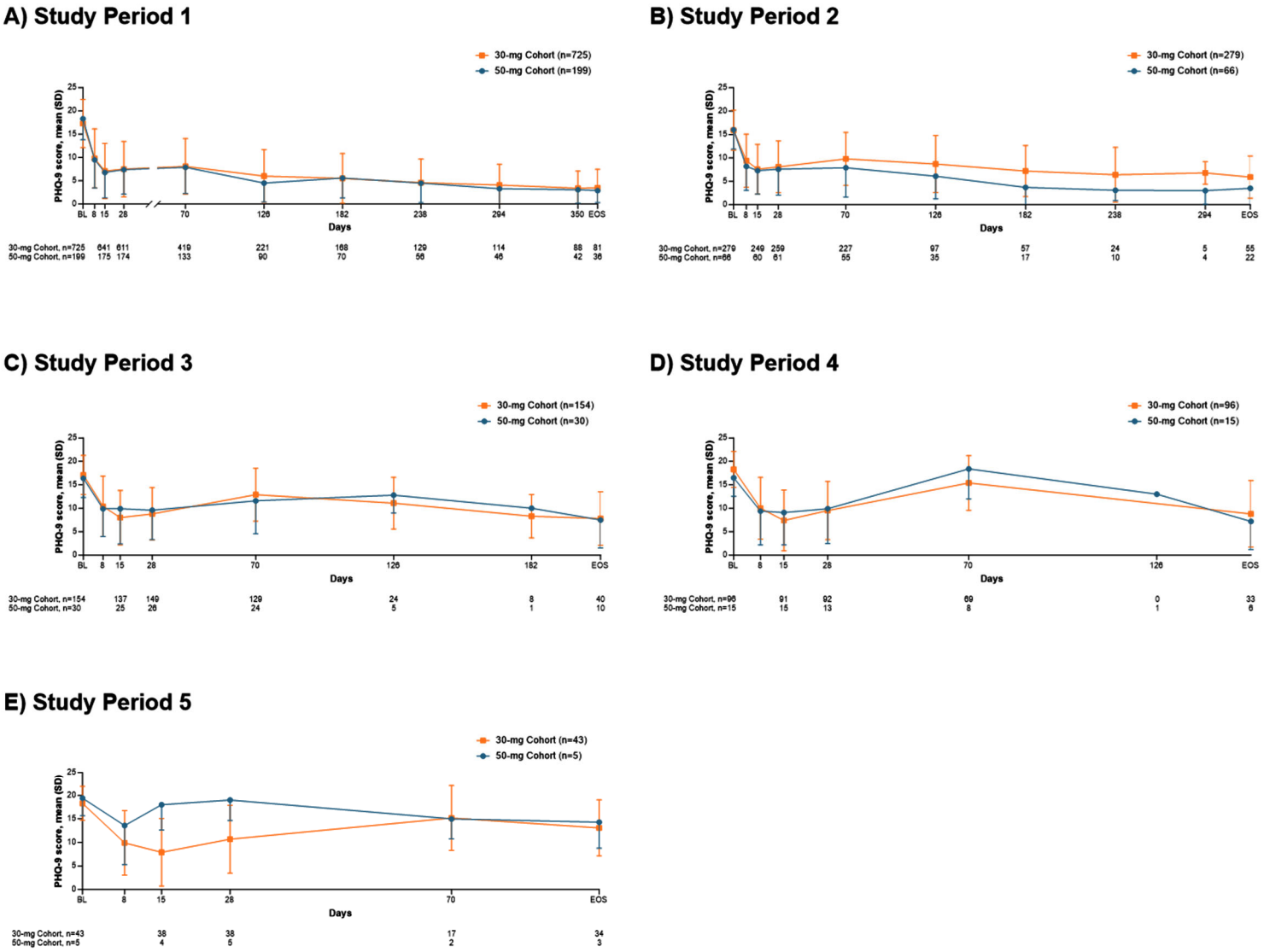


CGI-I response over time in the 30-mg Cohort (A) and 50-mg Cohort (B).

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

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

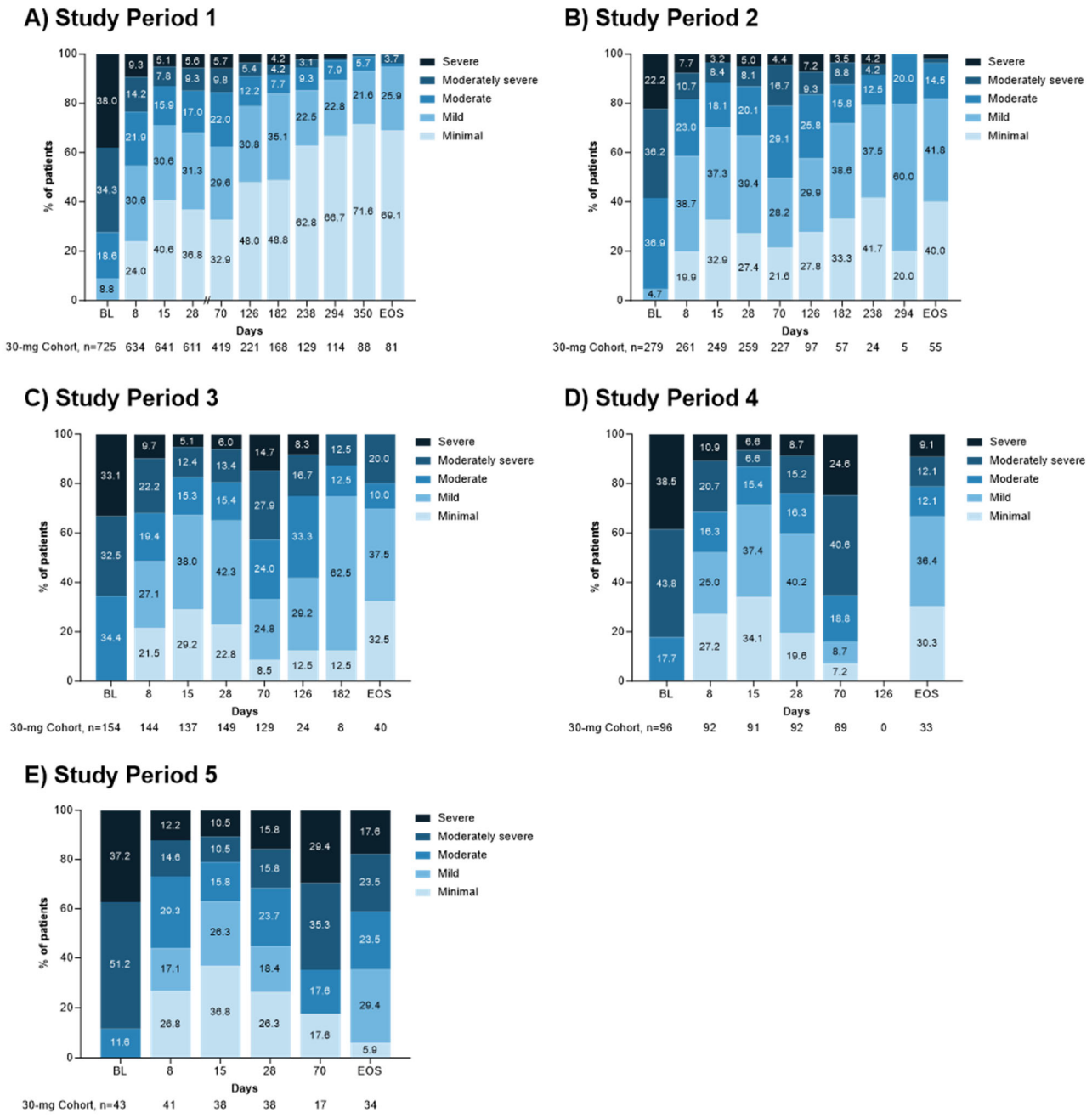
Supplementary Figure 6. Mean PHQ-9 score by study visit and study period.



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.

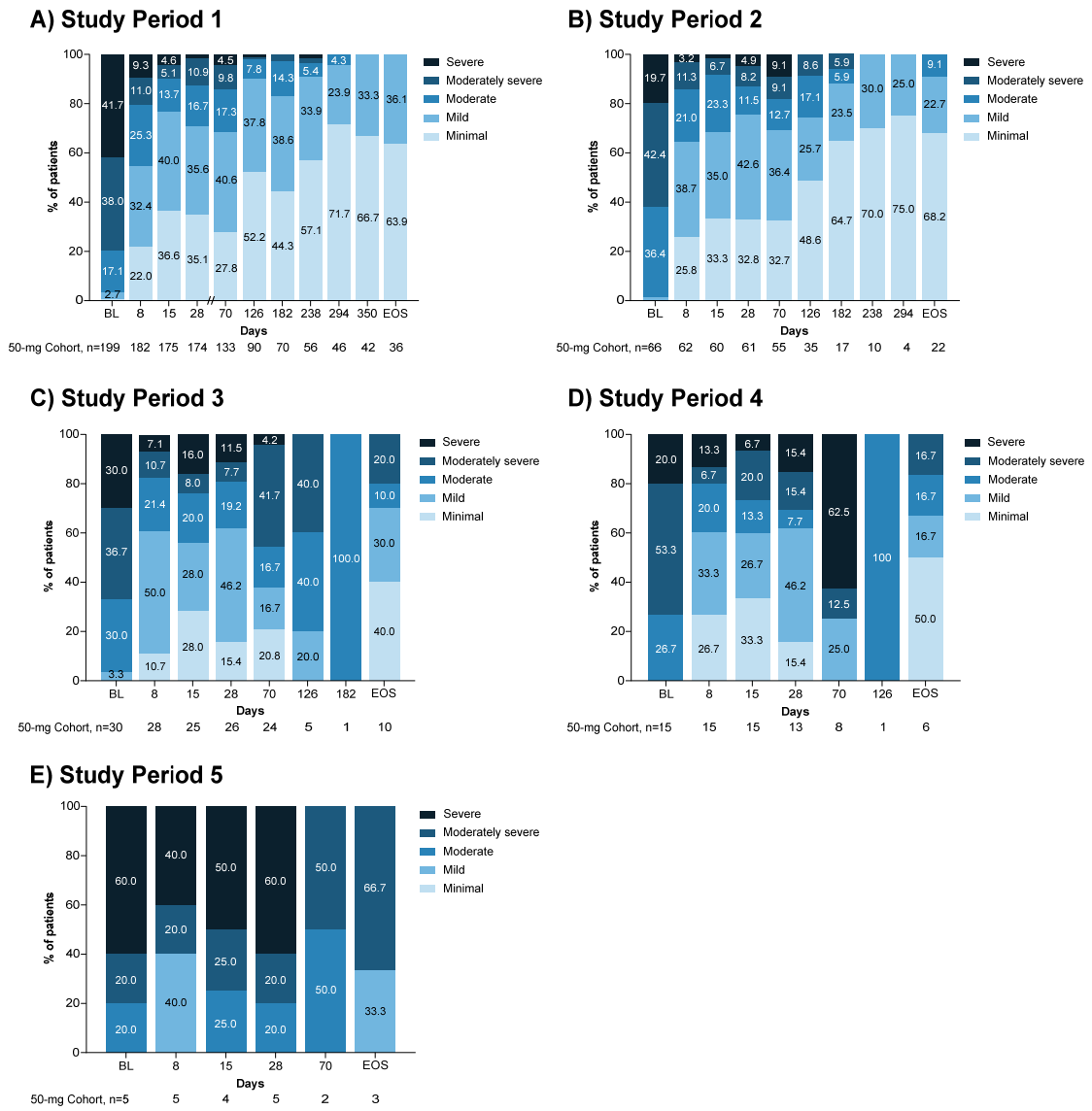


Data in study period 1 are presented from the safety set through D28 and from the full analysis set for Day 70 to EOS.

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.