Safety, Tolerability, and Efficacy of Zuranolone Repeat Treatment Courses in Adult Patients With Major Depressive Disorder–An Analysis of the Open-Label, Phase 3 SHORELINE Study

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INTRODUCTION

- Zuranolone is a positive allosteric modulator of both synaptic and extrasynaptic $GABA_A$ receptors and a neuroactive steroid being investigated in the LANDSCAPE and NEST clinical development programs as an oral, once-daily, 14-day treatment course for adults with major depressive disorder (MDD) and postpartum depression (PPD), respectively.[1-3]
  - It is hypothesized that enhancing GABAergic signaling pathways may restore network balance in brain areas dysregulated in depression.[4-6]
- Across the clinical development programs, in MDD and PPD, in 6 of 7 completed placebo-controlled studies, statistically significant improvement in depressive symptoms was observed in adults who received zuranolone 30 or 50 mg compared with patients receiving placebo as assessed by change from baseline in HAMD-17 total score.
- The ongoing SHORELINE Study (NCT03864614) is a Phase 3, open-label, longitudinal study evaluating the safety, tolerability, and need for repeat treatment courses with zuranolone 30 and 50 mg in adults with MDD followed for up to 1 year.[7]

OBJECTIVE

- This analysis of the SHORELINE Study reports completed safety and efficacy data in patients initially treated with zuranolone 30 mg (including patients who switched to 50 mg for repeat treatment) after initial and repeat treatment courses.

METHODS

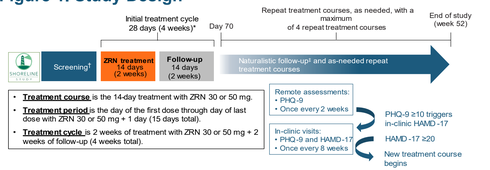
Study Population

- Adults (18–75 years) with MDD, 17-item Hamilton Rating Scale for Depression (HAMD-17) total score ≥20, and Montgomery–Åsberg Depression Rating Scale score ≥28.
- The concomitant use of antidepressant therapies is allowed as long as patients were on a stable dose for at least 60 days prior to Day 1 and agree to continue on the stable dose through the follow-up period.

Study Design

- The ongoing SHORELINE Study initially comprised a single cohort with zuranolone 30 mg as a starting dose (30-mg Cohort; **Figure 1**).
  - After a protocol amendment, a new cohort with zuranolone 50 mg was added (50-mg Cohort); patients who received zuranolone 30 mg initially received zuranolone 50 mg for repeat treatments.

Figure 1. Study Design



The SHORELINE Study was designed to evaluate efficacy in a naturalistic manner only. No statistical inferences can be drawn from efficacy outcome data.*Only responders (≥50% reduction in HAMD-17 total score from baseline) at Day 15 of the initial treatment course can continue in the SHORELINE Study. Need for repeat treatment courses is first assessed by PHQ-9. If PHQ-9 ≥10, a HAMD-17 assessment is performed within 1 week. If HAMD-17 total score ≥20, a repeat treatment course may be initiated. There is a minimum of 56 days (8 weeks) between zuranolone 14-day treatment courses to allow for a maximum of 5 treatment courses for the 1-year study period; a new repeat treatment course cannot start after Week 48. †Screening on Day –28 to Day –1 refers to timing relative to first day of treatment with zuranolone. ‡At least 6 weeks, maximum of 48 weeks. HAMD-17 = 17-item Hamilton Rating Scale for Depression; PHQ-9 = 9-item Patient Health Questionnaire; ZRN = zuranolone.

- Zuranolone is self-administered orally by patients once nightly with fat-containing food for 14 days.
- Only patients who achieve a response at Day 15 are eligible to continue in the study and receive repeat treatment; patients who continued in the study for ≥8 weeks after their last dose were eligible to receive a repeat treatment course.
  - Responders are defined as patients who achieve ≥50% reduction from baseline in HAMD-17 total score at Day 15 after the initial 14-day treatment course.
- The need for repeat treatment is assessed every 2 weeks.
  - At least 8 weeks are required between 2 consecutive zuranolone courses, allowing for a maximum of 5 treatment courses during the 1-year period.

Endpoints

- The primary endpoint is the safety and tolerability of the initial and repeat treatment courses through 1 year.
- Secondary efficacy endpoints include:
  - Need for repeat treatment courses.
  - Number of repeat treatment courses.
- The effect of initial treatment and/or repeat treatment courses assessed at the end of each treatment period (Day 15) assessed by:
  - Change from baseline in HAMD-17 total score.
  - HAMD-17 response (≥50% reduction in HAMD-17 total score from baseline).
  - HAMD-17 remission (HAMD-17 total score ≤7).

RESULTS

Table 1: Baseline Demographics and Clinical Characteristics

	Zuranolone 30-mg Cohort (n=725)
Age, mean ± SD, years	45.0 ± 14.2
Female sex, n (%)	489 (67.4)
Race, n (%)	
White	571 (78.8)
Black or African American	115 (15.9)
Asian	23 (3.2)
Multiracial	11 (1.5)
American Indian or Alaska Native	1 (0.1)
Native Hawaiian or other Pacific Islander	1 (0.1)
Other	3 (0.4)
Ethnicity, n (%)	
Not Hispanic or Latino	549 (75.7)
Hispanic or Latino	176 (24.3)
Years since initial diagnosis[a], mean ± SD	12.3 ± 11.3
Antidepressant use at baseline, n (%)	304 (41.9)
Depressive episodes – days since start of current episode[b], mean ± SD	412.4 ± 613.6
Number of depressive episodes experienced (including current episode), mean ± SD	7.1 ± 10.6
HAMD-17 total score, mean ± SD	25.3 ± 4.1

[a]Years since initial diagnosis was defined as years between the date of initial diagnosis and date of first dose. [b]Days since start of current episode was calculated as days between the date of first dose and start date of the current depressive episode.
HAMD-17 = 17-item Hamilton Rating Scale for Depression; SD = standard deviation.

Baseline Demographics and Disposition

- Overall, 725 patients received initial treatment with zuranolone 30 mg (including those who switched to 50 mg for repeat treatment; **Table 1**).
- The mean ± standard deviation age for participants was 45.0 ± 14.2 years; 67.4% were female (**Table 1**).

Safety and Tolerability

- Incidence of treatment-emergent adverse events (TEAEs) were highest in treatment courses 1 and 2; safety trends identified with repeated treatments were consistent with previous studies.
- The most common (>5% incidence in any course) TEAEs reported in the 30-mg Cohort across all treatment courses included headache, somnolence, upper respiratory infection, diarrhea, dizziness, dry mouth, sedation, and insomnia (**Table 2**).

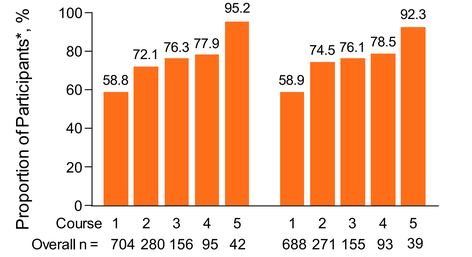
Table 2: Overall Safety and Tolerability of Zuranolone in the 30-mg Cohort (Treatment Courses 1–5)

n (%)	Treatment courses 1–5 (N=725)	Treatment course 1 (n=725)	Treatment course 2 (n=286)	Treatment course 3 (n=157)	Treatment course 4 (n=96)	Treatment course 5 (n=43)
Any 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)
≥1 SAE	20 (2.8)	6 (0.8)	1 (0.3)	1 (0.6)	0 (0.0)	0 (0.0)
Treatment discontinuation due to TEAE	20 (2.8)	16 (2.2)	3 (1.0)	0 (0.0)	0 (0.0)	1 (2.3)
Study withdrawal due to TEAE	32 (4.4)	19 (2.6)	4 (1.4)	1 (0.6)	0 (0.0)	1 (2.3)
Dose reduction due to TEAE	44 (6.1)	25 (3.4)	12 (4.2)	5 (3.2)	2 (2.1)	6 (14.0)
Death[a]	1 (0.1)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Common TEAEs (≥5% of patients in any treatment course)						
Headache	103 (14.2)	59 (8.1)	15 (5.2)	4 (2.5)	2 (2.1)	0 (0.0)
Somnolence	86 (11.9)	70 (9.7)	13 (4.5)	6 (3.8)	4 (4.2)	2 (4.7)
Dizziness	54 (7.4)	42 (5.8)	7 (2.4)	4 (2.5)	2 (2.1)	1 (2.3)
Dry mouth	43 (5.9)	32 (4.4)	7 (2.4)	1 (0.6)	0 (0.0)	1 (2.3)
Sedation	40 (5.5)	32 (4.4)	10 (3.5)	2 (1.3)	3 (3.1)	2 (4.7)

[a]Due to a TEAE with a fatal outcome and not limited to a Preferred Term of death.
SAE, serious adverse event; SD = standard deviation; TEAE = treatment-emergent adverse event.

- Most patients with TEAEs reported mild or moderate events across all treatment courses (91%).
- One patient in the overall population died during the study (>150 days after completing 2 treatment courses) due to a severe TEAE of intercranial hemorrhage and severe herpes simplex encephalitis; these events were not considered related to zuranolone by the investigator.
- There was no indication for increased suicidal ideation or behavior at any time point during the study, assessed by the Columbia Suicide Severity Rating Scale (**Figure 2**).

Figure 2. Proportion of Patients With No Suicidal Ideation and/or Behavior as Assessed by C-SSRS Evaluation in the 30-mg Cohort by Treatment Course



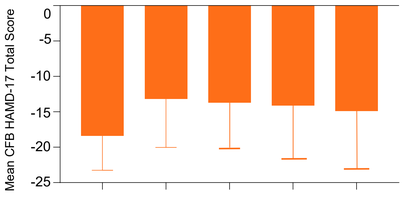
*Proportion of patients answering, "no suiciding ideation/behavior". Treatment cycle 1 includes all nonresponder, while only participants who are HAMD-17 responders (≥50% improvement in HAMD-17 total score from baseline) at Day 15 are included for treatment cycles 2-5.
C-SSRS = Columbia Suicide Severity Rating Scale; HAMD-17 = 17-item Hamilton Rating Scale for Depression..

- The safety findings and trends identified in any TEAE category were consistent with previous studies, in patients followed for up to 1 year.

Efficacy: Improvement in Depressive Symptoms

- Treatment with zuranolone demonstrated improvement in depressive symptoms (as measured by change from baseline in HAMD-17 total score) regardless of the number of previous treatment courses (**Figure 3**).

Figure 3. Change From Baseline in HAMD-17 Total Score At Day 15 in the 30-mg Cohort (Treatment Courses 1–5)



	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5
n =	489	266	151	93	39
Baseline, mean (SD) =	25.3 (4.19)	24.0 (3.26)	24.7 (3.23)	24.1 (2.56)	24.3 (2.92)

Treatment cycle 1 includes all nonresponder, while only participants who are HAMD-17 responders (≥50% improvement in HAMD-17 total score from baseline) at Day 15 are included for treatment cycles 2-5.
CFB = change from baseline; HAMD-17 = 17-item Hamilton Rating Scale for Depression.

Efficacy: Response and Remission

- Treatment with zuranolone 30 mg demonstrated sustained HAMD-17 response and remission regardless of the number of previous treatment courses.
- In total, 67.4% (489/725) of patients receiving zuranolone 30 mg achieved a HAMD-17 response at Day 15 of treatment course 1 and completed the first treatment course.
  - Of these patients, 68.5% (335/489) received only 1 or 2 treatment courses during their time in the study.
    - The median time to the first repeat treatment course was 135 days for patients in the zuranolone 30-mg Cohort.
  - The percentage of patients who achieved a response was generally consistent throughout treatment courses 2–5 (63.6%–71.8%).
  - The percentage of patients who experienced remission was generally consistent across all treatment courses (31.1%–54.6%).
    - The number of participants who received repeat treatment decreased with subsequent treatment courses.

CONCLUSIONS

- Treatment with zuranolone was generally well tolerated, with a safety profile consistent with that observed in other clinical trials of zuranolone to date.[1-3,8]
- The safety and tolerability of zuranolone was consistent over repeat treatment courses through up to 1 year.
- Patients treated with zuranolone experienced improvement in depressive symptoms regardless of the number of previous treatment courses, suggesting an ability to recapture the effect.
- Overall, the majority of patients required 1 or 2 treatment courses and the median time to the first repeat treatment was 135 days.
- These data support 14-day treatment courses with oral zuranolone as an episodic treatment for patients with MDD.

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Disclosures

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