Efficacy and Safety of Zuranolone in Adults With Major Depressive Disorder With and Without Use of Standard-of-Care Antidepressants at Baseline in the LANDSCAPE Clinical Development Program

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INTRODUCTION

- Major depressive disorder (MDD) is a multifactorial and heterogeneous disorder that may result from brain network dysregulation, including dysfunctional GABAergic signaling.[1-5]
- Standard-of-care (SOC) anti-depressant therapies (ADTs) typically require weeks to months to produce desired effects and necessitate long-term treatment to prevent relapse.[2,6]
  - There is a significant unmet need for innovative treatment options that can offer rapid and sustained improvements in depressive symptoms without chronic dosing.
- Zuranolone is an investigational, positive allosteric modulator of synaptic and extra-synaptic $GABA_A$ receptors and a neuroactive steroid in clinical development as an oral, once-daily, 14-day treatment course for adults with MDD in the LANDSCAPE clinical development program (**Figure 1**).[7-9]
  - Modulation of GABAergic signaling pathways may restore network balance in brain areas dysregulated in depression.[3,5,10]
- The efficacy and tolerability of zuranolone used as monotherapy or concomitantly with SOC ADTs in adults with MDD across the clinical development program have not been previously characterized.

Figure 1. LANDSCAPE: Zuranolone Clinical Development Program in MDD

LANDSCAPE PROGRAM

	Initiation			Maintenance	Co-Initiation with ADT
	Monotherapy or add-on to existing ADT			Monotherapy or add-on to existing ADT	Simultaneous start with ADT
	MOUNTAIN STUDY	WATERFALL STUDY	SHORELINE STUDY	SHORELINE STUDY	CORAL STUDY
Study #	MDD-201B (Ph2)	MDD-201A (Ph2)	MDD-201B (Ph2)	MDD-303 (Ph3)	MDD-305 (Ph3)
Design	RCT	RCT	RCT	Open-label; longitudinal	RCT
Primary objective	Efficacy: 30 mg vs placebo	Efficacy: 20 mg or 30 mg vs placebo[a]	Efficacy: 50 mg vs placebo	Long-term safety: 1-year follow-up (30 and 50 mg)[b]	Efficacy: 50 mg + open-label ADT vs placebo + open-label ADT
Primary endpoint	CFB in HAMD-17 at Day 15	CFB in HAMD-17 at Day 15	CFB in HAMD-17 at Day 15	Safety/tolerability over one year	CFB in HAMD-17 at Day 3
Population	HAMD-17 ≥22	HAMD-17 ≥22 MADRS ≥22	HAMD-17 ≥24	HAMD-17 ≥20 MADRS ≥28	HAMD-17 ≥24
Status	Completed	Completed	Completed	Ongoing	Completed

Grayed-out CORAL trial is not included in the analyses presented here.
[a]Data presented here are for the zuranolone 30 mg and placebo arms only.
[b]The SHORELINE Study initially enrolled patients using zuranolone 30 mg. After a protocol amendment, a new cohort with zuranolone 50 mg was added (50-mg Cohort); patients who received zuranolone 30 mg initially receive zuranolone 50 mg for repeat treatments.
ADT = antidepressant therapy; CFB = change from baseline; HAMD-17 = 17-item Hamilton Rating Scale for Depression; MADRS = Montgomery–Åsberg Depression Rating Scale; MDD = major depressive disorder; Ph = Phase; RCT = randomized, double-blind, placebo-controlled trial design.

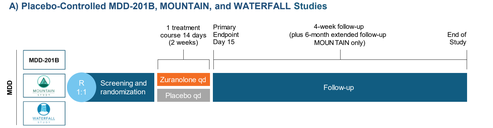
OBJECTIVE

- This analysis reports the efficacy of zuranolone as monotherapy or as an adjunct therapy to existing SOC ADT use in the following LANDSCAPE randomized clinical trials: MDD-201B Study (NCT03000530), MOUNTAIN Study (NCT03672175), WATERFALL Study (NCT04442490), and SHORELINE Study (NCT03864614).

METHODS

- The MDD-201B Study investigated zuranolone 30 mg or placebo; the MOUNTAIN Study investigated zuranolone 20 mg (data not reported) or 30 mg vs placebo; the WATERFALL Study investigated zuranolone 50 mg vs placebo; and the open-label SHORELINE Study investigated zuranolone 30 mg (completed) and 50 mg (ongoing; **Figures 1 and 2**).

Figure 2. 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.
[a]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 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.
[b]Screening on Day –28 to Day –1 refers to timing relative to first day of treatment with zuranolone. [c]At least 6 weeks, maximum of 48 weeks.
CFB = change from baseline; HAMD-17 = 17-item Hamilton Rating Scale for Depression; MDD = major depressive disorder; PHQ-9 = 9-item patient health questionnaire; qd = once daily; R = randomization; ZRN = zuranolone.

- Adult patients with MDD with a 17-item Hamilton Rating Scale for Depression (HAMD-17) total score ≥22 for the MDD-201B Study and the MOUNTAIN Study, ≥24 for the WATERFALL Study, and ≥20 for the SHORELINE Study were eligible (**Figure 1**).
- In all studies, concomitant use of SOC ADTs was permitted, provided that patients were on a stable dose for at least 60 days prior to enrollment (30 days in MDD-201B) and during the studies.
- The severity of depression was assessed using the HAMD-17 total score throughout treatment and follow up periods.
- Efficacy was evaluated by change from baseline (CFB) in the HAMD-17 total score.
- Safety outcomes were assessed by incidence and severity of treatment-emergent adverse events (TEAEs).

RESULTS

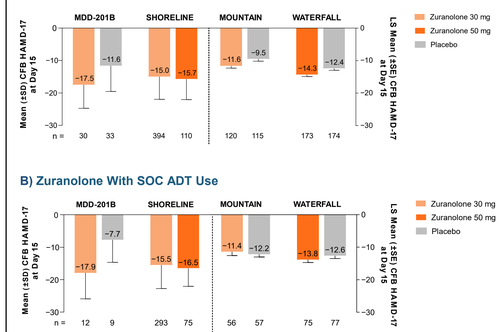
- Demographics and baseline clinical characteristics were generally balanced between treatment arms in the 3 placebo-controlled studies (**Table 1**).
- Adults with MDD demonstrated improvements in depressive symptoms (measured by mean CFB in HAMD-17 total score) at Day 15 (primary endpoint in the placebo-controlled studies) following treatment with zuranolone as monotherapy or as an adjunct therapy to SOC ADT use (**Figure 3**)

Table 1. Demographics and Baseline Characteristics (Placebo-Controlled Studies)

	MDD-201B		MOUNTAIN		WATERFALL	
	Zuranolone 30 mg (n=45)	Placebo (n=44)	Zuranolone 30 mg (n=192)	Placebo (n=190)	Zuranolone 50 mg (n=268)	Placebo (n=269)
Age, mean (SD), years	49.1 (13.6)	38.3 (12.2)	42.5 (11.8)	41.4 (12.3)	39.4 (12.3)	40.1 (12.6)
Female sex, n (%)	25 (55.6)	30 (68.2)	137 (71.4)	130 (68.4)	186 (69.4)	166 (61.7)
Race, n (%)						
White	7 (15.6)	16 (36.4)	108 (56.3)	118 (62.1)	169 (63.1)	206 (76.6)
Black/African American	36 (80.0)	28 (63.6)	75 (39.1)	60 (31.6)	75 (28.0)	46 (17.1)
Asian	1 (2.2)	0	3 (1.6)	5 (2.6)	13 (4.9)	4 (1.5)
Multiracial	0	0	4 (2.1)	5 (2.6)	7 (2.6)	5 (1.9)
American Indian or Alaskan Native	0	0	0	1 (0.5)	1 (0.4)	3 (1.1)
Native Hawaiian or other Pacific Islander	0	0	2 (1.0)	1 (0.5)	1 (0.4)	1 (0.4)
Other	1 (2.2)	0	0	0	2 (0.7)	4 (1.5)
Ethnicity, n (%)						
Hispanic or Latino	1 (2.2)	7 (15.9)	58 (21.6)	54 (20.1)	58 (21.6)	54 (20.1)
Not Hispanic or Latino	44 (97.8)	37 (84.1)	210 (78.4)	160 (84.2)	210 (78.4)	215 (79.9)
BMI, mean (SD), kg/m^2	30.0 (6.3)	29.9 (5.2)	29.6 (6.3)	31.5 (7.6)	29.6 (6.3)	30.3 (6.2)
HAMD-17 total score, mean (SD)	25.2 (2.6)	25.7 (2.4)	25.9 (2.9)	25.8 (3.1)	26.8 (2.6)	26.9 (2.7)
History of any antidepressant use, n (%)	29 (64.4)	31 (70.5)	133 (70.0)	133 (69.3)	183 (68.3)	190 (70.6)
Concurrent antidepressant use (any stable dose), n (%)	12 (26.7)	10 (22.7)	79 (41.6)	73 (38.0)	82 (30.5)	81 (30.2)

BMI = body mass index; HAMD-17 = 17-item Hamilton Rating Scale for Depression; n = number; SD = standard deviation.

Figure 3. Change From Baseline in HAMD-17 Total Score at Day 15 in the LANDSCAPE Studies



Data in MDD-201B and SHORLINE (left of dotted line) are mean ± SD. The SHORELINE Study was designed to evaluate efficacy in a naturalistic manner only. No statistical inferences can be drawn from efficacy outcome data. Data in MOUNTAIN and WATERFALL (right of dotted line) are LS mean ± SE. MOUNTAIN did not meet its primary endpoint.
ADT = antidepressant therapy; CFB = change from baseline; HAMD-17 = 17-item Hamilton Rating Scale for Depression; LS = least squares; n = number of patients at that visit; SD, standard deviation; SOC = standard-of-care.

- Collectively, across the 3 placebo-controlled trials, effects compared to placebo were consistently observed across trials for patients treated with zuranolone monotherapy. Importantly, patients treated with stable SOC ADT also showed improvements with zuranolone vs placebo, which similar to monotherapy, were observed across the 3 studies (**Table 2** and **Figure 3**).
  - Similarly, in the SHORELINE Study (interim data for 50 mg), patients receiving zuranolone monotherapy or zuranolone as an adjunct therapy to SOC ADTs demonstrated improvement in depressive symptoms at Day 15 (**Figure 3**) and improvements were sustained throughout the study (**Table 2**).

Table 2. Change From Baseline in HAMD-17 Total Score With Zuranolone as an Adjunct Therapy to SOC ADT Use

	MDD-201B[a]		MOUNTAIN[b]		WATERFALL[b]		SHORELINE[a]	
	Zuranolone 30 mg		Zuranolone 30 mg		Zuranolone 50 mg		Zuranolone 30 mg	Zuranolone 50 mg
Day	Without ADT (n=33)	With ADT (n=12)	Without ADT (n=132)	With ADT (n=60)	Without ADT (n=188)	With ADT (n=78)	Without ADT (n=421)	With ADT (n=304)	Without ADT (n=117)	With ADT (n=82)
3	−8.3 (7.0)	−10.8 (6.7)	−7.4 (0.5)	−8.6 (0.8)	−10.0 (0.4)	−9.8 (0.6)	—	—	—	—
28	−14.6 (8.5)	−18.5 (7.5)	−10.7 (0.6)	−11.0 (1.1)	−12.6 (0.6)[c]	−12.9 (0.9)[d]	−12.9 (7.8)	−13.8 (8.4)	−14.4 (6.8)	−14.9 (6.7)
42/45	−14.3 (8.6)	−16.9 (8.6)	−11.0 (0.7)	−11.2 (1.2)	−13.6 (0.7)	−13.6 (1.0)	—	—	—	—
70	—	—	−11.5 (0.7)	−12.1 (1.2)	—	—	−10.8 (8.4)[e]	−13.6 (9.7)[f]	−13.7 (7.1)[g]	−14.3 (7.5)[h]

[a]Data presented as mean (SD). [b]Data are presented as least squares mean (SE). [c]n=167. [d]n=72. [e]n=100. [f]n=175. [g]n=77. [h]n=57. WATERFALL and MDD-201 met their primary endpoint; MOUNTAIN was not significant at the primary endpoint.
ADT = antidepressant; CFB = change from baseline; HAMD-17 = 17-item Hamilton Rating Scale for Depression; SD = standard deviation; SE = standard error; SOC = standard-of-care.

- Zuranolone was generally well tolerated in the MDD-201B, MOUNTAIN, WATERFALL, and SHORELINE Studies.
  - The most common (>5% incidence in zuranolone arms) TEAEs included headache, somnolence, dizziness, sedation, upper respiratory tract infection, diarrhea, and fatigue (**Table 3**).
  - Among patients who experienced a TEAE, most had mild or moderate events (zuranolone vs placebo: MDD-201B, 100% vs 100%; MOUNTAIN, 99% vs 100%; WATERFALL, 97% vs 99%; SHORELINE zuranolone 30 mg vs 50 mg [treatment period 1], 99% vs 95%).
    - In LANDSCAPE clinical trials in patients with MDD to date, no TEAEs of weight gain or sexual dysfunction were reported, and no signal for increased suicidal ideation or suicidal behavior associated with zuranolone has been observed (data not shown).
- In the MOUNTAIN, WATERFALL, and SHORELINE Studies, the overall incidence of TEAEs was comparable between patients receiving zuranolone who were taking an ADT at baseline and those who were not (data not shown).

Table 3. Common TEAEs (>5% in Zuranolone Arms) in the LANDSCAPE Studies

Preferred Term, %	Zuranolone 30 or 50 mg	Placebo
Any TEAE	53.3–68.8	45.5–52.1
Headache	6.3–17.8	7.9–15.9
Somnolence	6.7–16.1	2.3–3.0
Dizziness	6.3–15.1	2.2–3.7
Nausea	3.8–11.1	2.3–4.7
Sedation	4.4–13.8	0.4–4.5
Diarrhea	0–13.8	5.2–6.8
Fatigue	1.1–10.0	0–3.2
URTI	0–8.1	0–3.7

Data shown as percentage ranges across MDD-201B, MOUNTAIN, WATERFALL, and SHORELINE. TEAEs are coded using MedDRA versions 19 (MDD-201B), 21 (MOUNTAIN), 23 (WATERFALL), and 24 (SHORELINE). A TEAE is defined as follows: MDD-201B, an AE with onset after the start of study drug, or any worsening of a pre-existing medical condition/AE with onset after the start of study drug and until 7 days after the last dose; MOUNTAIN, an AE with onset on or after the first dose of study drug but on or before last dose date + 1 day; WATERFALL, an on-treatment AE with onset on or after first dose of study drug + 1 day; SHORELINE, an AE with onset after the first dose of study drug (treatment cycle 1 data shown [Day 1 to Day 28]). Number of patients included in the safety set were as follows: MDD-201B (zuranolone 30 mg [n=45], placebo [n=44]); MOUNTAIN (zuranolone 30 mg [n=113], placebo [n=99]); WATERFALL (zuranolone 50 mg [n=161], placebo [n=120]); SHORELINE (zuranolone 30 mg [n=493], zuranolone 50 mg [n=137]).
AE = adverse event; TEAE = treatment-emergent AE; URTI = upper respiratory tract infection.

CONCLUSIONS

- The LANDSCAPE clinical development program studied the use of zuranolone as a monotherapy or adjunctive therapy to SOC ADTs. Adults with MDD who received zuranolone across 4 LANDSCAPE studies showed rapid and sustained improvement in depressive symptoms regardless of concomitant SOC ADT use.
- Zuranolone was generally well tolerated in adults with MDD regardless of concomitant use of SOC ADT across the 4 LANDSCAPE studies presented here.

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