Rapid Antidepressant Effects of Zuranolone in Patients With Major Depressive Disorder and Postpartum Depression: Overview of the LANDSCAPE and NEST Clinical Development Programs

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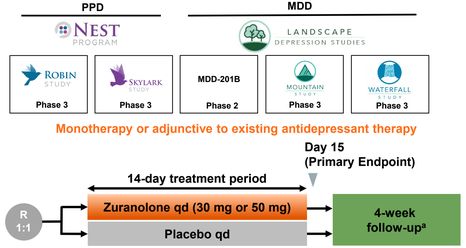
INTRODUCTION

- There is a need for innovative treatments for depression that can offer a rapid and sustained effect without the need for chronic treatment.
- γ-aminobutyric acid (GABA)-ergic and glutamatergic signaling play a key role in the maintenance and restoration of homeostasis under normal and stressful conditions.[1-3]
  - Disruption of GABA signaling, including reduced levels of GABA or altered expression of $GABA_A$ receptors, has been associated with depressive symptoms.[4-6]
- Neuroactive steroids (NAS) directly modulate GABAergic signaling pathways and may restore network balance in brain areas dysregulated in depression.[7,8]
- Zuranolone, an investigational positive allosteric modulator of both synaptic and extrasynaptic $GABA_A$ receptors and a NAS, is in clinical development as an oral, once-daily, 14-day treatment course for adults with major depressive disorder (MDD) and postpartum depression (PPD).
- Results from 5 completed, double-blind, placebo-controlled Phase 2 and 3 trials from the MDD (LANDSCAPE) and PPD (NEST) clinical development programs are reported here.

METHODS

- All studies reported here are completed and assessed the efficacy and safety of a 14-day treatment course of zuranolone in adults (**Figure 1**).
- Improvement in depressive symptoms was measured as change from baseline (CFB) in the 17-item Hamilton Rating Scale for Depression total score (HAMD-17).
- The 2 placebo-controlled PPD studies: ROBIN (N=153) and SKYLARK (N=200).
- The 3 placebo-controlled MDD studies: MDD-201B (N=89), MOUNTAIN (N=387), and WATERFALL (N=543).
- Least squares mean (LSM) CFB, corresponding standard errors (SE), and p values are reported; for response and remission data, p values were determined from odds ratios.
- Statistical tests were 2-sided (α=0.05).
- No adjustment for multiplicity was conducted across secondary and other endpoints; unless indicated otherwise, p values are nominal.

Figure 1. Study Designs



Study Population:

- **ROBIN (NCT02978326, double-blind, zuranolone 30 mg)**
  - Baseline HAMD-17 ≥26
- **SKYLARK (NCT04442503, double-blind, zuranolone 50 mg)**
  - Baseline HAMD-17 ≥26
- **MDD-201B (NCT03000530, double-blind, zuranolone 30 mg)**
  - Baseline HAMD-17 ≥22
- **MOUNTAIN (NCT03672175, double-blind, zuranolone 20 mg [not shown] and 30 mg)**
  - Baseline HAMD-17 ≥22
  - Baseline MADRS ≥32
- **WATERFALL (NCT04442490, double-blind, zuranolone 50 mg)**
  - Baseline HAMD-17 ≥24

Endpoints:

- **Primary efficacy endpoint (all 5 completed studies):** CFB in HAMD-17 total score at Day 15 after a once-daily, 14-day treatment course of zuranolone.
- **Secondary endpoints** included other efficacy and safety/tolerability outcomes.

[a]The MOUNTAIN Study also included a 6-month extended follow-up.
NOTE: Patients in MDD-201B were inpatients for the first 7 days of treatment.
CFB = change from baseline; HAMD-17 = 17-item Hamilton Rating Scale for Depression; MADRS = Montgomery–Åsberg Depression Rating Scale; MDD = major depressive disorder; PPD = postpartum depression; qd = once daily dosing; R = randomization.

RESULTS

- Baseline demographics were generally balanced between treatment arms in each of the 5 completed trials (**Table 1**).

Table 1. Demographics and Patient Characteristics at Baseline[a]

	PPD (NEST)				MDD (LANDSCAPE)					
	ROBIN		SKYLARK		MDD-201B		MOUNTAIN[b]		WATERFALL	
Characteristics	ZRN 30 mg (N = 78)	PBO (N = 73)	ZRN 50 mg (N = 98)	PBO (N = 98)	ZRN 30 mg (N = 45)	PBO (N = 44)	ZRN 30 mg (N = 166)	PBO (N = 157)	ZRN 50 mg (N = 268)	PBO (N = 269)
Age, mean (SD), years	29.2 (5.4)	27.4 (5.4)	30.0 (5.9)	31.0 (6.0)	49.1 (13.6)	38.3 (12.2)	42.3 (11.8)	41.4 (12.2)	39.4 (12.3)	40.1 (12.6)
Female sex, n (%)	78 (100)	73 (100)	98 (100)	98 (100)	25 (55.6)	30 (68.2)	121 (72.9)	106 (67.5)	186 (69.4)	166 (61.7)
Race or Ethnicity, n (%)										
White	45 (57.7)	39 (53.4)	68 (69.4)	69 (70.4)	7 (15.6)	16 (36.4)	94 (56.6)	96 (61.1)	169 (63.1)	206 (76.6)
Black	31 (39.7)	32 (43.8)	25 (25.5)	18 (18.4)	36 (80.0)	28 (63.6)	64 (38.6)	54 (34.4)	75 (28.0)	46 (17.1)
Other[c]	1 (1.3)	2 (2.7)	5 (5.1)	11 (11.2)	2 (4.4)	0	8 (4.8)	7 (4.5)	24 (9.0)	17 (6.3)
Hispanic/Latino	18 (23.1)	16 (21.9)	33 (33.7)	42 (42.9)	1 (2.2)	7 (15.9)	27 (16.3)	26 (16.6)	58 (21.6)	54 (20.1)
HAMD-17 total score at baseline, mean (SD)[d]	28.4 (2.1)	28.8 (2.3)	28.6 (2.5)	28.8 (2.3)	25.2 (2.6)	25.7 (2.4)	25.9 (2.9)	25.8 (3.1)	26.8 (2.6)	26.9 (2.7)
Use of antidepressants at baseline, n (%)	16 (20.5)	13 (17.8)	15 (15.3)	15 (15.3)	12 (26.7)	10 (22.7)	47 (28.3)	49 (31.2)	79 (29.5)	81 (30.1)

[a]Safety Set, defined as all patients who received at least 1 dose of double-blind study drug; [b]For the MOUNTAIN Study, baseline demographics and characteristics are reported for patients with MADRS ≥32 and HAMD-17 ≥22 at screening and day 1 (prior to dosing) who received at least 1 dose of double-blind study drug; [c]Other included Asian, American Indian, Alaska Native, Native Hawaiian, Pacific Islander, multiple, other race, and/or not reported; [d]Mean (SD) HAMD-17 total scores at baseline reported for all randomized patients in the Safety Set with valid baseline and at least 1 post-baseline efficacy evaluation.
HAMD-17 = 17-item Hamilton Rating Scale for Depression total score; MADRS = Montgomery–Åsberg Depression Rating Scale; MDD = major depressive disorder; PBO = placebo; PPD = postpartum depression; ZRN = zuranolone.

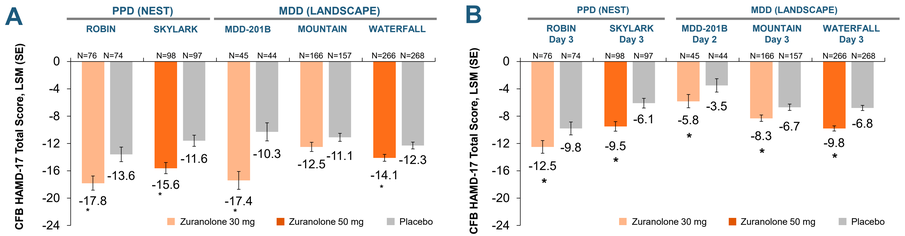
- Treatment with zuranolone led to significant improvements in depressive symptoms vs placebo at Day 15 (primary endpoint) in 4 of the 5 completed trials (p<0.05; **Figure 2A**; NOTE: MOUNTAIN did not meet its primary endpoint), and nominally significant improvements were observed as early as Day 2 or 3 in all 5 completed trials (p<0.05; **Figure 2B**).
- In previous reports, numerical improvements in depressive symptoms were shown to be sustained through Day 42/45.[9]

Table 2. Patient Disposition[a]

	Overall Ranges	
	Zuranolone 30 mg or 50 mg, %	Placebo, %
Completed study	72.3–94.8	73.9–90.8
Discontinued study	5.2–27.7	9.2–26.1
Reasons for discontinuation		
AEs	1–4.4	0–2.5
Withdrawal by patient	2.2–14.5	2.6–12.1
Lost to follow-up	0–7.2	2.6–8.2
AEs leading to treatment discontinuation	1.3–4.4	0–3.8

[a]Data reported are for all randomized patients in each of the 5 studies. NOTE: The MOUNTAIN Study included a 6-month follow-up period.
AE = adverse event.

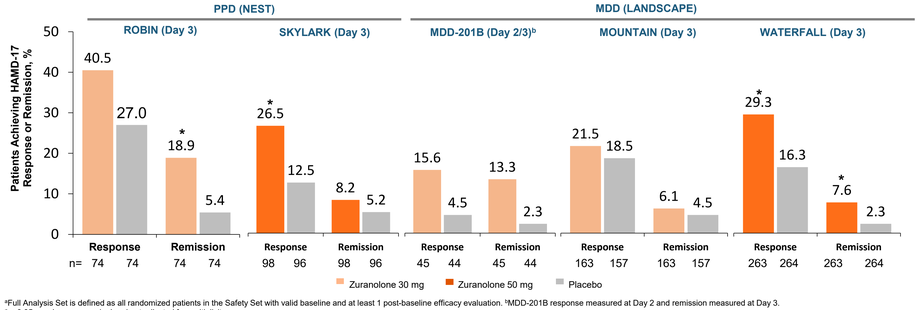
Figure 2. CFB HAMD-17 Total Scores[a]; A) Day 15 (primary endpoint); B) Day 2/3



[a]Full Analysis Set is defined as all randomized patients in the Safety Set with valid baseline and at least 1 post-baseline efficacy evaluation.
*p<0.05; p values for ROBIN, MDD-201B, and MOUNTAIN Day 2/3 (secondary endpoint) are nominal and not adjusted for multiplicity. WATERFALL p values at Day 3 were nominal because the first key secondary endpoint was not met.
SKYLARK p values are statistically significant as CFB in HAMD-17 at Day 3 was a key secondary endpoint adjusted for multiplicity.
NOTE: These clinical trials differ in sample size, patient population, entry criteria, and study sites, as well as other design elements. No direct comparison can be made across these clinical trials based on the graph above.
CFB = change from baseline; HAMD-17 = 17-item Hamilton Rating Scale for Depression; LS = least squares; MDD = major depressive disorder; PPD = postpartum depression.

- HAMD-17 response (≥50% reduction from baseline in HAMD-17) and remission (HAMD-17 ≤7) rates were numerically greater in patients receiving zuranolone vs placebo as early as Day 2 or 3 (**Figure 3**).

Figure 3. HAMD-17 Response and Remission at Day 2/3[a]



[a]Full Analysis Set is defined as all randomized patients in the Safety Set with valid baseline and at least 1 post-baseline efficacy evaluation. [b]MDD-201B response measured at Day 2 and remission measured at Day 3.
*p<0.05; p values are nominal and not adjusted for multiplicity.
HAMD-17 = 17-item Hamilton Rating Scale for Depression; MDD = major depressive disorder; n = number of patients at that visit; PPD = postpartum depression.

- The safety profile and the most common treatment-emergent adverse events (TEAEs) during the double-blind period across 5 studies are shown in **Table 3**.
- The majority of patients receiving zuranolone and experiencing a TEAE reported TEAEs mild or moderate in severity (**Table 3**).
- No signal for increased suicidal ideation or suicidal behavior vs baseline per the Columbia Suicide Severity Rating Scale (data not shown).
- Data from the 20-item Physician Withdrawal Checklist (SKYLARK, MOUNTAIN, and WATERFALL) and AEs (MDD-201B and ROBIN) suggest completion or discontinuation of treatment with zuranolone was not associated with withdrawal effects (data not shown).

Table 3. Safety[a]

	Overall Ranges	
	Zuranolone 30 mg or 50 mg, %	Placebo, %
Any TEAE, %	53.3–66.3	44.6–53.1
Mild	50.5–75.0	53.8–75.0
Moderate	25.0–47.6	23.1–44.1
SAE, %	0–2.0	0–1.4
Most Common TEAEs (>5% in any treatment arm during double-blind period[b]), %		
Headache	6.3–17.8	7.4–15.9
Somnolence	6.7–26.5	2.3–11.0
Dizziness	5.7–13.8	2.2–10.2
Nausea	3.6–11.1	2.3–8.2
URTI	0–7.7	0–2.1
Sedation	4.4–11.2	0–4.5
Fatigue	1.1–6.8	0–2.6
Diarrhea	0–6.4	2.0–6.8

[a]Safety Set, defined as all patients who received at least 1 dose of double-blind study drug; [b]MDD-201B TEAEs reported for treatment period + 7 days.
NOTE: Suicidal ideation and suicidal behavior were not included due to incidence <5% in treatment arms. No deaths occurred during the double-blind period (Days 1-42/45) of these trials. AEs are coded using the then current version of the Medical Dictionary for Regulatory Activities (ROBIN: version 19.1, SKYLARK: version 24.0, MDD-201b: version 19.1, MOUNTAIN, version 21.0, and WATERFALL: version 23.0).
SAE = serious adverse event; TEAE = treatment-emergent adverse event; URTI = upper respiratory tract infection.

CONCLUSIONS

- The primary endpoint (improvement in depressive symptoms with zuranolone vs placebo at Day 15, as assessed by CFB in HAMD-17) was met across 4 of the 5 completed placebo-controlled trials summarized here.
- Improvement in depressive symptoms was observed with zuranolone vs placebo as early as Day 2/3 in the 5 completed trials from the MDD and PPD clinical development programs.
  - As early as Day 2/3, greater HAMD-17 response and remission rates were also observed.
- Across trials and doses to-date, treatment with zuranolone has been generally well tolerated, with a consistent safety and tolerability profile.

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