The Neuroactive Steroid (NAS) Zuranolone in Major Depressive Disorder: The Landscape Development Program of an Investigational, Oral, Positive Allosteric Modulator (PAM) of GABA<sub>A</sub> Receptors

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Introduction

- Major depressive disorder (MDD) is characterized by a period of depressive symptoms lasting at least two weeks that has been associated with gamma-aminobutyric acid (GABA) dysregulation.\(^1,4\)
- Depression is widely considered and treated as a chronic condition and may require multiple treatment steps to reach remission.\(^2,3\)
- Zuranolone (SAGE-217) is an investigational, oral NAS GABA<sub>A</sub> Allosteric Modulator (PAM) of GABA<sub>A</sub> Receptors.
- In a pivotal, double-blind, randomized study in MDD (NCT03000530), zuranolone demonstrated rapid (Day 2) and sustained (Day 28) clinically meaningful and statistically significant improvements in depressive symptoms versus placebo. The study met the primary endpoint of reduction in depressive symptoms at Day 15 vs. placebo.\(^6\) Zuranolone improved objective sleep efficiency versus placebo in a Phase 1 study in healthy volunteers (NCT03284933).\(^8\)
- The ongoing Phase 3 Landscape Development program aims to examine the safety and efficacy of zuranolone on depressive symptoms at multiple doses (MOUNTAIN), as initial and as-needed repeat-use treatment (SHORELINE), as a fixed, repeated treatment regimen for relapse prevention (REDWOOD), and in patients with co-morbid MDD and insomnia (RAINFOREST).

**STUDY DESIGN** MOUNTAIN (NCT03672175) examined efficacy and safety of 14-day dosing with zuranolone or placebo.

**RESULTS**
- The MOUNTAIN study did not meet its primary endpoint of a statistically significant reduction from baseline compared to placebo in HAM-D total score at Day 15.
- Rapid onset of effect of zuranolone 30 mg was noted beginning at Day 3 and statistical significance from placebo was noted at all visits during the treatment period leading up to Day 15 (least squares mean difference from placebo, p-value): Day 3 (-1.6, p=0.016), Day 8 (-2.1, p=0.008), and Day 12 (-2.1, p=0.018). Secondary endpoint p-values were not adjusted for multiplicity.\(^4\)

**STUDY DESIGN** SHORELINE (NCT03864614) evaluates the safety, tolerability, and need for repeat-use zuranolone in adults with MDD.

**STUDY DESIGN** REDWOOD (NCT04007387) assesses the efficacy and safety of zuranolone with a fixed, repeat treatment regimen for relapse prevention in adults with MDD.

**STUDY DESIGN** RAINFOREST (NCT03771664) examines the efficacy and safety of zuranolone in adults with comorbid MDD and insomnia.

Conclusions

The Landscape Program aims to provide evidence for treatment effects in major depressive episodes and may support a treat-as-needed paradigm in the event of symptom recurrence, with potential for positive impacts on co-morbid insomnia.