# Zuranolone (Anciennement SAGE-217): Essai de Phase 3 dans le Trouble Dépressif Majeur (MDD)

Poster #: P147

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## Introduction

- Over 300 million people globally are estimated to experience depression annually, approximately 4.5% of the world population.[1,2]
- Major Depressive Disorder (MDD) is characterized by a period of depressive symptoms lasting at least 2 weeks and is associated with changes in affect, cognition, and function.[3]
- A significant number of individuals with MDD (14-31%) have attempted suicide.[4,5]
- In the STAR*D study, about one third of patients remitted after the first-line antidepressant treatment, and of those achieving remission, typically 1 to 2 months of antidepressant therapy was required.[6,7]
- Zuranolone (formerly SAGE-217) is an investigational, oral neuroactive steroid $GABA_A$ receptor positive allosteric modulator that binds to both synaptic and extrasynaptic $GABA_A$ receptors, which is distinct from benzodiazepines, which only bind to synaptic receptors.[8-11]
- Zuranolone achieved the primary endpoint of a clinically meaningful and statistically significant improvement in depressive symptoms at Day 15 of treatment compared with placebo as measured by an improvement in the Hamilton Rating Scale for Depression (HAM-D) total score in an earlier pivotal study in MDD (NCT03000530) and was generally well tolerated.[12]
- The MOUNTAIN Study (NCT03672175) is a phase 3, multicenter, double-blind, randomized, placebo-controlled study that evaluated the efficacy and safety of two doses of zuranolone (at 20 mg or 30 mg) in adults with MDD.

## Methods

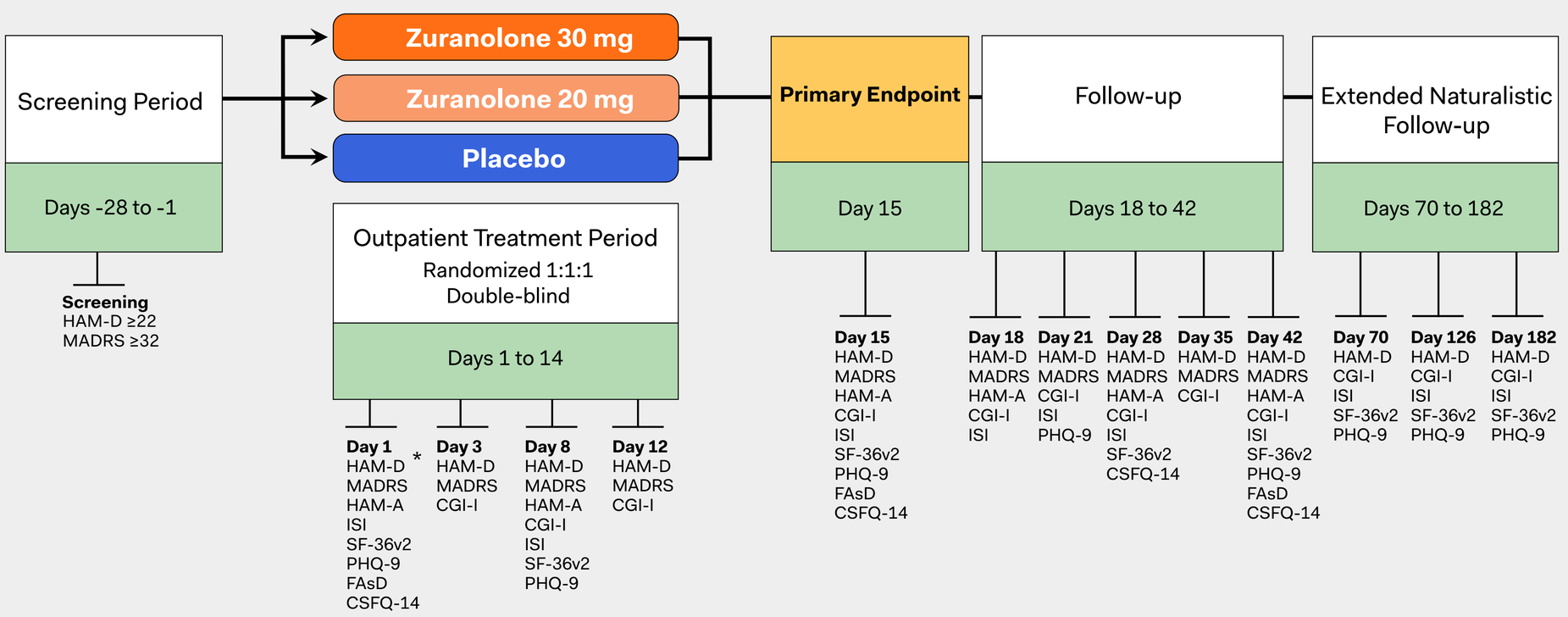
- Patients were ages 18-65, with MDD diagnosed by structured clinical interview, symptoms persisting ≥4 weeks, a screening Montgomery-Åsberg Depression Rating Scale (MADRS) score ≥32, and a screening HAM-D total score ≥22.
  - A protocol amendment while the study was underway added the requirement for a HAM-D score ≥22 at baseline.
- Patients were stratified based on baseline antidepressant use and randomized 1:1:1 to zuranolone 30 mg, zuranolone 20 mg, or placebo.
- Exclusion criteria included attempted suicide associated with the current depressive episode, treatment resistant depression, or medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
- Concomitant antidepressant medication use was permitted at a stable dose from 60 days prior to Day 1 through Day 42.
- Targeted enrollment was 525 patients. Assuming a two-sided alpha level of 0.05, a sample size of 399 evaluable subjects provided 90% power to detect a placebo-adjusted treatment difference of approximately 4 points in the primary endpoint.
- Study drug (zuranolone or placebo) was administered as identical gelatin capsules on an outpatient basis, daily, in the evening, for two weeks.
- Safety and tolerability were assessed by the Safety Set, including all subjects administered study drug.
- Efficacy measures were assessed from the Full Analysis Set (all Safety Set patients with a valid baseline HAM-D total score and at least 1 post-baseline HAM-D total score) and the Modified Full Analysis Set (comprised of all patients in the Full Analysis Set with a HAM-D total score ≥22 at baseline). See table below for an outline of efficacy measures.
- Evaluation of the primary endpoint and non-categorical secondary efficacy assessments were conducted using a mixed-effects model for repeated measures and model-based point estimates (least-squares means).
- Categorical secondary measures were assessed using generalized estimating equation methods.
- Safety and tolerability were evaluated by adverse event reporting, the Columbia Suicide Severity Rating Scale, the 20-item Physician Withdrawal Checklist, and standard clinical assessments.

| PRIMARY ENDPOINT | CONCEPTS ASSESSED |
|---|---|
| 17-item Hamilton Rating Scale for Depression (HAM-D) Change From Baseline, Day 15 | Depression |
| **SECONDARY ENDPOINTS** | |
| **Clinician-Reported** | |
| HAM-D Change From Baseline, Timepoints Excluding Day 15 | Depression |
| Montgomery-Åsberg Depression Rating Scale (MADRS) Change From Baseline | Depression |
| Hamilton Rating Scale for Anxiety (HAM-A) Change From Baseline | Anxiety |
| Clinical Global Impression - Improvement (CGI-I) Response | Global Function |
| **Patient-Reported** | |
| Insomnia Severity Index (ISI) sleep parameters | Insomnia |
| 36-item Short Form Survey Version 2 (SF-36v2) | Health-Related Quality of Life |
| 9-item Patient Health Questionnaire (PHQ-9) | Depression |
| **OTHER ENDPOINTS** | |
| **Patient-Reported** | |
| Fatigue Associated with Depression Questionnaire (FAsD) | Fatigue |
| Changes in Sexual Functioning Questionnaire Short Form (CSFQ-14) | Sexual Function |

## Conclusions

- In the MOUNTAIN Study, the primary endpoint was the change from baseline in the 17-item HAM-D total score at Day 15. Secondary endpoints included the change from baseline in HAM-D score at other timepoints, MADRS score, and HAM-A scores.
  - The HAM-D and MADRS are not typically used in clinical practice, but they are validated, clinician-rated scales used for measuring the severity of depressive symptoms in clinical trials.[13-17]
  - HAM-D and MADRS items are directly correlated with the Diagnostic and Statistical Manual of Mental Disorders diagnostic criteria for MDD.[13-17]
  - Topline data for the MOUNTAIN Study became available in December 2019.
- The MOUNTAIN Study is part of a broader clinical development program to understand the potential efficacy and safety of zuranolone for the treatment of MDD, including the ongoing REDWOOD (NCT04007367) and SHORELINE (NCTNCT03864614) studies.

## Study Design




*HAM-D total score of ≥22 was also implemented as a later cutoff during baseline assessments.

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