Zuranolone in Major Depressive Disorder: A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial

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Disclosures

- Dr. Anita H. Clayton reports grants from Allergan, Endoceutics, Janssen, and Sage Therapeutics, Inc; consulting fees from Acadia, Alkermes, Allergan, AMAG Pharmaceuticals, Daré Biosciences, Fabre-Kramer, Ovoca Bio, Palatin Technologies, S1 Biopharma, Sage Therapeutics, Inc., Sprout Pharmaceuticals, Takeda, and Lundbeck; royalties from Ballantine Books/Random House, the Changes in Sexual Function Questionnaire, and Guilford Publications; and stock in Euthymics and S1 Biopharma.

- Zuranolone (SAGE-217) is an investigational compound in clinical development and is not approved in any country for any use.

- Sage Therapeutics, Inc. sponsored the studies of zuranolone.
Major Depressive Disorder (MDD) and the Role of Gamma-aminobutyric Acid (GABA)

- Globally, over 300 million people, or roughly 4.5% of the world’s population are estimated to suffer from depression annually.\(^1,2\)

- Enhancing GABAergic inhibition may restore excitatory/inhibitory balance to regulate brain network activity, which has been proposed to reduce depressive symptoms.\(^3-5\)

- Neuroactive steroids (NAS) that act as GABA\(_A\) receptor positive allosteric modulators (PAMs) activate both synaptic and extrasynaptic GABA\(_A\) receptors to produce phasic and tonic inhibitory currents to potentially enhance GABAergic inhibition.\(^4,6-8\)

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Zuranolone Pivotal Phase 3 MOUNTAIN Study (MDD-301)

**Study Design**

- The Phase 3 MOUNTAIN Study randomized 581 patients with MDD to receive zuranolone (20 mg or 30 mg) or placebo, once-nightly for 2 weeks.
  - The study consisted of a 2-week treatment period (Days 1-14) followed by a 28-day follow-up period (Days 15-42) and an extended follow-up period through Day 182.
  - Changes in depressive symptoms were assessed across multiple measures of depression, including the 17-item Hamilton Rating Scale for Depression total score (HAMD-17). Secondary endpoints were not adjusted for multiplicity.
  - Safety and tolerability were assessed by adverse event (AE) reporting and standard clinical assessments.

**Key Inclusion Criteria**

- Males and females; 18 to 65 years
- SCID diagnosis of MDD
- MADRS≥32 and HAMD-17≥22
- Stable doses of antidepressants at baseline

**Key Exclusion Criteria**

- Attempted suicide in current episode
- Uncontrolled medical conditions
- Currently taking benzodiazepines, barbiturates, GABA\textsubscript{A} modulators, or non-GABA anti-insomnia medications
- Failure of 2 or more antidepressants in current episode (treatment-resistant depression)

**Study Design Diagram**

- **Screening**: 4 weeks
- **Primary Endpoint**: HAMD-17 total score at Day 15
- **Observational Follow-Up**: Weekly through Day 42, then every two months thereafter through Day 182

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Data on File. Sage Therapeutics, Inc. Cambridge, MA.

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### MOUNTAIN Study in MDD

#### Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Zuranolone 30 mg (n=166)</th>
<th>Zuranolone 20 mg (n=159)</th>
<th>Placebo (n=157)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years – mean, years (SD)</strong></td>
<td>42.3 (12)</td>
<td>41.9 (12)</td>
<td>41.4 (12)</td>
</tr>
<tr>
<td><strong>Female sex – n (%)</strong></td>
<td>121 (73)</td>
<td>112 (70)</td>
<td>106 (68)</td>
</tr>
<tr>
<td><strong>Race or ethnic group – n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>2 (1.2)</td>
<td>3 (1.9)</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Black/African-American</td>
<td>64 (38.6)</td>
<td>56 (35.2)</td>
<td>54 (34.4)</td>
</tr>
<tr>
<td>Multiple</td>
<td>4 (2.4)</td>
<td>1 (0.6)</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>White</td>
<td>94 (56.6)</td>
<td>99 (62.3)</td>
<td>96 (61.1)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (1.2)</td>
<td>0</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td><strong>Ethnicity – n (%)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hispanic/Latino</td>
<td>27 (16.3)</td>
<td>31 (19.5)</td>
<td>26 (16.6)</td>
</tr>
<tr>
<td><strong>Weight – mean, kg (SD)</strong></td>
<td>89.7 (22.4)</td>
<td>87.3 (20.2)</td>
<td>89.5 (22.9)</td>
</tr>
<tr>
<td><strong>Baseline HAMD-17 score – mean (SD)</strong></td>
<td>25.9 (2.9)</td>
<td>25.8 (2.8)</td>
<td>25.8 (3.1)</td>
</tr>
<tr>
<td><strong>Use of antidepressants at baseline – n (%)</strong></td>
<td>47 (28)</td>
<td>46 (29)</td>
<td>49 (31)</td>
</tr>
</tbody>
</table>
The MOUNTAIN study did not meet its primary endpoint of change in HAMD-17 total score from baseline at Day 15.

Statistically significant difference from placebo in the zuranolone 30 mg group was achieved at Day 3 and at all measured timepoints prior to Day 15.

Zuranolone 20 mg did not separate from placebo at any time point.

*p=0.0157, †p=0.0080, ‡p=0.0175 for zuranolone 30 mg vs placebo.
Post-hoc Analysis of the MOUNTAIN Study
Patients with Measurable Drug Detection

- Post-hoc analysis revealed that in the MOUNTAIN Study, approximately 9% of patients in the zuranolone 30 mg treatment group had no measurable drug concentration on Day 8 or 15, consistent with non-compliance in taking zuranolone.

- Excluding these patients from the primary analysis set (zuranolone 30 mg vs placebo) resulted in statistical significance at all measured timepoints through, and including, Day 15.

\[ p=0.0113, \ †p=0.0024, \ ‡p=0.0064, \ §p=0.0478 \] for zuranolone 30 mg vs placebo.
MOUNTAIN Study in MDD
Safety Through Day 42

- The percentage of patients who had at least one AE during the 2-week treatment and 28-day follow-up periods was 54.2% in the zuranolone 30 mg group, 50.0% in the zuranolone 20 mg group and 48.9% in the placebo group.
- Serious Adverse Events in Double-blind period: 5 patients overall.
  - Treatment period: 2 patients receiving zuranolone 30 mg.
    - 1 suicide attempt (Day 5, patient with a longstanding history of MDD and a previous suicide attempt).
    - 1 bile duct stone (Day 2, requiring removal in a patient with a prior bile duct repair).
  - Follow-up period: 3 patients, 1 in each treatment group, all occurring at least 1 week following cessation of treatment.
    - 1 syncope and associated injuries (Day 28, zuranolone 30 mg, which occurred with dehydration and orthostatic hypotension during exercise in a patient with a history of bradycardia).
    - Multiple SAEs related to medical complications of cocaine ingestion (Day 39, zuranolone 20 mg).
    - 1 suicidal ideation (Day 22, placebo).
- No adverse events of loss of consciousness were reported.
- No signal for increased suicidal ideation or suicidal behavior compared to baseline, as measured by the Columbia-Suicide Severity Rating Scale.
- No clinically significant changes in vital signs or clinical laboratory parameters or ECGs, based on adverse events.

### Adverse Events ≥5% Through Day 42

<table>
<thead>
<tr>
<th></th>
<th>Zuranolone 30 mg (n=192)</th>
<th>Zuranolone 20 mg (n=188)</th>
<th>Placebo (n=190)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any – n (%)</td>
<td>104 (54.2)</td>
<td>94 (50.0)</td>
<td>93 (48.9)</td>
</tr>
<tr>
<td>Headache</td>
<td>12 (6.3)</td>
<td>21 (11.2)</td>
<td>14 (7.4)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>11 (5.7)</td>
<td>14 (7.4)</td>
<td>7 (3.7)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>13 (6.8)</td>
<td>11 (5.9)</td>
<td>8 (4.2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>13 (6.8)</td>
<td>3 (1.6)</td>
<td>5 (2.6)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12 (6.3)</td>
<td>11 (5.9)</td>
<td>10 (5.3)</td>
</tr>
<tr>
<td>Sedation</td>
<td>9 (4.7)</td>
<td>11 (5.9)</td>
<td>6 (3.2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (3.6)</td>
<td>10 (5.3)</td>
<td>9 (4.7)</td>
</tr>
</tbody>
</table>
Conclusions

- The MOUNTAIN Study did not meet its primary endpoint of change in HAMD-17 total score from baseline at Day 15.
  - Patients in the zuranolone 30 mg group achieved statistically significant reductions in HAMD-17 total score at Days 3, 8, and 12 (p<0.018 for each time point). The 20 mg dose did not separate from placebo in this dose-ranging study.
  - In a post-hoc analysis of the MOUNTAIN Study that excluded patients with no measurable drug concentration, statistically significant improvements in depressive symptoms favoring zuranolone 30 mg were observed at all measured time points through and including Day 15.
  - Zuranolone was generally well-tolerated and showed a similar safety profile as seen in earlier studies. The most common AEs in the MOUNTAIN Study were headache, dizziness, somnolence, fatigue, diarrhea, sedation, and nausea.
  - Two patients receiving zuranolone 30 mg experienced serious adverse events (SAEs) during treatment while three patients, one in each treatment group, reported SAEs during follow-up.

- These data support the investigation of higher doses of zuranolone in future clinical trials, and the continued development of NAS GABA\textsubscript{A} receptor PAMs in MDD.

Seeing the brain differently makes a world of difference.