Zuranolone Clinical Data in Patients With a Depressive Episode in Major Depressive Disorder

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Disclosures

• Dr. Lasser is an employee of Sage Therapeutics, Inc. with stock/stock options.

• Zuranolone (SAGE-217), SAGE-324, SAGE-689, SAGE-718, and SAGE-904 are investigational compounds in clinical development and are not approved in any country for any use. Brexanolone injection is approved by the United States (US) Food and Drug Administration (FDA) indicated for the treatment of postpartum depression in adults; brexanolone injection is not approved outside the US for any use.

• Sage Therapeutics, Inc. sponsored the studies of zuranolone.
GABA is the Major Inhibitory Neurotransmitter in the Brain

- Gamma aminobutyric acid (GABA) is an abundant and ubiquitous inhibitory neurotransmitter in the brain.
  - Present in 30-50% of all neurons.\(^1\)
- GABA dysfunction can occur in many different brain regions with potential downstream effects.
- The GABA\(_A\) receptor family is complex with diverse physiology, pharmacology and function:\(^1,2\)
  - **Physiology**: Found in different brain regions and neuronal circuits.\(^1\)
  - **Pharmacology**: Includes 19 different receptor subunits.\(^2\)
  - **Function**: Differing synaptic locations manifesting as phasic vs. tonic inhibitory tone.\(^1\)


GABA\(_A\) receptors are prevalent throughout the brain

*Synaptic and extrasynaptic GABA\(_A\) receptors in mouse brain*
Clinical Translation of Allosteric Modulators

• Allosteric modulators indirectly influence the effects of a ligand that directly activates or deactivates the target, often receptors, enzymes, transporters.¹

• ‘Dimmer’ switch rather than traditional ‘On-Off.’

• Positive allosteric modulators (PAMs) amplify receptor response without directly activating the receptor; negative allosteric modulators (NAMs) reduce receptor responsiveness to the endogenous ligand.

GABA_{A}R PAM
brexanolone, zuranolone (SAGE-217), SAGE-324, SAGE-689

NMDAR PAM
SAGE-718, SAGE-904

Clinical Translation: ‘Reverse Engineering’ Allopregnanolone

Understanding the role of allopregnanolone in postpartum depression (PPD)

- Allopregnanolone is a PAM of GABA\(_A\) receptors\(^1\):
  - Phasic inhibition through intra-synaptic.\(^2\)
  - Tonic inhibition through extra-synaptic.\(^2\)

- Developed library of GABA\(_A\) receptor PAMs, including brexanolone, a synthetic analogue of allopregnanolone\(^3\) administered as an IV infusion, and oral molecules zuranolone, SAGE-324, and SAGE-689.\(^4\)

Clinical studies with NAS in PPD and MDD

- Expanding from PPD population to MDD.
- Exploring clinical profile of potentially rapid and durable effect.
- Move from IV to oral therapy, with potential to re-frame treatment with non-chronic approach.

‘Reverse Engineering’ Allopregnanolone: Balancing GABA Dysfunction in Pregnancy and Postpartum

Changes in steroid hormone levels in pregnancy result in a decrease in both GABA_A gamma-2 and delta subunit expression.*

*Multiple etiologies may contribute to PPD.

Reverse Engineering Allopregnanolone: GABA_A R PAMs Mediate Both Phasic and Tonic Inhibition

Figure adapted from Jacob TC, et al. and Reddy DS, et al.¹ ²

Zuranolone (oral) Activity at GABA_A Rs (in vitro)³

<table>
<thead>
<tr>
<th>Receptor</th>
<th>EC_{50} (nM)</th>
<th>E_{max} (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>α₁β₂γ₂</td>
<td>374</td>
<td>1041</td>
</tr>
<tr>
<td>α₄β₂δ</td>
<td>163</td>
<td>640</td>
</tr>
</tbody>
</table>

Zuranolone

- Zuranolone is an investigational oral neuroactive steroid (NAS) GABA<sub>A</sub>R PAM. 1-3
- Zuranolone is orally bioavailable. 1,4
- PK/PD profile supports once-daily, oral dosing in clinical studies. 1,4
- Phase 2 clinical modeling analyses were supportive of a 2-week dosing regimen in MDD. 5

Chemical structure of zuranolone adapted from Martinez-Botella G, et al. 3

Trial of SAGE-217 in Patients with Major Depressive Disorder

Handan Gunduz-Bruce, M.D., Christopher Silber, M.D., Inder Kaul, M.D., Anthony J. Rothschild, M.D., Robert Riesenber, M.D., Abdul J. Sankoh, Ph.D., Haihong Li, Ph.D., Robert Lasser, M.D., Charles F. Zorumski, M.D., David R. Rubinow, M.D., Steven M. Paul, M.D., Jeffrey Jonas, M.D., James J. Doherty, Ph.D., and Stephen J. Kanes, M.D., Ph.D.
Zuranolone met the primary endpoint of the trial, demonstrating a statistically significant improvement in depressive symptoms compared with placebo after 2 weeks of treatment as measured by an improvement in the 17-item Hamilton Rating Scale for Depression total score ([HAMD-17]; -17.4 ± 1.3 vs -10.3 ± 1.3; Least-squares mean (LSM) difference in change, -7.0 points; 95% CI, -10.2 to -3.9; p<0.001].

Zuranolone achieved a clinically meaningful and statistically significant improvement in depressive symptoms at Day 2 and at all measured time points compared with placebo as measured by an improvement in HAMD-17 total score through Day 28. Secondary endpoints were not adjusted for multiplicity.

Zuranolone was generally well-tolerated.

- The most common adverse events (AEs) (≥5%) in the MDD-201 study included headache, dizziness, nausea, and somnolence.
# LANDSCAPE Program

**Broad Program Underway Across Numerous Studies, Indications**

<table>
<thead>
<tr>
<th>STUDY</th>
<th>POSTPARTUM DEPRESSION (PPD)</th>
<th>MAJOR DEPRESSIVE DISORDER (MDD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT #</td>
<td>PPD-201</td>
<td>PPD-301</td>
</tr>
<tr>
<td>Indication</td>
<td>PPD</td>
<td>PPD</td>
</tr>
<tr>
<td>Phase</td>
<td>Phase 3</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Primary Objectives</td>
<td>Efficacy: 30 mg vs placebo</td>
<td>Efficacy: 50 mg vs placebo</td>
</tr>
<tr>
<td>Status</td>
<td>Completed</td>
<td>Enrolling</td>
</tr>
</tbody>
</table>
Zuranolone Pivotal Phase 3 MOUNTAIN (MDD-301)

Study Design

1:1:1 Randomized, Double-Blind

14-Day Treatment

- Patients with moderate-severe MDD
  HAMD-17 ≥ 22 and MADRS ≥ 32

- Zuranolone 30 mg
- Zuranolone 20 mg
- Placebo

Naturalistic Follow-up

- Day 15 Primary Endpoint
- Day 42 Follow-up
- 6 Month Post Naturalistic Follow-up

- Double-blinded until Day 42, placebo-controlled, 482 subjects randomized.
  - Key inclusion criteria: Males and females; 18 to 65 years; SCID diagnosis of MDD; Montgomery-Åsberg Depression Rating Scale (MADRS) ≥32 and HAMD-17 ≥ 22; Stable baseline antidepressants permitted.
  - Key exclusion criteria: Attempted suicide in current episode; Uncontrolled medical conditions; Currently taking benzodiazepines, barbiturates, GABA_A modulators, or non-GABA anti-insomnia medications; Failure of 2 or more antidepressants in current episode (treatment-resistant depression).

- Primary Endpoint: LSM change from baseline in HAMD-17 total score at Day 15.
- Changes in depressive symptoms were assessed across multiple measures of depression, including HAMD-17 total score.
  - Secondary endpoints and post-hoc analyses were not adjusted for multiplicity.

- Safety and tolerability were assessed by AE reporting and standard clinical assessments.
### Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</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>
</tr>
<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>
## MOUNTAIN Study in MDD

### Disposition

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Zuranolone 30 mg</th>
<th>Zuranolone 20 mg</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screened</td>
<td></td>
<td></td>
<td></td>
<td>1351</td>
</tr>
<tr>
<td>Randomized</td>
<td>194</td>
<td>194</td>
<td>193</td>
<td>581</td>
</tr>
<tr>
<td>Received study medication</td>
<td>192</td>
<td>188</td>
<td>190</td>
<td>570</td>
</tr>
<tr>
<td>Completed Day 42</td>
<td>164 (85.4)</td>
<td>171 (91.0)</td>
<td>167 (87.9)</td>
<td>502 (88.1)</td>
</tr>
<tr>
<td>Discontinued by Day 42</td>
<td>28 (14.6)</td>
<td>17 (9.0)</td>
<td>23 (12.1)</td>
<td>68 (11.9)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>3 (1.6)</td>
<td>1 (0.5)</td>
<td>5 (2.6)</td>
<td>9 (1.6)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>4 (2.1)</td>
<td>5 (2.7)</td>
<td>3 (1.6)</td>
<td>12 (2.1)</td>
</tr>
<tr>
<td>Non-compliance with study drug</td>
<td>1 (0.5)</td>
<td>0</td>
<td>1 (0.5)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Physician decision</td>
<td>1 (0.5)</td>
<td>0</td>
<td>2 (1.1)</td>
<td>3 (0.5)</td>
</tr>
<tr>
<td>Withdrawal by subject</td>
<td>17 (8.9)</td>
<td>9 (4.8)</td>
<td>11 (5.8)</td>
<td>37 (6.5)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (1.0)</td>
<td>2 (1.1)</td>
<td>1 (0.5)</td>
<td>5 (0.9)</td>
</tr>
</tbody>
</table>
MOUNTAIN Study in MDD

Primary Endpoint: HAMD-17 Total Score Change From Baseline at Day 15

- 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.

*\( p=0.0157, \hat{p}=0.0080, \ddot{p}=0.0175 \) for zuranolone 30 mg vs placebo.
Post-hoc Analysis of the MOUNTAIN Study

Patients with Measurable Drug Concentration

- 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 at either Day 8 or Day 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
Post-hoc Analysis of the MOUNTAIN Study

Patients with Measurable Drug Concentration and HAMD-17≥24

- Post-hoc analysis revealed that in patients with both a measurable drug concentration of zuranolone and an initial HAMD-17≥ 24, zuranolone 30 mg was associated with a mean reduction of 14.0 in HAMD-17 total score compared to 11.4 for placebo at Day 15 (LSM Difference -2.6, p=0.0174).

* p=0.0153, † p=0.0029, ‡ p=0.0050, § p=0.0174 for zuranolone 30 mg vs placebo.

Data on File. Sage Therapeutics, Inc. Cambridge, MA.
MOUNTAIN Study in MDD
Safety Through Day 42

- The percentage of patients who had at least one adverse event 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 (SAEs):
  - 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 (Day 39, zuranolone 20 mg, which were related to medical complications of cocaine ingestion).
      - 1 suicidal ideation (Day 22, placebo).

- No AES 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 AES.

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**Adverse Events ≥5% Through Day 42**

<table>
<thead>
<tr>
<th>TEAEs, n (%)</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 TEAE</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 a statistically significant reduction from baseline compared to placebo in HAMD-17 total score at Day 15.
  - The MOUNTAIN Study showed statistically significant differences from placebo in the zuranolone 30 mg group at Day 3 and at all measured timepoints prior to Day 15.
  - In post-hoc analyses of patients with zuranolone 30 mg with baseline HAMD-17≥24 and/or measurable drug detection, significant improvements in depressive symptoms were observed at all measured time points.
  - Zuranolone was generally well-tolerated and showed a similar safety profile as in earlier studies. The most common AEs in the MOUNTAIN study were headache, dizziness, somnolence, fatigue, diarrhea, sedation, and nausea.

- Additional studies with zuranolone in the LANDSCAPE Program are ongoing. These studies will provide more insight into zuranolone in patients with MDD.
Seeing the brain differently makes a world of difference