A Phase 3, Double-Blind, Placebo-Controlled Trial of Zuranolone in Postpartum Depression: Assessment of Depressive Symptoms Across Multiple Measures

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2nd Joint Congress of the DGBP and AGNP
March 3-6, 2020
Berlin, Germany
Disclosures

Dr. Junker is a contractor of Sage Therapeutics, Inc.

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.
Postpartum Depression: Background

- Postpartum depression (PPD) is one of the most common medical complications during and after pregnancy.\(^1\)\(^-\)\(^15\)
- In the EU-8*, the overall average prevalence of PPD has been estimated to be 1 in 9 new mothers, ranging from 5.5-13.5% among EU-8 member countries.\(^16\)
- PPD can impair a mother’s overall function, including the ability to fulfill personal responsibilities and engage in daily activities.\(^17\)\(^-\)\(^18\)
- PPD symptoms can be associated with a significant impairment in mother-infant bonding\(^19\) and maternal function, including breastfeeding\(^20\),\(^21\) and caring for the child, with implications for the child’s health and development.\(^22\)\(^-\)\(^24\)
- Suicide is a leading cause of maternal death.\(^25\)

*United Kingdom, France, Germany, Italy, Sweden, the Netherlands, Denmark, and Austria

\(^16\) Data on File, Sage Therapeutics, Inc. (Summary of PPD prevalence estimates in the EU-8 by PPD diagnosis and severity: Jan 2019).
PPD Has Been Associated With Network Dysregulation

- PPD has been associated with altered functional connectivity of the default mode network, salience, and central executive networks.\(^1\)\(^-\)\(^4\)

- Neuroactive steroids, through their modulation of GABA\(_\text{A}\) receptors, regulate inhibition-excitation balance within neural networks.\(^5\)

- Dysfunctional signaling of γ-aminobutyric acid (GABA), the major inhibitory neurotransmitter of the central nervous system, has been implicated in the etiology of PPD\(^1\),\(^6\) and major depressive disorder (MDD).\(^7\)\(^-\)\(^8\)

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The GABA System May Adapt to Changes During Pregnancy and the Postpartum Period\textsuperscript{1,2}

As neuroactive steroid levels increase during pregnancy,\textsuperscript{3,4} GABA receptors downregulate.\textsuperscript{1,2}

Zuranolone

- Zuranolone (SAGE-217) is an investigational oral NAS GABA$_{A}$R PAM.$^{1-3}$
- Zuranolone binds to both synaptic and extrasynaptic GABAARs, enhancing inhibitory activity of the GABAergic system, the major inhibitory neurotransmission system in the brain.$^{3-7}$
- Zuranolone is orally bioavailable.$^{1,8}$
- PK/PD profile supports once-daily, oral dosing in clinical studies.$^{1,8}$
- Phase 2 clinical modeling analyses were supportive of a 2-week dosing regimen.$^{9}$

Chemical structure of zuranolone adapted from Martinez Botella$^{3}$

Zuranolone: Phase 3 PPD (Robin)

**Study Design**

- **Study Design**
  - **Inclusion criteria**: Women ages 18-45, ≤ 6 months postpartum, PPD (major depressive episode with onset in 3rd trimester or ≤4 weeks postpartum), and a 17-item HAM-D score ≥ 26.
  - **Primary endpoint**: LS Mean change from baseline in HAM-D total score at Day 15.
    - Secondary endpoints: HAM-D total score at all time points, HAM-D response (≥50% reduction), HAM-D remission (total score ≤7), and MADRS.
    - Statistical analysis of secondary endpoints were not adjusted for multiplicity.

![Zuranolone Flowchart](#)
## Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PBO (N=74)</th>
<th>Zuranolone (N=76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27.4 (5.3)</td>
<td>29.3 (5.4)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>18 (24.3)</td>
<td>16 (21.1)</td>
</tr>
<tr>
<td>Not Hispanic/Latino</td>
<td>56 (75.7)</td>
<td>60 (78.9)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td>31 (41.9)</td>
<td>31 (40.8)</td>
</tr>
<tr>
<td>White</td>
<td>40 (54.1)</td>
<td>44 (57.9)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (4.1)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162.3 (7.1)</td>
<td>165.0 (7.4)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80.2 (23.6)</td>
<td>85.1 (19.1)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.3 (8.1)</td>
<td>31.1 (6.2)</td>
</tr>
<tr>
<td>Baseline HAM-D total score</td>
<td>28.8 (2.3)</td>
<td>28.4 (2.1)</td>
</tr>
</tbody>
</table>

Data are from the efficacy set, and are n (%) or mean (SD).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PBO (N=74)</th>
<th>Zuranolone (N=76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressant Use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline antidepressant use</td>
<td>13 (17.6)</td>
<td>16 (21.1)</td>
</tr>
<tr>
<td>Family History of PPD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10 (13.5)</td>
<td>10 (13.2)</td>
</tr>
<tr>
<td>No</td>
<td>64 (86.5)</td>
<td>66 (86.8)</td>
</tr>
<tr>
<td>Onset of PPD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd Trimester</td>
<td>31 (41.9)</td>
<td>33 (42.1)</td>
</tr>
<tr>
<td>Within 4 weeks of delivery</td>
<td>43 (58.1)</td>
<td>44 (57.9)</td>
</tr>
</tbody>
</table>

- Two patients randomized to PBO received at least one dose of zuranolone and were included in the zuranolone group in the safety population.
- One zuranolone patient was excluded from the efficacy population due to no post-baseline efficacy assessments.
Statistically Significant Decreases in Primary Endpoint of Change from Baseline on Day 15 in HAM-D Total Score

- **DAY 3**
  - PBO: -9.8
  - Zuranolone: -12.5
  - p = 0.0252

- **PRIMARY ENDPOINT (DAY 15)**
  - PBO: -13.6
  - Zuranolone: -17.8
  - p = 0.0028

- **DAY 45**
  - PBO: -15.1
  - Zuranolone: -19.2
  - p = 0.0027

* p=0.0252; † p=0.0106; § p=0.0321; ‖ p=0.0027 vs PBO.
HAM-D Response and Remission Rates: Significant Improvements for Zuranolone vs. Placebo

* *p<0.05 vs PBO.*
Statistically Significant Decreases in MADRS Total Score Change From Baseline for Zuranolone vs. Placebo

-30 -25 -20 -15 -10 -5 0 5 10 15 20 25 30

0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45

14-DAY TREATMENT PERIOD
FOLLOW-UP PERIOD DAYS 15 TO 45

LSM MADRS Total Score Change From Baseline (±SE)

PBO (N = 76) Zuranolone (N = 74)

*p=0.0322; †p=0.0180; ‡p=0.0271; §p=0.0018; vs PBO.
### Zuranolone Safety Data

<table>
<thead>
<tr>
<th>TEAE, n (%)</th>
<th>PBO (N=73)</th>
<th>Zuranolone (N=78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>38 (52.1)</td>
<td>47 (60.3)</td>
</tr>
<tr>
<td>Severe AE</td>
<td>3 (4.1)</td>
<td>3 (3.8)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>1 (1.4)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>AE-drug discontinuation</td>
<td>0</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Most Common TEAEs, ≥5% patients in either treatment group, n(%)**

<table>
<thead>
<tr>
<th></th>
<th>PBO (N=73)</th>
<th>Zuranolone (N=78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>8 (11)</td>
<td>12 (15.4)</td>
</tr>
<tr>
<td>Headache*</td>
<td>9 (12.3)</td>
<td>7 (9.0)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4 (5.5)</td>
<td>6 (7.7)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>1 (1.4)</td>
<td>6 (7.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (2.7)</td>
<td>5 (6.4)</td>
</tr>
<tr>
<td>Sedation</td>
<td>0</td>
<td>4 (5.1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (8.2)</td>
<td>3 (3.8)</td>
</tr>
<tr>
<td>Vomiting*</td>
<td>4 (5.5)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Abnormal dreams*</td>
<td>4 (5.5)</td>
<td>0</td>
</tr>
<tr>
<td>Hyperhidrosis*</td>
<td>4 (5.5)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Greater in PBO vs. zuranolone

- A similar proportion of patients reported treatment emergent adverse events (TEAEs) in the zuranolone group compared with the placebo group (PBO).¹
- Somnolence, headache, dizziness, upper respiratory tract infection, diarrhea, and sedation were the most common (≥5%) AEs in the zuranolone group.
- There was no signal for increased suicidal ideation or suicidal behavior compared with baseline, as measured by the Columbia-Suicide Severity Rating Scale.
- Serious AE (2 subjects)
  - Confusional state (zuranolone) on Day 3, resolved on the same day, probably related. Dose interrupted and reduced and completed the study.
  - Cholelithiasis/pancreatitis (placebo) started on Day 32 and resolved on Day 36 with cholecystectomy.
Conclusions

- In this Phase 3, double-blind, placebo-controlled trial in women with PPD, zuranolone achieved rapid (by Day 3) and sustained (through Day 45) improvements in depressive symptoms compared to placebo.
  - The primary endpoint of a statistically significant reduction in the HAM-D total score at Day 15 compared with placebo was achieved.
  - Secondary endpoints, including MADRS total score and categorical measures of HAM-D response and remission, supported the primary endpoint result.
- Zuranolone was generally well tolerated, with the most common TEAEs being somnolence, headache, dizziness, upper respiratory tract infection, diarrhea, and sedation.
- There was one serious adverse event in the zuranolone group (confusional state) which resolved following dose interruption.
- These data support the potential for neuroactive steroids in the treatment of mood disorders.
Seeing the brain differently makes a world of difference.