Pivotal, Randomized, Placebo-Controlled Trial of Zuranolone (SAGE-217) in Postpartum Depression: Association Between HAM-D and PHQ-9

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Introduction

- Postpartum depression (PPD) are the most common medical complications during and after pregnancy. In the United States, estimates of new mothers experiencing symptoms of PPD vary by state from 8-22%, with an overall average of 13%.1
- Under- or untreated PPD may negatively impact the mother, infant, and partner.2,3
- PPD is associated with thoughts of self-harm, and symptoms of depression can persist for over a decade.4
- Children of mothers with PPD exhibit short-term and long-term physical and behavioral deficits.5,6

Conclusions

- Zuranolone met the primary endpoint of improvement in depressive symptoms by Day 15 as assessed by change in baseline in HAM-D total score compared with placebo.
- Zuranolone achieved rapid (by Day 3) and durable (through Day 45) reductions in depressive symptoms by a clinician-reported measure (HAM-D) that significantly correlated with a patient-reported outcome measure (PHQ-9).

Methods

- Patients (n=151) were women, ages 18-45, with a minimum of 6 months postpartum, diagnosed with PDD (as defined in a major depressive episode with onset in the 3rd trimester or ≤4 weeks postpartum) and a baseline HAM-D total score ≥22.
- Patients were randomized 1:1 to receive zuranolone 30 mg or placebo once daily for two weeks as outpatients, with follow-up through Day 45.
- The primary endpoint was the change from baseline in HAM-D total score at Day 15. Secondary endpoints included HAM-D total score at all other time points. PHQ-9 score was an exploratory endpoint.
- Change from baseline in HAM-D (using least-squares [LS] means) was evaluated using least-squares (LS) means from a mixed-effect model for repeated measures (MMRM). Secondary and exploratory endpoints were not adjusted for multiplicity.
- The relationships between HAM-D and PHQ-9 absolute scores and change from baseline were assessed by Pearson correlations.
- Safety and tolerability were assessed by adverse event reporting, standard clinical assessments. The Columbus – Suicide Severity Rating Scale (C-SSRS) was also assessed.

Results

Demographics and Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=78</th>
<th>Zuranolone N=78</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>64 (82.1)</td>
<td>65 (83.3)</td>
<td>0.899</td>
</tr>
<tr>
<td>Black</td>
<td>4 (5.1)</td>
<td>4 (5.1)</td>
<td>1.000</td>
</tr>
<tr>
<td>Other</td>
<td>10 (13.0)</td>
<td>9 (11.5)</td>
<td>0.777</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>39.2 (6.9)</td>
<td>39.3 (6.9)</td>
<td>0.952</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>73.5 (13.9)</td>
<td>72.7 (13.5)</td>
<td>0.682</td>
</tr>
</tbody>
</table>

- Zuranolone demonstrated a statistically significant decrease in LS mean HAM-D total score compared with placebo (-17.8 vs. -13.6, p=0.0028) at the Day 15 primary endpoint.
- Statistically significant improvements occurred as early as Day 3 (-15.4 vs. -9.6, p=0.002) and were sustained through Day 45 (-10.3 vs. -15.1, p<0.001).

PHQ-9 Absolute Total Score and Change from Baseline Moderately Correlated with HAM-D at Day 45 in the Pooled Population

<table>
<thead>
<tr>
<th>Visit Day</th>
<th>Absolute Total Score (N)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (N=151)</td>
<td>15.9 (6.7)</td>
<td></td>
</tr>
<tr>
<td>15 (N=151)</td>
<td>4.3 (6.7)</td>
<td></td>
</tr>
</tbody>
</table>

- HAM-D and PHQ-9 total scores were significantly and modestly (0.5-0.7) correlated at Day 45 (r=0.56, p<0.001).

TEAEs

- Any TEAEs: Placebo (N=78) 45 (57.7%), Zuranolone (N=78) 61 (78.2%), p=0.001
- Placebo: 1-7
- Zuranolone: 1-16

- Serious Adverse Events: Placebo: 0 (0.0%), Zuranolone: 1 (1.3%), p=0.499

- There was no increased signal for suicidality/depression as assessed by the C-SSRS.

- Zuranolone was generally well tolerated.

- Zuranolone demonstrated statistically significant improvements in the patient-reported measure (PHQ-9) at Day 45.
- Zuranolone was generally well-tolerated, with favorable overall TEAEs (≥5% of patients) being confusional state, headache, diarrhea, and somnolence.

- Zuranolone demonstrated statistically significant improvements in the patient-reported measure (PHQ-9) at Day 45.

- Zuranolone demonstrated a statistically significant decrease in LS mean PHQ-9 total score compared with placebo (-9.0 vs. -5.6, p=0.009) at Day 45 and numerically greater decreases in PHQ-9 total scores at all post-baseline time points.

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- PHQ-9 Absolute Total Score and Change from Baseline Moderately Correlated with HAM-D at Day 45 in the Pooled Population

- PHQ-9 Absolute Total Score

- PHQ-9 Change from Baseline Score

- LS MEAN HAM-D CHANGE FROM BASELINE: SIGNIFICANT HAM-D REDUCTIONS FAVORING ZURANOLONE COMPARED WITH PLACEBO

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