ZURANOLONE DEMONSTRATES SIGNIFICANT, RAPID AND SUSTAINED REDUCTION IN HAMD-17 TOTAL SCORE AND MADRS VERSUS PLACEBO

**Results**

**DEMOGRAPHICS AND CHARACTERISTICS**

<table>
<thead>
<tr>
<th>ZURANOLONE</th>
<th>PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (SE)</td>
<td>29.3 (5.4)</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>31:25</td>
</tr>
</tbody>
</table>

**ZURANOLONE**

- Age, years (SE): 29.3 (5.4)
- Sex (M:F): 31:25

**PLACEBO**

- Age, years (SE): 27.4 (5.3)
- Sex (M:F): 29:25

**Efficacy (%)**

<table>
<thead>
<tr>
<th>ZURANOLONE</th>
<th>PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hispanic or Latino</td>
<td>16 (21.1)</td>
</tr>
</tbody>
</table>

**RACE (%)**

| Black or African-American | 31 (40.8) | 31 (41.9) |
| White | 44 (57.9) | 50 (64.1) |

**Other**

| 1 (1.3) | 1 (1.3) |

**HEIGHT (cm)**

<table>
<thead>
<tr>
<th>ZURANOLONE</th>
<th>PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm)</td>
<td>165.7 (7.4)</td>
</tr>
</tbody>
</table>

**Weight, kg (SE)**

<table>
<thead>
<tr>
<th>ZURANOLONE</th>
<th>PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg (SE)</td>
<td>85.1 (19.1)</td>
</tr>
</tbody>
</table>

**BMI, kg/m² (SE)**

<table>
<thead>
<tr>
<th>ZURANOLONE</th>
<th>PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>31.6 (6.2)</td>
</tr>
</tbody>
</table>

**Baseline Antidepressant Use (SE)**

<table>
<thead>
<tr>
<th>ZURANOLONE</th>
<th>PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline HAMD-17 Total Score (SE)</td>
<td>29.4 (2.1)</td>
</tr>
</tbody>
</table>

**Outcome**

- Two patients randomized to Placebo 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.

**EMERGENT ADVERSE EVENTS**

<table>
<thead>
<tr>
<th>ZURANOLONE</th>
<th>PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>47 (60)</td>
</tr>
<tr>
<td>Severe AE</td>
<td>8 (10)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>1 (1)</td>
</tr>
<tr>
<td>AE-discontinuation</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

**Most Common TEAEs, ≥5% of patients, n (%)**

- Somnolence: 12 (15)
- Headache: 7 (9)
- Dizziness: 6 (8)
- Upper respiratory tract infection: 6 (8)
- Diarrhea: 5 (6)
- Sedation: 4 (5)
- Nausea: 3 (4)
- Vomiting: 2 (3)
- Abnormal dreams: 1 (1)
- Abdominal pain: 0 (0)
- Arthralgia: 0 (0)
- Hypersomnia: 0 (0)
- Hyperhidrosis: 0 (0)
- Hypertension: 0 (0)

**IMPROVEMENTS IN HAMD-17 RESPONSE AND REMISSION RATES WITH ZURANOLONE VERSUS PLACEBO**

**TREATMENT-EMERGENT ADVERSE EVENTS**

- Any AE: 47 (60)
- Severe AE: 8 (10)
- Serious AE: 1 (1)
- AE-discontinuation: 1 (1)

**METHODS**

- The zuranolone trial in PPD enrolled women (n=151), ages 18-45, ≤6 months postpartum, with PPD defined here as a major depressive episode with onset in the 3rd trimester or 5 weeks postpartum, and a Hamilton Rating Scale for Depression (HAM-D-17) total score ≥26 at baseline.
- Patients were randomized to receive oral zuranolone 30 mg or placebo daily for 14 days as outpatients, with follow-up to Day 45.
- The primary endpoint was the change from baseline (CFB) in HAMD-17 total score at Day 15.
- Secondary endpoints included HAMD-17 total score at all other time points and categorical assessment of HAMD-17 response (reduction ≥50%) and remission (total score ≤7), and the change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS). Secondary endpoints were not adjusted for multiplicity.
- Safety and tolerability were assessed by TEAE reporting and standard clinical assessments.

**RESULTS**

- Two patients randomized to Placebo 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.

**DISCUSSION**

- The most common (≥5%) AEs in the zuranolone group were somnolence, headache, dizziness, upper respiratory tract infection, diarrhea, and sedation.
- In both treatment groups, most TEAEs were reported to be mild or moderate.
- Six patients (3%) from each group experienced severe TEAEs.
- Three patients in the zuranolone group experienced: sedation (n=1); hypomanic state (n=1); mania (n=1).
- Three patients in the placebo group experienced: back pain, muscle spasms (n=1); headache, orthopaedical pain (n=1); meningitis (n=1).
- Somnolence and sedation related events leading to dose reduction or discontinuation.
- Three patients in the zuranolone group had doses reduced to 20 mg due to confusional state (serious adverse events described above), somnolence (mild), or sedation (moderate), and one patient discontinued study drug early due to intermittent sedation (severe).

**CONCLUSIONS**

- In this Phase 3 double-blind, randomized, placebo-controlled trial, zuranolone treatment resulted in rapid (by Day 3) and sustained at all measure timepoints (Day 45) improvements in depressive symptoms relative to placebo.
- The primary endpoint was achieved, with statistically significant reductions in HAMD-17 total score at Day 15 relative to placebo.
- Secondary endpoints, including MADRS and categorical measures of HAMD-17 response and remission, supported the primary endpoint result.
- Zuranolone was generally well tolerated relative to placebo.
- AEs occurring in ≥5% of zuranolone patients were 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 results support the further development of zuranolone as a potential treatment for PPD.

**METHODS**

- The ROBIN trial, A Phase 3, Double-Blind, Placebo-Controlled Trial of Zuranolone in Postpartum Depression

**CONCLUSIONS**

- Zuranolone demonstrated a statistically significant decrease in HAMD-17 total score compared with placebo (−17.8 versus −13.6, p = 0.0028) at the Day 15 primary endpoint.
- Statistically significant separation started at Day 3 (−12.5 versus −9.8, p = 0.0252) and was sustained at all measure timepoints through Day 45 (−19.2 versus −15.1, p = 0.0027).
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- Zuranolone demonstrated a statistically significant decrease in MADRS compared with placebo starting at Day 8 (−20.3 versus −16.3, p = 0.0232) and was sustained at all measure timepoints through Day 45 (−24.8 versus −19.0, p = 0.0018).

**IMPROVEMENTS IN HAMD-17 RESPONSE AND REMISSION RATES WITH ZURANOLONE VERSUS PLACEBO**

**TREATMENT-EMERGENT ADVERSE EVENTS**

- Patients Reporting TEAE, n (%) | ZURANOLONE, N=76 | PLACEBO, N=74
- Any AE | 47 (60) | 38 (52)
- Severe AE | 8 (10) | 3 (4)
- Serious AE | 1 (1) | 1 (1)
- AE-discontinuation | 1 (1) | 0 (0)

**Most Common TEAEs, ≥5% of patients, n (%)**

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