Zuranolone (Anciennement SAGE-217):
ESSAI DE PHASE III DANS LA DÉPRESSION POSTNATALE

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Zuranolone est un composé expérimental, qui n’a pas été approuvé par l’Agence européenne des médicaments (European Medicines Agency, EMA) pour quelque utilisation que ce soit.
Nom : GRESSIER Florence

- J'ai plusieurs liens d'intérêts :

  Bourse : Institut Servier (2011-2012)
  Interventions ponctuelles : EISAI, Laboratoires Servier, Lundbeck, Sage Therapeutics
Disclaimers

Dr. Deligiannidis is currently funded by the Feinstein Institute for Medical Research and Zucker Hillside Hospital of Northwell Health. She was an investigator for Sage Therapeutics, Inc. studies of brexanolone injection and Zuranolone and serves as a consultant to Sage Therapeutics, Inc. In addition, she receives NIMH grant support and royalties from an NIH employee invention.

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

Zuranolone (formerly SAGE-217) is an investigational compound and is not approved by the EMA for any use.
Postpartum Depression: Background

• Postpartum depression (PPD) is a common medical complication during and after pregnancy.¹

• 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% among EU-8 member countries.²

• Untreated PPD may negatively impact mother, infant, and partner.³⁻¹⁹
  • Maternal suicide is a leading cause of mortality in the postpartum period, and depression symptoms can extend over a decade.³⁻⁸
  • Children of mothers with PPD exhibit short- and long-term deficits.⁷,⁹⁻¹⁴
  • Partners of women with PPD are also more likely to develop depression.¹⁵⁻¹⁸

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

A synthesized hypothesis for the role of GABA dysfunction in the pathophysiology of PPD

Risk/Triggers*

Acute
- Hormonal fluctuations¹
- Inflammatory factors²
- Epigenetic factors³

Chronic
- Genetic factors⁴
- History of depression⁵,⁶
- History of trauma⁷,⁸
- Chronic stress⁹
- Socioeconomic factors⁹

*Subset of multiple risk factors associated with PPD. GABA=gamma-aminobutyric acid; HPA=hypothalamic-pituitary-adrenal.

Inability of the GABA system to regulate neural network activity is associated with PPD

Altered GABA Function¹⁰

Dysregulated Neural Networks¹¹,¹²

Postpartum Depressive Episode

Symptoms of PPD¹³
- Feeling sad, hopeless, empty, or overwhelmed
- Crying more often than usual or for no apparent reason
- Worrying/anxiety
- Feeling moody, irritable, restless
- Feelings of anger or rage
- Difficulty bonding with infant

Zuranolone: Background

• Zuranolone (formerly SAGE-217) is an investigational oral neuroactive steroid GABA_A receptor positive allosteric modulator (PAM). Zuranolone binds to both synaptic and extrasynaptic GABA_A receptors, which is distinct from benzodiazepines, which only bind to synaptic GABA_A receptors.¹,²

• Pharmacokinetic/pharmacodynamic profile supports once-daily, oral dosing.³,⁴

• Demonstrated positive results in a pivotal study in major depressive disorder.⁵

In vitro GABA_A receptor activity²

Zuranolone plasma concentration over time³

Zuranolone: Phase 3 PPD (Robin) 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: Least-squares mean (LSM) 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), MADRS, CGI-I, and the Hamilton Rating Scale for Anxiety (HAM-A).
  - Statistical analyses of secondary endpoints were not adjusted for multiplicity.
Zuranolone: Phase 3 PPD trial

**Baseline patient and disease 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 Hispanic/Latino</td>
<td>18 (24.3)</td>
<td>16 (21.1)</td>
</tr>
<tr>
<td>Race 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>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 antidepressant use</td>
<td>13 (17.6)</td>
<td>16 (21.1)</td>
</tr>
<tr>
<td>Baseline HAM-D</td>
<td>28.8 (2.3)</td>
<td>28.4 (2.1)</td>
</tr>
</tbody>
</table>

- Two patients randomized to PBO received at least one dose of zuranolone and were included in the zuranolone safety population.
- One zuranolone patient was excluded from the efficacy population due to no post-baseline efficacy assessments.
Zuranolone: Phase 3 PPD trial

*Change from baseline in HAM-D total score*

- **Day 3**
  - Zuranolone: -12.5 vs PBO: -9.8; p=0.0252

- **Day 15 (Primary Endpoint)**
  - Zuranolone: -17.8 vs PBO: -13.6; p=0.0028

- **Day 45**
  - Zuranolone: -19.2 vs PBO: -15.1; p=0.0027

*p=0.0252; †p=0.0106; ‡p=0.0028; §p=0.0321; ‖p=0.0027 vs PBO.*
Zuranolone: Phase 3 PPD trial
*Change from baseline in MADRS total score*

- **Day 15**
  - Zuranolone: -22.1 vs PBO: -17.6; p=0.0180

- **Day 45**
  - Zuranolone: -24.8 vs PBO: -19.0; p=0.0018

*LSM MADRS Total Score Change From Baseline (±SE)*

*p=0.0322; †p=0.0180; ‡p=0.0271; §p=0.0018; vs PBO.*
Zuranolone: Phase 3 PPD trial

**HAM-D total score response and remission rates**

**HAM-D total score response**
Reduction of HAM-D total score ≥50% from baseline

**HAM-D total score remission**
HAM-D total score ≤7

<table>
<thead>
<tr>
<th>Days</th>
<th>Zuranolone (N=76)</th>
<th>PBO (N=74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 3</td>
<td>27</td>
<td>5</td>
</tr>
<tr>
<td>Day 8</td>
<td>41</td>
<td>19</td>
</tr>
<tr>
<td>Day 15</td>
<td>45</td>
<td>32</td>
</tr>
<tr>
<td>Day 21</td>
<td>48</td>
<td>23</td>
</tr>
<tr>
<td>Day 45</td>
<td>56</td>
<td>29</td>
</tr>
</tbody>
</table>

Patients Achieving Response, %

<table>
<thead>
<tr>
<th>Days</th>
<th>Zoranolone (N=76)</th>
<th>PBO (N=74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 3</td>
<td>72*</td>
<td>45</td>
</tr>
<tr>
<td>Day 8</td>
<td>72†</td>
<td>42</td>
</tr>
<tr>
<td>Day 15</td>
<td>56</td>
<td>53</td>
</tr>
<tr>
<td>Day 21</td>
<td>57</td>
<td>42</td>
</tr>
<tr>
<td>Day 45</td>
<td>75‡</td>
<td>53‡</td>
</tr>
</tbody>
</table>

Patients Achieving Remission, %

*p=0.0127; †p=0.0049; ‡p=0.0216; §p=0.0200; ¶p=0.0110; ††p=0.0091 vs PBO.
Zuranolone: Phase 3 PPD trial

*Change from baseline in HAM-A total score*

- **Day 3**
  - Zuranolone: -12.0 vs PBO: -8.9; \( p=0.0169 \)

- **Day 15**
  - Zuranolone: -16.6 vs PBO: -12.7; \( p=0.0063 \)

- **Day 45**
  - Zuranolone: -18.6 vs PBO: -13.6; \( p=0.0002 \)

\( p=0.0169; \) \( p=0.0010; \) \( p=0.0063; \) \( p=0.0119; \) \( p=0.0002 \) vs PBO.
Zuranolone: Phase 3 PPD trial

Adverse Events

<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(%):

- **Somnolence**: 8 (11) vs. 12 (15.4)
- **Headache**: 9 (12.3) vs. 7 (9.0)
- **Dizziness**: 4 (5.5) vs. 6 (7.7)
- **Upper respiratory tract infection**: 1 (1.4) vs. 6 (7.7)
- **Diarrhea**: 2 (2.7) vs. 5 (6.4)
- **Sedation**: 0 vs. 4 (5.1)
- **Nausea**: 6 (8.2) vs. 3 (3.8)
- **Vomiting**: 4 (5.5) vs. 1 (1.3)
- **Abnormal dreams**: 4 (5.5) vs. 0
- **Hyperhidrosis**: 4 (5.5) vs. 0

*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.¹
- 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.

¹Greater in PBO vs. zuranolone
Zuranolone: Phase 3 PPD trial

Summary and Conclusions

• Zuranolone, an investigational oral compound, achieved the primary endpoints of a statistically significant reduction in HAM-D score at Day 15.
  • The effect was rapid, with significant reductions in HAM-D observed by Day 3, and sustained through Day 45.
  • HAM-D total score results were supported by multiple secondary endpoints.

• Zuranolone was generally well tolerated.
  • The most common (≥5%) AEs in the zuranolone study group were somnolence, headache, dizziness, upper respiratory tract infection, diarrhea, and sedation.

• These findings support the potential utility of neuroactive steroid GABA<sub>A</sub>R PAMs in the treatment of PPD.
Thank You