Insights from the Clinical Development of the Neuroactive Steroid Zuranolone in MDD and PPD

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Disclosures

Professor Vieta has an interest in relation with one or more organisations that could be perceived as a possible conflict of interest in the context of the subject of this presentation. The relationships are summarized below:

<table>
<thead>
<tr>
<th>Interest</th>
<th>Name of Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grant</td>
<td>AB-Biotics, Almirall, Astra-Zeneca, Bristol-Myers Squibb, Elan, Eli Lilly, The European 7th Framework Program, Ferrer, Forest, GlaxoSmithKline, Janssen-Cilag, Novartis, Otsuka, Pfizer, Richter, Sanofi-Aventis, Seny Foundation, Servier, The Spanish Ministry of Health (CIBERSAM), Telefonica, The Spanish Ministry of Science and Education, The Stanley Medical Research Institute</td>
</tr>
<tr>
<td>Advisory boards</td>
<td>Allergan, Angelini, Astra-Zeneca, Bristol-Myers Squibb, Dainippon Sumitomo Pharma, Eli Lilly, Esteve, Ferrer, GlaxoSmithKline, Janssen, Lundbeck, MSD, Novartis, Otsuka, Pfizer, Richter, Roche, Sage Therapeutics, Sanofi-Aventis, Servier, Shire, Sunovion, Takeda, Teva, UBC</td>
</tr>
<tr>
<td>Other involvement</td>
<td>Consultant for Abbott, Angelini, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Forest Research Institute, GlaxoSmithKline, Janssen, Jazz, Lundbeck, MSD, Novartis, Otsuka, Pierre-Fabre, Pfizer, Sanofi-Aventis, Servier, Shire, Solvay, Sunovion</td>
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Support for Professor Vieta’s presentation at ECNP was provided by Sage Therapeutics, Inc. The views expressed during this presentation are entirely the presenter’s own.

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.
Zuranolone

• Zuranolone (SAGE-217) is an investigational oral NAS GABA<sub>A</sub> receptor PAM, being investigated in adults with major depressive disorder (MDD) and postpartum depression (PPD).<sup>1-5</sup>

• Zuranolone is orally bioavailable.<sup>1,6</sup>

• PK/PD profile supports once-daily, oral dosing in clinical studies.<sup>1,6</sup>

• Phase 2 clinical modeling analyses were supportive of a 2-week dosing regimen.<sup>7</sup>

Zuranolone plasma concentration over time<sup>8</sup>

**Mean Zuranolone Plasma Concentration (ng/mL)**

- **0**
- **10**
- **20**
- **30**
- **40**
- **50**
- **60**
- **70**
- **80**
- **90**
- **100**
- **110**
- **120**

- **0**
- **10**
- **20**
- **30**
- **40**
- **50**

- **Time (Hours)**

**30 mg Solution, Fasted**

**30 mg Capsules, Fasted**

**30 mg Capsules, High Fat**

**30 mg Capsules, Standard**

*30 mg Capsules in Fed state

NAS=neuroactive steroid; PAM=positive allosteric modulator; PK/PD=pharmacokinetics/pharmacodynamics

## NEST and LANDSCAPE Programs

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

<table>
<thead>
<tr>
<th>Study</th>
<th>NCT #</th>
<th>Indication</th>
<th>Phase</th>
<th>Primary Objectives</th>
<th>Status</th>
<th>MAJOR DEPRESSIVE DISORDER (MDD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>POSTPARTUM DEPRESSION (PPD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>PPD-201</td>
<td>02978326</td>
<td>Severe PPD</td>
<td>Phase 3</td>
<td>Efficacy: 30 mg vs placebo</td>
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<td>Efficacy: 50 mg vs placebo</td>
<td>Enrolling</td>
<td>MDD-302</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Efficacy: 30 mg vs placebo</td>
<td>Planned</td>
<td>MDD-305</td>
</tr>
</tbody>
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**Primary Objectives**

- **Efficacy:**
  - 30 mg vs placebo
  - 50 mg vs placebo
  - 30 mg vs placebo
  - 30 mg vs placebo
  - 30 mg vs placebo
  - 50 mg vs placebo
  - Efficacy as Rapid-response in MDD 50 mg + ADT vs placebo + ADT

**Status**

- Completed
- Enrolling
- Completed
- Completed
- Enrolling
- Stopped
- 30 mg Enrollment completed; Enrolling 50 mg
- Enrollment halted

**Notes:**

- PSG = polysomnography
- ADT = antidepressant therapy

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*PSG=polysomnography; ADT=antidepressant therapy*
Pivotal Study in PPD (ROBIN)  
**Change from Baseline in HAMD-17 Total** ¹

- The zuranolone 30 mg and placebo arms included 76 and 74 patients that were randomized and included in the efficacy analyses, respectively.

- Baseline demographics and patient characteristics were well balanced between the two treatment arms, and zuranolone was generally well tolerated, as previously described.²

- Zuranolone met the primary endpoint, reducing depressive symptoms assessed by CFB in the 17-item Hamilton Rating Scale for Depression total score (HAMD-17) at Day 15 versus placebo (CFB±SE: ZRN: -17.8±1.04, placebo: -13.6±1.07, p=0.0028).

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¹ LSM=least-squares mean; CFB=change from baseline

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

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

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

* *p=0.0252; †p=0.0106; ††p=0.0028; ‡p=0.0321; §p=0.0027 vs placebo. Secondary endpoints were not adjusted for multiplicity.

The zuranolone 30 mg and placebo arms included 45 and 44 patients that were randomized and included in the efficacy analyses, respectively.

Baseline demographics and patient characteristics were generally well balanced between the two treatment arms, except age, sex, and percent of black patients, and zuranolone was generally well tolerated as previously described.¹

Zuranolone met the primary endpoint, reducing depressive symptoms assessed by CFB in the HAMD-17 at Day 15 versus placebo (CFB±SE: ZRN: -17.4±1.31, placebo: -10.3±1.33, p<0.0001).

* p=0.0223; † p=0.0010; ‡ p=0.0233; § p=0.0066; ¶ p=0.0019; †† p=0.0043; ‡‡ p=0.0318; ** p<0.0001; ††† p=0.0064; ‡‡‡ p=0.0243 vs placebo.

Secondary endpoints were not adjusted for multiplicity.

LSM=least-squares mean; CFB=change from baseline

MOUNTAIN Study in MDD

Phase 3 Results

- The zuranolone 30 mg, zuranolone 20 mg and placebo arms included 166, 159, and 157 patients that were randomized and included in the efficacy analyses, respectively.¹,²

- Baseline demographics and patient characteristics were well balanced between the three treatment arms and have been described in detail previously.¹,²

- Zuranolone was generally well tolerated, as previously described. The most common TEAEs occurring in ≥5% of patients who received zuranolone were headache, dizziness, somnolence, fatigue, diarrhea, sedation, and nausea.¹-³

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.

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.

Data on File, MLIB-3365, Topline Results Memo, Study [217-MDD-301], Sage Therapeutics, Inc. [2019].
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<td>MDD</td>
<td>Phase 3</td>
<td>Efficacy: 50 mg vs placebo</td>
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<td>MDD-302</td>
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<td>MDD</td>
<td>Phase 3</td>
<td>Re-treatment efficacy: 1-year</td>
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<td>MDD</td>
<td>Phase 3</td>
<td>Relapse safety: 1-year follow-up (30 and 50 mg)</td>
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<td>Co-morbid MDD and Insomnia</td>
<td>Phase 3</td>
<td>PSG efficacy on insomnia symptoms (30 mg vs placebo)</td>
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<td>MDD-305</td>
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<td>MDD</td>
<td>Phase 3</td>
<td>Efficacy as Rapid-response in MDD 50 mg + ADT vs placebo + ADT</td>
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</tbody>
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**POSTPARTUM DEPRESSION (PPD)**

**MAJOR DEPRESSIVE DISORDER (MDD)**

- PSG = polysomnography; ADT = antidepressant therapy
NEST and LANDSCAPE Programs
Broad Programs Underway Across Numerous Studies, Indications

PPD-301: Postpartum Depression Therapy

- Diagnosis of PPD with symptoms present for at least 4 weeks; HAMD-17 ≥ 26 at screening and Day 1 (prior to dosing)
- 1:1 Randomized, Double-Blind
  - Zuranolone 50 mg
  - Placebo
- 14-Day Treatment
- Controlled Follow-Up
  - Day 15 Primary Endpoint
  - Day 42 Follow-Up

MDD-301B: Episodic Therapy in Patients with MDD

- Diagnosis of MDD with symptoms present for at least 4 weeks; HAMD-17 ≥ 24 at screening and Day 1 (prior to dosing)
- 1:1 Randomized, Double-Blind
  - Zuranolone 50 mg
  - Placebo
- 14-Day Treatment
- Controlled Follow-Up
  - Day 15 Primary Endpoint
  - Day 42 Follow-Up
LANDSCAPE Program
Broad Program Underway Across Numerous Studies, Indications

MDD-303: Safety of Zuranolone Re-Treatment in Patients with MDD

- Diagnosis of MDD with symptoms present for at least 4 weeks
- Zuranolone 50 mg
- 14-Day Treatment
- Follow-Up: Days 15-28
- Observation: Zuranolone 50 mg
  Up to 11 Months Follow-Up
  Treat-as-needed

MDD-305: Acute Rapid Response in MDD in Conjunction With an Antidepressant Therapy

- Diagnosis of MDD with symptoms present for at least 4 weeks; HAMD-17 ≥ 24 at screening and Day 1 (prior to dosing)
- 1:1 Randomized, Added to Open-Label ADT, Double-Blind
- Zuranolone 50 mg + Open-Label ADT
- Placebo + Open-Label ADT
- 14-Day Treatment
- Controlled Follow-up:
  - Day 15 Primary Endpoint
  - Day 42 Follow-up
Conclusions

• The ROBIN Study in PPD and the MDD-201 Study each met their primary endpoint of a statistically significant reduction from baseline compared with placebo in HAMD-17 total score at Day 15.

• The MOUNTAIN Study did not meet its primary endpoint but 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 measurable drug concentration, significant improvements in depressive symptoms were observed at all measured time points.

• Zuranolone was generally well tolerated in the ROBIN Study, the MDD-201 Study, and the MOUNTAIN Study, and showed a similar safety profile across trials.

• Additional zuranolone studies within the NEST and LANDSCAPE Program are ongoing, and will provide further insight into zuranolone treatment in patients with MDD and PPD.
Seeing the brain differently makes a world of difference