A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study Evaluating the Efficacy of Zuranolone in the Treatment of Adult Patients with Major Depressive Disorder

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Disclosures

- Dr. Anita H. Clayton reports grants from Allergan, Endoceutics, Janssen, and Sage Therapeutics, Inc; consulting fees from Acadia, Alkermes, Allergan, AMAG Pharmaceuticals, Daré Biosciences, Fabre-Kramer, Ovoca Bio, Palatin Technologies, S1 Biopharma, Sage Therapeutics, Inc., Sprout Pharmaceuticals, Takeda, and Lundbeck; royalties from Ballantine Books/Random House, the Changes in Sexual Functioning Questionnaire, and Guilford Publications; and stock in Euthymics and S1 Biopharma.
No Single Biological or Environmental Factor Is Responsible for the Onset of MDD\(^1-4\)

**Risk Factors\(^2\)**
- Genetic + Epigenetic Susceptibility
- Environmental Triggers

**Biological Mechanisms\(^1-4\)**
- Altered Neurotransmission
- Neuroplasticity
- Stress
- Inflammation

**Dysregulated Brain Network Function\(^1-4\)**

**Depressive Symptoms\(^1-4\)**
- Mood
- Cognitive
- Social
- Somatic

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GABA is the Major Inhibitory Neurotransmitter in the Brain

- Gamma aminobutyric acid (GABA) is an abundant and ubiquitous inhibitory neurotransmitter in the brain.
  - Present in 30-50% of all neurons.¹
- GABA dysfunction can occur in many different brain regions with potential downstream effects.
- The GABA subunit receptor family is complex with diverse physiology, pharmacology and function:¹,²
  - Physiology: Found in different brain regions and neuronal circuits.¹
  - Pharmacology: Includes 19 different receptor subunits.²
  - Function: Differing synaptic locations manifesting as phasic vs. tonic inhibitory tone.¹

GABA subunit receptors are prevalent throughout the brain.

Neuroactive Steroids Modulate Phasic and Tonic Inhibition

Figures adapted from Jacob et al. and Reddy et al.¹,²


GABA

Benzodiazepine binding site

Positive allosteric modulator (PAM) binding site

Synaptic GABAₐ receptors¹,²

Addition of allopregnanolone²

50 pA

200 ms

Presynaptic terminal

GABA

Neuroactive steroid (NAS)

 Postsynaptic terminal

GABA

Synaptic GABAₐ receptors

Extrasynaptic GABAₐ receptors

GABA

Addition of allopregnanolone²

100 pA

30 s

Figures adapted from Jacob et al. and Reddy et al.¹,²

Reduced GABAergic Function in MDD
Abnormal GABAergic function may be one factor contributing to depression

Allopregnanolone

- Allopregnanolone is an endogenous NAS that is a potent PAM of GABA<sub>A</sub> receptors.¹

Decreased Allopregnanolone CSF levels Correlated with Greater HAMD-17 Severity²

![Graph showing the correlation between Allopregnanolone levels and HAMD-17 score](image)

Negative correlation exists between the severity of depression by 17-point Hamilton Rating Scale for Depression (HAMD-17) and ALLO levels in CSF at base line \( r = -0.8161; p < 0.001 \); Pearson’s Product Moment Correlation. Each point is the mean of determinations of ALLO in four CSF fractions.

Zuranolone (SAGE-217)

- Zuranolone is an investigational oral NAS GABA_A receptor PAM.\(^1\) 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.\(^3,4\)

Potent Activity at GABA_A Receptors (\textit{in vitro})\(^5\)

<table>
<thead>
<tr>
<th>Receptor</th>
<th>EC(_{50}) (nM)</th>
<th>E(_{max}) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\alpha_1\beta_2\gamma_2)</td>
<td>374</td>
<td>1041</td>
</tr>
<tr>
<td>(\alpha_4\beta_3\delta)</td>
<td>163</td>
<td>640</td>
</tr>
</tbody>
</table>

**LANDSCAPE Program**

*Broad Program Underway Across Numerous Studies, Indications*

<table>
<thead>
<tr>
<th>STUDY</th>
<th>POSTPARTUM DEPRESSION (PPD)</th>
<th>MAJOR DEPRESSIVE DISORDER (MDD)</th>
<th>TO BE NAMED</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT #</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase</td>
<td>Phase 3</td>
<td>Phase 3</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Primary Objectives</td>
<td>Efficacy: 30 mg vs placebo</td>
<td>Efficacy: 50 mg vs placebo</td>
<td>Efficacy as Rapid-response in MDD 50 mg + SSRI vs placebo</td>
</tr>
<tr>
<td>Status</td>
<td>Completed</td>
<td>Completed</td>
<td>Enrollment halted</td>
</tr>
<tr>
<td></td>
<td>Enrolling</td>
<td>Completed</td>
<td>Enrollment halted</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enrolling</td>
<td>Enrollment completed; Enrolling 50 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Enrollment halted</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Enrolling soon</td>
</tr>
</tbody>
</table>

**STUDY**
- **PPD-201**
- **PPD-301**
- **MDD-201**
- **MDD-301A**
- **MDD-301B**
- **MDD-302**
- **MDD-303**
- **MDD-304**
- **MDD-305**

**NCT #**
- 02978326
- N/A
- 03000530
- 03672175
- N/A
- 04007367
- 03864614
- 03771664
- N/A

**Indication**
- PPD
- PPD
- MDD
- MDD
- MDD
- MDD
- Co-morbid MDD and Insomnia
- MDD

**Phase**
- Phase 3
- Phase 3
- Phase 2
- Phase 3
- Phase 3
- Phase 3
- Phase 3
- Phase 3

**Primary Objectives**
- Efficacy: 30 mg vs placebo
- Efficacy: 50 mg vs placebo
- Efficacy: 30 mg vs placebo
- Efficacy: 50 mg vs placebo
- Re-treatment efficacy: 1-year Relapse Prevention (30 mg vs placebo)
- Re-treatment safety: 1-year follow-up (30 and 50 mg)
- PSG efficacy on insomnia symptoms (30 mg vs placebo)
- Efficacy as Rapid-response in MDD 50 mg + SSRI vs placebo

**Status**
- Completed
- Enrolling
- Completed
- Completed
- Enrolling
- Enrollment halted
- 30 mg Enrollment completed; Enrolling 50 mg
- Enrollment halted
- Enrolling soon

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Zuranolone: Pivotal Study in PPD (ROBIN)

Study Design

- Double-blinded, placebo-controlled, 151 subjects randomized.
  - 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 Hamilton Depression Rating Scale (HAMD-17) total score ≥ 26.
- Primary endpoint: Least Square Mean (LSM) change from baseline in HAMD-17 total score at Day 15.
  - Secondary endpoints were not adjusted for multiplicity.
- Safety and tolerability were assessed by adverse event (AE) reporting and standard clinical assessments.

Kanes SJ. CINP; October 3-5, 2019; Athens, Greece.
Zuranolone: Pivotal Study in PPD (ROBIN)
Change from Baseline in HAMD-17 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.

Kanes SJ. CINP; October 3-5, 2019; Athens, Greece.
Zuranolone: Pivotal Study in PPD (ROBIN)

**Adverse Events**

- The percentage of patients who had at least one AE during the treatment period was 60% in the zuranolone group and 52% in the placebo group.
- The most common treatment-emergent AEs (TEAEs, ≥5%) were:
  - Zuranolone group: Somnolence, headache, dizziness, upper respiratory tract infection, diarrhea, and sedation.
  - Placebo group: Headache, somnolence, nausea, dizziness, vomiting, abnormal dreams, and hyperhidrosis.
- 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; confusional state, n=1; migraine, n=1.
  - Three patients in the placebo group experienced: back pain, muscle spasms n=1; headache, oropharyngeal pain n=1; menorrhagia n=1.
- Two patients (1 from each group) experienced serious TEAEs.
  - One patient in the zuranolone group experienced a confusional state on Day 3, resolved on the same day. Dosing was interrupted, reduced and the patient completed the study.
  - One patient in the placebo group experienced Cholelithiasis/pancreatitis starting on Day 32 and resolving on Day 36 with cholecystectomy.
- Somnolence and sedation related events leading to dose reductions/discontinuations.
  - Three patients in the zuranolone group had doses reduced to 20 mg due to confusional state (serious, described above), somnolence (mild), or sedation (moderate), and one patient discontinued study drug early due to intermittent sedation (severe).

### Patients Reporting TEAE, n (%)

<table>
<thead>
<tr>
<th></th>
<th>Zuranolone, N=78</th>
<th>PBO, N=73</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>47 (60)</td>
<td>38 (52)</td>
</tr>
<tr>
<td>Severe AE</td>
<td>3 (4)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>AE-drug discontinuation</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

### Most Common TEAEs, ≥5% Patients, n (%)

<table>
<thead>
<tr>
<th></th>
<th>Zuranolone, N=78</th>
<th>PBO, N=73</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>12 (15)</td>
<td>8 (11)</td>
</tr>
<tr>
<td>Headache</td>
<td>7 (9)</td>
<td>9 (12)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6 (8)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>6 (8)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (6)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Sedation</td>
<td>4 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (4)</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (1)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>0</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>0</td>
<td>4 (6)</td>
</tr>
</tbody>
</table>

A TEAE is an AE with onset after the start of study drug, or worsening of pre-existing medical condition or AE with onset after the start of study drug. Severe AEs are defined as AEs that were incapacitating, with inability to perform normal activities. Serious AEs were defined as any untoward medical occurrence resulting in death, was life-threatening (at time of event), required inpatient hospitalization, resulted in persistent or significant disability, or was a congenital anomaly. Data shown are from the Safety Population.
Zuranolone: Pivotal Study in MDD (Double-Blind RCT)

**Study Design**

- **Patients with moderate-severe MDD**
  HAMD-17 ≥22

1:1 Randomized, Double-Blind

- **Placebo (PBO)**

Zuranolone 30 mg

Days 1-7 Inpatient

Days 8-14 Outpatient

**14 Day Treatment**

- **Day 15 Primary Endpoint**

- **Day 42 Follow-up**

- **Naturalistic Follow-up**

- **Key Inclusion Criteria:** Female and male subjects with unipolar depression for ≥4 weeks; Aged 18-65 years; HAMD-17 total score ≥22.

- **Key Exclusion Criteria:** History of suicide attempt; Treatment-resistant depression; Initiation or change of psychotropics within 30 days prior to screening.

- **Primary endpoint:** LSM change from baseline in HAMD-17 total score at Day 15.
  - Secondary endpoints were not adjusted for multiplicity.

- **Safety and tolerability were assessed by AE reporting and standard clinical assessments.**

Kanes SJ, CINP; Oct 3-5, 2019; Athens, Greece.
Pivotal MDD Double-Blind RCT (MDD-201)
Change From Baseline in HAMD-17 Total Score

LSM HAMD-17 Total Score Change From Baseline (±SE)

Day 2
Zuranolone: -5.8 vs PBO: -3.5; p=0.0223

Day 15 (Primary Endpoint)
Zuranolone: -17.4 vs PBO: -10.3; p<0.0001

*p=0.0223; †p=0.0010; ‡p=0.0233; §p=0.0066; ††p=0.0043; #p=0.0318; **p<0.0001; ††p=0.0064; ‡‡p=0.0243 vs. PBO.

Kanes SJ, CINP; Oct 3-5, 2019; Athens, Greece.
Zuranolone: Pivotal Study in MDD (Double-Blind RCT)

Adverse Events

- There were no serious adverse events and no deaths during this trial.
- The percentage of patients who had at least one adverse event during the treatment period was 53% in the zuranolone group and 45% in the placebo group.
- The most common adverse events that occurred in at least 5% of patients in the zuranolone group were headache, dizziness, nausea, and somnolence.

### Adverse Events During the Treatment Period*

<table>
<thead>
<tr>
<th>AEs, n (%)</th>
<th>Zuranolone Group, N=45</th>
<th>Placebo Group, N=44</th>
<th>Total, N=89</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with a serious adverse event†</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Patients with severe adverse event‡</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Patients with at least one adverse event</td>
<td>24 (53)</td>
<td>20 (45)</td>
<td>44 (49)</td>
</tr>
</tbody>
</table>

**AEs reported in 3 or more patients**

- Headache: 8 (18) | 7 (16) | 15 (17) |
- Dizziness: 5 (11) | 1 (2) | 6 (7) |
- Nausea: 5 (11) | 1 (2) | 6 (7) |
- Somnolence: 3 (7) | 1 (2) | 4 (5) |
- Dry mouth: 2 (4) | 2 (5) | 4 (5) |
- Sedation: 2 (4) | 2 (5) | 4 (5) |
- Chromaturia: 1 (2) | 4 (9) | 5 (6) |
- Decreased appetite: 1 (2) | 2 (5) | 3 (3) |
- Insomnia: 1 (2) | 2 (5) | 3 (3) |
- Pruritus: 1 (2) | 2 (5) | 3 (3) |
- Diarrhea: 0 | 3 (7) | 3 (3) |
- Irritability: 0 | 3 (7) | 3 (3) |

* Adverse events during the treatment period are those that started or worsened from the time of the first dose of the trial intervention through 7 days after the last dose.
† A serious adverse event was defined as any adverse event, occurring while the patient was receiving the trial medication or placebo, that resulted in death, was immediately life-threatening, led to inpatient hospitalization or prolongation of hospitalization, caused persistent or clinically significant disability or incapacity, or resulted in a congenital abnormality or birth defect.
‡ A severe adverse event was defined as any event that was incapacitating or caused an inability to perform normal activities of daily living.

**Zuranolone Pivotal Phase 3 MOUNTAIN (MDD-301)**

**Study Design**

1:1:1 Randomized, Double-Blind

- **Patients with moderate-severe MDD**
  - HAMD-17 $\geq 22$ and MADRS $\geq 32$

Placebo (PBO)

Zuranolone 20 mg

Zuranolone 30 mg

Day 15 Primary Endpoint

Day 42 Follow-up

6 Month Post Naturalistic Follow-up

- **Double-blinded until Day 42, placebo-controlled, 482 subjects randomized.**
  - Key inclusion criteria: Males and females; 18 to 65 years; SCID diagnosis of MDD; Montgomery- Åsberg Depression Rating Scale (MADRS) $\geq 32$ and HAMD-17 $\geq 22$; Stable baseline antidepressants permitted.
  - Key exclusion criteria: Attempted suicide in current episode; Uncontrolled medical conditions; Currently taking benzodiazepines, barbiturates, GABAA modulators, or non-GABA anti-insomnia medications; Failure of 2 or more antidepressants in current episode (treatment-resistant depression).

- **Primary Endpoint:** LSM change from baseline in HAMD-17 total score at Day 15.

- **Changes in depressive symptoms were assessed across multiple measures of depression, including the HAMD-17.**
  - Secondary endpoints and post hoc analyses were not adjusted for multiplicity.

- **Safety and tolerability were assessed by AE reporting and standard clinical assessments.**

Data on File. Sage Therapeutics, Inc. Cambridge, MA.
# MOUNTAIN Study in MDD

## Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Zuranolone 30 mg, N=166</th>
<th>Zuranolone 20 mg, N=159</th>
<th>Placebo, N=157</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years – mean, years (SD)</strong></td>
<td>42.3 (12)</td>
<td>41.9 (12)</td>
<td>41.4 (12)</td>
</tr>
<tr>
<td><strong>Female sex – n (%)</strong></td>
<td>121 (73)</td>
<td>112 (70)</td>
<td>106 (68)</td>
</tr>
<tr>
<td><strong>Race or ethnic group – n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>2 (1.2)</td>
<td>3 (1.9)</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Black/African-American</td>
<td>64 (38.6)</td>
<td>56 (35.2)</td>
<td>54 (34.4)</td>
</tr>
<tr>
<td>Multiple</td>
<td>4 (2.4)</td>
<td>1 (0.6)</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>White</td>
<td>94 (56.6)</td>
<td>99 (62.3)</td>
<td>96 (61.1)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (1.2)</td>
<td>0</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td><strong>Ethnicity – n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>27 (16.3)</td>
<td>31 (19.5)</td>
<td>26 (16.6)</td>
</tr>
<tr>
<td><strong>Weight – mean, kg (SD)</strong></td>
<td>89.7 (22.4)</td>
<td>87.3 (20.2)</td>
<td>89.5 (22.9)</td>
</tr>
<tr>
<td><strong>Baseline HAMD-17 score – mean (SD)</strong></td>
<td>25.9 (2.9)</td>
<td>25.8 (2.8)</td>
<td>25.8 (3.1)</td>
</tr>
<tr>
<td><strong>Use of antidepressants at baseline – n (%)</strong></td>
<td>47 (28)</td>
<td>46 (29)</td>
<td>49 (31)</td>
</tr>
</tbody>
</table>
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.

*\( p=0.0157 \), †\( p=0.0080 \), ‡\( p=0.0175 \) for zuranolone 30 mg vs placebo.
Post-hoc Analysis of the MOUNTAIN Study

Patients with Measurable Drug Concentration

- 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, 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 timepoints through, and including, Day 15.

* Data on File. Sage Therapeutics, Inc. Cambridge, MA.
Post-hoc Analysis of the MOUNTAIN Study

Patients with Measurable Drug Concentration and HAMD-17 ≥ 24

- Post-hoc analysis revealed that in patients with both a measurable drug concentration of zuranolone and an initial HAMD-17 ≥ 24, zuranolone 30 mg was associated with a mean reduction of 14.0 in HAMD-17 total score compared to 11.4 for placebo at Day 15 (LS Mean Difference -2.6, p=0.0174).

Data on File. Sage Therapeutics, Inc. Cambridge, MA.

*p=0.0153, †p=0.0029, ‡p=0.0050, §p=0.0174 for zuranolone 30 mg vs placebo.
**Adverse Events ≥5% Through Day 42**

<table>
<thead>
<tr>
<th>TEAEs, n (%)</th>
<th>Zuranolone 30 mg, N=192</th>
<th>Zuranolone 20 mg, N=188</th>
<th>Placebo, N=190</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td>104 (54.2)</td>
<td>94 (50.0)</td>
<td>93 (48.9)</td>
</tr>
<tr>
<td>Headache</td>
<td>12 (6.3)</td>
<td>21 (11.2)</td>
<td>14 (7.4)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>11 (5.7)</td>
<td>14 (7.4)</td>
<td>7 (3.7)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>13 (6.8)</td>
<td>11 (5.9)</td>
<td>8 (4.2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>13 (6.8)</td>
<td>3 (1.6)</td>
<td>5 (2.6)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12 (6.3)</td>
<td>11 (5.9)</td>
<td>10 (5.3)</td>
</tr>
<tr>
<td>Sedation</td>
<td>9 (4.7)</td>
<td>11 (5.9)</td>
<td>6 (3.2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (3.6)</td>
<td>10 (5.3)</td>
<td>9 (4.7)</td>
</tr>
</tbody>
</table>

**MOUNTAIN Study in MDD Safety Through Day 42**

- The percentage of patients who had at least one adverse event during the 2-week treatment and 28-day follow-up periods was 54.2% in the zuranolone 30 mg group, 50.0% in the zuranolone 20 mg group and 48.9% in the placebo group.
- Serious Adverse Events in **Double-blind period**: 5 patients overall.
  - Treatment period: 2 patients receiving zuranolone 30 mg.
    - 1 suicide attempt (Day 5, patient with a longstanding history of MDD and a previous suicide attempt).
    - 1 bile duct stone (Day 2, requiring removal in a patient with a prior bile duct repair).
  - **Follow-up period**: 3 patients, 1 in each treatment group, all occurring at least 1 week following cessation of treatment.
    - 1 syncope and associated injuries (Day 28, zuranolone 30 mg, which occurred with dehydration and orthostatic hypotension during exercise in a patient with a history of bradycardia).
    - Multiple SAEs related to medical complications of cocaine ingestion (Day 39, zuranolone 20 mg).
    - 1 suicidal ideation (Day 22, placebo).
- No adverse events of loss of consciousness were reported.
- No signal for increased suicidal ideation or suicidal behavior compared to baseline, as measured by the Columbia-Suicide Severity Rating Scale.
- No clinically significant changes in vital signs or clinical laboratory parameters or ECGs, based on adverse events.
Conclusions

• Zuranolone met its primary endpoint for both the Phase 2 MDD study and the ROBIN Study in PPD, by achieving a statistically significant change from baseline in HAMD-17 total score at Day 15.

• The MOUNTAIN Study did not meet its primary endpoint of change in HAMD-17 total score from baseline at Day 15.
  – Patients in the zuranolone 30 mg group achieved statistically significant reductions in HAMD-17 total score at Days 3, 8, and 12 (p<0.018 for each time point). The 20 mg dose did not separate from placebo in this dose-ranging study.
  – In a post-hoc analysis of the MOUNTAIN Study that excluded patients with no measurable drug concentration, statistically significant improvements in depressive symptoms favoring zuranolone 30 mg were observed at all time points through and including Day 15.
  – Zuranolone was generally well-tolerated and showed a similar safety profile as seen in earlier studies. The most common AEs in the MOUNTAIN Study were headache, dizziness, somnolence, fatigue, diarrhea, sedation, and nausea.

• These data support the investigation of higher doses of zuranolone in future clinical trials, and the continued development of NAS GABA_A receptor PAMs in PPD and MDD.
Seeing the brain differently makes a world of difference.