Staying Up to Date with Evolving Postpartum Depression Pathophysiology and Treatment Research

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Faculty Disclosures

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Learning Objectives

● Examine the impact of delayed diagnosis on outcomes in Post Partum Depression (PPD) and best practices for management

● Explore pathophysiological mechanisms related to the expression of PPD symptoms

● Review clinical trial safety, efficacy, and dosing for current and emerging therapeutics for PPD
Pretest Survey
Part 1
Diagnostic Delay, Screening Needs, and Importance of Early Identification
The Patient Perspective
Diagnosis and the Stigma of Seeking Help
1 in 13 women experience an episode of Major Depressive Disorder during Pregnancy

1 in 7 women experience an episode of Major Depressive Disorder in the Postpartum Period

Major depressive disorder with peripartum onset (DSM-5)

Specifier can be applied to mood symptoms during pregnancy or within the 4 weeks following delivery

50% of "postpartum" major depressive episodes actually begin prior to delivery. Thus, these episodes are called peripartum.

Peripartum major depressive episodes are similar to non-puerperal depression but they often have severe anxiety and even panic attacks

Prospective studies have demonstrated that mood and anxiety symptoms during pregnancy, as well as "baby blues," increase the risk for a postpartum depressive episode
ACOG recommends screening at least once during the perinatal period\(^1\)

Continue meds that work throughout pregnancy

### Prevention

- Maximize non-pharmacologic interventions
  - Nutrition
  - Sleep hygiene
  - Psychotherapy (CBT, IPT)
  - Exercise
  - Meditation Yoga
  - Childcare Support

### Treatment

- SSRIs
  - No evidence of increased risk of major malformations or cardiovascular malformations in children of pregnant women exposed to SSRIs
  - Psychotherapy
  - Childcare Support

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Burden of Postpartum depression

Children miss crucial bonding which can increase their risk for future behavioral and developmental challenges

Loss of income and economic security

Increase risk for poor physical health

Costly for families and society at large

Half of perinatal women with depression in the US will not receive the treatment they need

Impact of delayed diagnosis

Shame, stigma and misinterpretation of symptoms
More challenging and costly to treat
Multigenerational consequences

Screening Practices

Joint APA-ACOG Guidelines of depression recommend the Edinburgh Postnatal Depression Scale (EPDS) or the Patient Health Questionnaire (PHQ-2 or 9) for screening

Full diagnostic evaluation

Early diagnosis is crucial
EDINBURGH POSTNATAL DEPRESSION SCALE

Edinburgh Postnatal Depression Scale (EPDS) 1

Name: ___________________________ Address: ___________________________
Your Date of Birth: ___________________ Your Phone: ___________________
Baby's Date of Birth: ___________________ Phone: ___________________

Score ≥10 is a reliable indicator of perinatal depression.

Avoids misinterpretation of normal pregnancy/postpartum-related symptoms as depression.

Free and available in more than 23 languages.

Edinburgh Postnatal Depression Scale 1 (EPDS); 2005.
Effects of Untreated Depressive Disorders on Obstetrical & Neonatal Outcomes

**Adverse health behaviors**
- Less compliance with prenatal care (Zukerman et al 1989)
- Poor nutrition, substance use in pregnancy (Zuckerman et al 1989; Peterson et al 2016)
- Negatively impact maternal weight

**Poor obstetric outcomes**
- Preterm birth, low birth weight, NICU admission, prolonged hospital stay, cesarean delivery (Malm et al 2015)
- Neonatal behavioral differences, such as irritability and decreased activity

**Impaired Bonding/Attachment**
- Impaired mother–infant bonding which is associated with poor developmental and emotional outcomes in offspring (Deave et al. 2008; DiPietro et al. 2006; Punamaki et al. 2006)

**Suicide and Infanticide**
- 19.3% women with PPD report thoughts of self-harm (Wisner et al 2013)
- 41% depressed mothers with child <3yo have filicidal thoughts (Jennings et al 1999)

Part 2
Advances in the Understanding of the Pathophysiology of PPD
The pathophysiology of perinatal depression is complex.

**Endocrine Mechanisms**
A subset of women with PPD are susceptible to fluctuating reproductive hormone levels during the peripartum period.1

**Epigenetic Mechanisms**
Estradiol-mediated epigenetic mechanisms may be associated with PPD risk.2

**Synaptic Transmission Mechanisms**
Alterations in monoamines (serotonin receptors) and neurotransmitters (GABA receptors and glutamate) have been implicated in PPD.3-7

**Neural Network Mechanisms**
Imaging studies have demonstrated altered activity in the amygdala, prefrontal cortex, cingulate cortex, and insula in PPD.10,11

**Inflammatory Mechanisms**
Altered levels of immune system factors have been associated with PPD.3

**Neurosteroid Mechanisms**
Altered levels of allopregnanolone and dysfunction in NAS signaling have been observed in PPD.4

**Stress Mechanisms**
Dysfunction of the HPA axis has been implicated in women with PPD and animal models of PPD, particularly

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Neuroactive steroids are pregnenolone metabolites which modulate GABAergic and glutamatergic neurotransmission

Neuroactive steroids (NAS)
Natural or synthetic steroids which act on the brain by serving as transcription factors in the regulation of gene expression or by interacting with membrane-bound NT receptors

Many NAS are positive allosteric modulators (PAMs) of the GABA$_A$-R, enhancing tonic or phasic GABAergic inhibition via facilitating negatively charged Cl$^-$ ion flow

NAS, their synthesizing enzymes and synaptic & extrasynaptic GABA$_A$R have been localized throughout the stress neurocircuit (hypothalamus (PVN), BNST, mPFC, hippocampus, amygdala)

CNS NAS have important roles in HPA response in both acute and chronic stress conditions

NAS enhance tonic and phasic inhibition through synaptic and extrasynaptic GABA$_A$R

See source for original image: https://www.nature.com/articles/nrn1703

Physiologic perinatal changes in NAS concentrations are associated with GABAergic system neuroplasticity

Plasma and CNS NAS levels rise during pregnancy and fall precipitously post-delivery\(^1-3\)

- e.g. progesterone 120-150ng/mL in late gestation -> 10ng/mL within 24 hrs. delivery -> 0.5ng/mL at 10 weeks pp

Perinatal changes in surface expression of cortical and subcortical GABA\(_{\text{AR}}\) isoforms \(^4,5\)

- Reduced \(\delta\) GABA\(_{\text{AR}}\) expression in pregnancy, returns postpartum\(^6\)

Perinatal changes in glutamic acid decarboxylase (GAD) mRNA expression are associated with changes in [GABA]\(^7\)

- High ALLO assoc. with inhibition of GAD, raising [GLU] and reducing [GABA] in several rat brain areas\(^8\)

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Perinatal depression is associated with neural network dysregulation

Neuroactive steroids (NAS), through their modulation of GABA\textsubscript{A} receptors, regulate inhibition-excitation balance within neural networks.\textsuperscript{5,6}

PND has been associated with altered functional connectivity of the default mode network, salience, and central executive networks.\textsuperscript{1-4}

Women with PND have altered postpartum resting-state connectivity that is associated with plasma allopregnanolone concentrations and HAM-D total score. (Deligiannidis KM 2019)

# Potential mechanisms implicated in PND pathophysiology in relation to potential MOA mediating antidepressant effects of allopregnanolone (ALLO)

<table>
<thead>
<tr>
<th>Mechanism of action of ALLO</th>
<th>Implicated in PND pathophysiology</th>
<th>Potential mechanisms mediating the AD effects of ALLO</th>
</tr>
</thead>
<tbody>
<tr>
<td>GABAergic dysfunction</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>HPA axis dysfunction</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>NAS deficits</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Altered network communication</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Neuroinflammation</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Genetic predisposition</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Actions on membrane PROG receptors/G-protein-coupled receptors</td>
<td>-</td>
<td>?</td>
</tr>
<tr>
<td>Metabotropic regulation of GABA receptors</td>
<td>-</td>
<td>?</td>
</tr>
</tbody>
</table>

+: strong relationship; -: no known interaction; ?: relationship is currently undetermined
Adapted from Walton & Maguire, 2021
ALLO mediates affective switching through modulation of oscillatory states

ALLO and ALLO analogs can modulate network states within, and between, the medial prefrontal cortex (mPFC) and basolateral amygdala (BLA)—nodes for emotional and valence processing.

- Chronic stress corrupts the mPFC-BLA network states which can be restored by treatment with 5α-reduced NAS
- Chronic unpredictable stress (CUS) impairs endogenous NAS signaling in the BLA, and knockdown of 5α-reductase type 1 and 2 in the BLA is sufficient to induce network and behavioral deficits similar to those observed following CUS.
- Overexpression of 5α-reductase type 1 and 2 in the BLA improves behavioral outcomes in mice subjected to CUS.

=> Endogenous neurosteroids set a baseline affective tone and chronic stress impairs endogenous neurosteroid signaling, thereby disrupting network and behavioral states.

- ALLO is able to shift the network state in the BLA through delta subunit-containing GABAARs, although not exclusively through this mechanism.
- SGE-516 largely prevents the brain-wide altered functional connectivity and behavioral state induced by CUS in mice
- It is hypothesized that ALLO acts on delta subunit-containing GABAARs to shift the network to a healthy network state that is more stable and can persist in the absence of the compound.

Part 3
Expanding the Clinician Toolbox: Current and Emerging Treatments for PPD
The Patient Perspective
Finding Success with Treatment
CASE

34yo G1P1 with history of MDD presents with EPDS 19 at 4 weeks postpartum.
Patient had elected to discontinue citalopram during pregnancy.
Prior failed trial of sertraline but good response to citalopram.
She is currently breastfeeding.
What do I do?
SSRIs

The reproductive safety data on SSRIs exceeds what is known about most other medicines used in pregnancy.

Consistent conclusions that the absolute risk of SSRI exposure in pregnancy is small $^{1-3}$

No evidence of increased risk of major malformations or cardiovascular malformations in children of pregnant women exposed to SSRIs$^4$

No clear association with ASD

PPHN baseline risk of 1 to 2 per 1000, unclear association with ssRI exposure after 20 weeks when controlling for other confounders

Poor neonatal adaptation estimated prevalence 5-30%, symptoms self-resolve

SNRIs

Generally less studied, however the bulk of data for venlafaxine, desvenlafaxine* and duloxetine is reassuring from a teratogenicity perspective

- No systematic studies in human for desvenlafaxine but its closely related to venlafaxine, likely safe

Venlafaxine may increase diastolic BP – proceed with caution in patients with gHTN and pre-eclampsia
Bupropion

Generally less studied, however the bulk of data from a teratogenicity perspective is reassuring

Caution in pre-eclampsia as this medication can lower seizure threshold

May lower milk supply
Mirtazapine

Limited data but no known reports of teratogenicity
May be helpful for patients with hyperemesis gravidarum

TCAs & MAOis

TCAs not associated with teratogenicity and are considered generally safe in breastfeeding
– doxepine is reasonable in pregnancy but not for breastfeeding

No safety data for MAOis
General Prescribing Principles

Use what has worked in the past
No clear differences between most SSRIs in pregnancy
  – Sertraline has lowest RID
Use the lowest EFFECTIVE dose
Avoid polypharmacy and multiple exposures
Treat to remission
A change in medication may lead to relapse
Due to pharmacokinetics of pregnancy, may need 20-30% drug increase by 2nd or 3rd trimester
Breastfeeding & Antidepressants

Relative infant doses less than 10% of maternal dosage are acceptable per FDA and AAP

Antidepressant RIDs

- Bupropion 0.2-2.0
- Citalopram 3-10
- Desvenlafaxine 5.5-8.1
- Doxepin: AVOID: reports of hypotonia, sedation, vomiting, suppressed respiratory rate, weight loss
- Duloxetine <1
- Escitalopram 5.2-7.9
- Fluoxetine 0.6-14.6 (long half-life)
- Fluvoxamine <2
- Mirtazapine 0.5-3
- Nortriptyline 0.87-3.71 (watch for dry mouth, constipation, urinary retention)- favored TCA in lactation
- Paroxetine 1.2-2.8
- Sertraline 0.4-3
- Venlafaxine 6-9

Atypical Antipsychotics

Reassuring safety data in pregnancy and breastfeeding\(^1,2\)

Lurasidone, Iloperidone, paliperidone no human data

Risk of metabolic syndrome in pregnancy

2011 FDA warning for neonatal EPS based on 69 case reports but most had confounders like SUD

Placental passage: olanzapine (72%) - haloperidol (65.5%) - risperidone (49.2%) - quetiapine (23.8%)

RID <10% for all

– Aripiprazole may decrease milk supply

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Brexanolone

**Brexanolone** is an IV administered, exogenous version of allopregnanolone, synaptic and extrasynaptic GABA-A receptor PAM

- First FDA-approved treatment in postpartum depression (2019)
- Brexanolone is administered as a 60-hour infusion
- Active ingredient molecular formula: C21H34O2
- Metabolism: non-CYP, keto-reduction, glucuronidation, sulfation
- As per the US Prescribing Information, the dose regimen is administered as a continuous intravenous (IV) infusion over a total of 60 hours (step-wise up and down-titration)
- The recommended dosage is a titration up to 90 µg/kg/hour.
- A reduction in dosage to 60 µg/kg/hour may be considered for patients who do not tolerate 90 µg/kg/hour.
- Calculated maximum RID [relative infant dose] for brexanolone during infusion is 1.3%¹

Brexanolone IV: Three placebo-controlled RCTs (Hummingbird)

Women with PPD
- Study A: HAMD-17 ≥26
- Study B: HAMD-17 ≥26
- Study C: HAMD-17 20-25

Studies A and C Randomized: 1:1
Study B Randomized: 1:1:1

- Placebo (PBO)
- BRX 90 µg/kg/h (BRX90, Studies A-C)
- BRX 60 µg/kg/h (BRX60, Study B)

60 Hour continuous IV infusion

Hour 60 Primary Endpoint
Day 7 Follow-up
Day 30 Follow-up

Study A: Phase 2; N=21
Study B: Phase 3; N=138
Study C: Phase 3; N=108

Primary endpoint: least-squares mean (LSM) change from baseline in HAMD-17 total score at Hour 60.
Secondary endpoints included LSM change from baseline in HAMD-17 total score at all other time points. Secondary endpoints were not adjusted for multiplicity.
Umbrella protocol allowed pre-planned integrated study dataset analysis, efficacy BRX90 and safety all BRX.

Brexanolone: Integrated PPD efficacy analysis

Change from baseline in HAMD-17 total score

Brexanolone: Integrated PPD Efficacy Analysis

HAMD-17 Response and Remission Rates

**HAMD-17 response**
Reduction of HAMD-17 score $\geq 50\%$ from baseline

<table>
<thead>
<tr>
<th>Time</th>
<th>BRX90 (N=102)</th>
<th>Placebo (N=107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 Hours</td>
<td>51*</td>
<td>41</td>
</tr>
<tr>
<td>48 Hours</td>
<td>70$^\dagger$</td>
<td>50</td>
</tr>
<tr>
<td>60 Hours</td>
<td>75$^\dagger$</td>
<td>56</td>
</tr>
<tr>
<td>Day 3</td>
<td>75$^\dagger$</td>
<td>56</td>
</tr>
<tr>
<td>Day 7</td>
<td>62$^\dagger$</td>
<td>47</td>
</tr>
<tr>
<td>Day 30</td>
<td>70$^\ddagger$</td>
<td>62</td>
</tr>
</tbody>
</table>

**HAMD-17 remission**
HAMD-17 score $\leq 7$

<table>
<thead>
<tr>
<th>Time</th>
<th>BRX90 (N=102)</th>
<th>Placebo (N=107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 Hours</td>
<td>26$^\dagger$</td>
<td>15</td>
</tr>
<tr>
<td>48 Hours</td>
<td>40$^\dagger$</td>
<td>21</td>
</tr>
<tr>
<td>60 Hours</td>
<td>50$^\dagger$</td>
<td>26</td>
</tr>
<tr>
<td>Day 3</td>
<td>50$^\dagger$</td>
<td>26</td>
</tr>
<tr>
<td>Day 7</td>
<td>43$^\ddagger$</td>
<td>28</td>
</tr>
<tr>
<td>Day 30</td>
<td>47</td>
<td>45</td>
</tr>
</tbody>
</table>

* $p=0.018$; $^\dagger p<0.001$; $^\ddagger p=0.005$; $^\ddagger p=0.041$; $^\ddagger p=0.014$; $^\ddagger p=0.009$ vs placebo.

Adverse events across all placebo-controlled RCTs of brexanolone injection

Adverse reactions in placebo-controlled studies in patients with PPD reported in ≥ 2% of Brexanolone injection-treated patients and greater than placebo-treated patients

<table>
<thead>
<tr>
<th>Category</th>
<th>Placebo (n=107)</th>
<th>Maximum dosage 60 µg/kg/hour (n=38)</th>
<th>Maximum dosage 90 µg/kg/hour (Recommended dosage) (n=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td></td>
<td></td>
<td>3%</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1%</td>
<td></td>
<td>2%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>1%</td>
<td></td>
<td>3%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td></td>
<td></td>
<td>2%</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td></td>
<td></td>
<td>2%</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness, presyncope, vertigo</td>
<td>7%</td>
<td>13%</td>
<td>12%</td>
</tr>
<tr>
<td>Loss of consciousness</td>
<td></td>
<td></td>
<td>3%</td>
</tr>
<tr>
<td>Sedation, somnolence</td>
<td>6%</td>
<td>21%</td>
<td>13%</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flushing, hot flush</td>
<td></td>
<td></td>
<td>2%</td>
</tr>
</tbody>
</table>

Excessive sedation and sudden LOC black box warning

Brexanolone caused sedation and somnolence that required dose interruption or reduction in 5% of brexanolone-treated patients compared to 0% in placebo.

LOC or altered state of consciousness during the brexanolone infusion occurred in 4% of the brexanolone-treated patients compared with 0% in placebo.

All patients with LOC or altered state of consciousness recovered with dose interruption; fully recovered within 15-60 minutes.

Brexanolone can only be prescribed at certified facilities through a Risk Evaluation and Mitigation Strategy (REMS) safety program.


Zuranolone is a synthetic analog of allopregnanolone and is a PAM of synaptic and extrasynaptic GABA-A receptors\(^1\)

- Non-FDA approved, investigational use only
- The only difference between brexanolone and zuranolone is the addition of a cyanopyrazole ring to the structure of brexanolone\(^2,3\)
- PK/PD profile consistent with once daily oral dosing
- Mean RID is 0.314% for D1 through D11 (30mg dosing)

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Zuranolone: pivotal placebo-controlled RCT in PPD (ROBIN)

Inclusion criteria: Women ages 18-45, ≤6 months postpartum, PPD (major depressive episode with onset in 3rd trimester or ≤4 weeks postpartum), and a HAMD-17 ≥ 26.

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

- Secondary endpoints included HAMD-17 total score at all time points.
- Statistical analyses of secondary endpoints were not adjusted for multiplicity.

Zuranolone: pivotal placebo-controlled RCT in PPD (ROBIN)

Change From Baseline in HAMD-17 total score

Kanes SJ. CINP; October 3-5, 2019; Athens, Greece.
Zuranolone: pivotal placebo-controlled RCT in PPD (ROBIN)

**HAMD-17 Response and Remission Rates**

### HAMD-17 response
Reduction of HAMD-17 score ≥50% from baseline

<table>
<thead>
<tr>
<th>Day 3</th>
<th>Day 8</th>
<th>Day 15</th>
<th>Day 21</th>
<th>Day 45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zuranolone (N=76)</td>
<td>41%</td>
<td>65*%</td>
<td>72†%</td>
<td>75‡%</td>
</tr>
<tr>
<td>Placebo (N=74)</td>
<td>27%</td>
<td>45%</td>
<td>48%</td>
<td>56%</td>
</tr>
</tbody>
</table>

### HAMD-17 remission
HAMD-17 score ≤7

<table>
<thead>
<tr>
<th>Day 3</th>
<th>Day 8</th>
<th>Day 15</th>
<th>Day 21</th>
<th>Day 45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zuranolone (N=76)</td>
<td>19§%</td>
<td>32%</td>
<td>45‖%</td>
<td>42%</td>
</tr>
<tr>
<td>Placebo (N=74)</td>
<td>5%</td>
<td>19%</td>
<td>23%</td>
<td>29%</td>
</tr>
</tbody>
</table>

*p=0.0127; †p=0.0049; ‡p=0.0216; §p=0.0200; ‖p=0.0110; ¶p=0.0091 vs placebo.

Zuranolone: Pivotal placebo-controlled RCT in PPD (ROBIN)

Adverse Events

- A similar proportion of patients reported TEAEs in the zuranolone group compared with the placebo group.
- Somnolence, headache, dizziness, upper respiratory tract infection, diarrhea, and sedation were the most common (≥5%) AEs in the zuranolone group.
- There were no episodes of LOC.
- There was no signal for increased suicidal ideation or suicidal behavior compared with baseline, as measured by the Columbia-Suicide Severity Rating Scale.

<table>
<thead>
<tr>
<th>TEAE, n (%)</th>
<th>Zuranolone (N=78)</th>
<th>Placebo (N=73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>47 (60.3)</td>
<td>38 (52.1)</td>
</tr>
<tr>
<td>Severe AE</td>
<td>3 (3.8)</td>
<td>3 (4.1)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>1 (1.3)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>AE-drug discontinuation</td>
<td>1 (1.3)</td>
<td>0</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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

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

* Greater in placebo vs. Zuranolone
**Zuranolone: phase 3 double-blind, placebo-controlled RCT in PPD (SKYLARK)**

**Primary Endpoint**
- Change from baseline (CFB) in HAMD-17 total score at Day 15

**Key Secondary Endpoints**
- CFB in HAMD-17 total score at Days 3, 28, and 45

**Inclusion**
- Major depressive episode that began from third trimester to ≤ 4 weeks postpartum; ≤ 12 months postpartum at Day 1
- Agreed not to provide breastmilk ≤ 7 days following the last dose
- Stable ADT use ≥ 30 days prior to Day 1 was continued throughout study

**Exclusion**
- History of nonfebrile seizures, bipolar disorder, psychotic disorder, attempted suicide, or risk of suicide in the current episode
- Use of benzodiazepines, barbiturates, GABA<sub>A</sub> receptor modulators, non-GABA anti-insomnia medications, and first- or second-generation antipsychotics

ADT = antidepressant therapy; CGI-S = Clinical Global Impression-Severity; EPDS = Edinburgh Postnatal Depression Scale; GABA = γ-aminobutyric acid; HAM-A = Hamilton Anxiety Rating Scale; HAMD-17 = 17-Item Hamilton Rating Scale for Depression; PPD = postpartum depression; qd = once daily; R = randomisation; TEAE = treatment-emergent adverse event.

a Randomisation was stratified based on antidepressant treatment use at baseline. b Zuranolone 50 mg and placebo administered in the evening with fat-containing food. 2 Dose could be reduced to 40 mg as needed based on tolerability.

Change from Baseline (CFB) in HAMD-17 Total Score on Day 15 and Days 28, and 45\textsuperscript{a}

**Primary Endpoint and Key Secondary Endpoints**

<table>
<thead>
<tr>
<th>Day 3: Key secondary endpoint</th>
<th>Day 15: Primary endpoint</th>
<th>Day 28: Key secondary endpoint</th>
<th>Day 45: Key secondary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>-9.5</td>
<td>-11.6</td>
<td>-13.4</td>
<td>-14.4</td>
</tr>
<tr>
<td>* p = 0.0008</td>
<td>* p = 0.0007</td>
<td>* p = 0.0445</td>
<td>* p = 0.0067</td>
</tr>
</tbody>
</table>

LS Mean (SE)\textsuperscript{b} CFB HAMD-17 Total Score

<table>
<thead>
<tr>
<th>Day</th>
<th>ZRN, n</th>
<th>PBO, n</th>
<th>ZUR, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>98</td>
<td>96</td>
<td>98</td>
</tr>
<tr>
<td>8</td>
<td>93</td>
<td>95</td>
<td>93</td>
</tr>
<tr>
<td>15</td>
<td>93</td>
<td>90</td>
<td>93</td>
</tr>
<tr>
<td>21</td>
<td>84</td>
<td>83</td>
<td>84</td>
</tr>
<tr>
<td>28</td>
<td>77</td>
<td>85</td>
<td>85</td>
</tr>
<tr>
<td>45</td>
<td>84</td>
<td>85</td>
<td>85</td>
</tr>
</tbody>
</table>

**HAMD-17 at Baseline, Mean (SD)**

<table>
<thead>
<tr>
<th>Zuranolone 50 mg</th>
<th>28.6 (2.49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>28.8 (2.34)</td>
</tr>
</tbody>
</table>

FAS = full analysis set; HAMD-17 = 17-Item Hamilton Rating Scale for Depression; LS = least squares; MMRM = mixed model of repeated measures; PBO = placebo.

\textsuperscript{a} Statistically significant (per fixed hierarchal testing for key secondary endpoints). Data at Days 8 and 21 were not adjusted for multiplicity, and p-values were considered nominal.

\textsuperscript{b} FAS was defined as all randomised participants who were administered zuranolone 50 mg or placebo with valid baseline and \geq 1 postbaseline efficacy endpoint assessment. LS mean and treatment difference along with CI and p-values were calculated using MMRM. The key secondary endpoints were tested in the following fixed sequence to control for multiplicity: CFB in HAMD-17 at Days 3, 28, and 45. If an endpoint was not significant at the 5% level, the following endpoints in the sequence were interpreted only with nominal p-value.

HAMD-17 response and remission

p-values designated as: *<0.05, †<0.01, ‡<0.001. Response was defined as having ≥50% reduction from baseline in HAMD-17 total score, and remission was defined as a HAMD-17 total score of ≤7. Secondary endpoints were not adjusted for multiplicity and are to be interpreted with nominal p-values.

HAMD-17 = 17-item Hamilton Rating Scale for Depression.

Treatment-emergent adverse events (safety set)

<table>
<thead>
<tr>
<th></th>
<th>Zuranolone 50 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=98</td>
<td>n=98</td>
</tr>
<tr>
<td><strong>TEAE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On treatment</td>
<td>65 66.3</td>
<td>52 53.1</td>
</tr>
<tr>
<td>Posttreatment</td>
<td>59 60.2</td>
<td>41 41.8</td>
</tr>
<tr>
<td>Mild</td>
<td>21 21.4</td>
<td>27 27.6</td>
</tr>
<tr>
<td>Moderate</td>
<td>33 33.7</td>
<td>39 39.8</td>
</tr>
<tr>
<td>SEvere AE</td>
<td>29 29.6</td>
<td>12 12.2</td>
</tr>
<tr>
<td><strong>SAE</strong></td>
<td>3 3.1</td>
<td>1 1.0</td>
</tr>
<tr>
<td>AE leading to dose reduction</td>
<td>16 16.3</td>
<td>1 1.0</td>
</tr>
<tr>
<td>AE leading to treatment discontinuation</td>
<td>4 4.1</td>
<td>2 2.0</td>
</tr>
<tr>
<td>AE leading to withdrawal from study</td>
<td>1 1.0</td>
<td>1 1.0</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>TEAE ≥5%</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>26 26.5</td>
<td>5 5.1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>13 13.3</td>
<td>10 10.2</td>
</tr>
<tr>
<td>Sedation</td>
<td>11 11.2</td>
<td>1 1.0</td>
</tr>
<tr>
<td>Headache</td>
<td>9 9.2</td>
<td>13 13.3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 6.1</td>
<td>2 2.0</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 5.1</td>
<td>6 6.1</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>5 5.1</td>
<td>4 4.1</td>
</tr>
<tr>
<td>COVID-19</td>
<td>5 5.1</td>
<td>0 0</td>
</tr>
</tbody>
</table>

The most common AEs with ZRN (≥5%) included somnolence, dizziness, sedation and headache.

No loss of consciousness, withdrawal symptoms, or increased suicidal ideation/behavior were observed.
Ganaxolone:

Ganaxolone is a 3β-methylated synthetic analog of allopregnanolone

Like allopregnanolone, is an extrasynaptic and synaptic GABA$_{A}$R PAM, but it differs significantly in its lack of affinity for estrogen or progesterone receptors

investigated in different doses and formulations (IV, PO) for the treatment of PPD

Phase 2 trial results completed with results available on clinicaltrials.gov

The sponsor halted further development of ganaxolone for PPD

Magnolia

- phase 2a, double-blind placebo controlled multiple-dose escalation study in women with severe PPD
- Part I: 140 µg/kg/h (highest dose of 3 doses) associated with a change from baseline in HAMD-17 of 15.1, 16.9, and 15.7 at 48h, 60h, and 34 days
- Part 2: mean reduction in HAM-D17 scores of 6.1 at 6h, and 7.7 at 24h treated with ganaxolone

Amaryllis

- open-label dose optimization trial that evaluated a 28-day low-dose and high-dose oral treatment of ganaxolone (675 mg – 1125 mg)
- the low dose showed a mean HAMD-17 reduction of 0.8, 9.8, and 12.2 at 24 hours, 14 days, and 28 days of treatment, respectively. The high dose showed a mean HAMD-17 reduction of 2.7, 9.3 and 14.5 at 24 hours, 14 days, and 28 days of treatment, respectively.

Additional neuroactive steroids under development for postpartum depression

**Brii-296**: novel GABA<sub>A</sub> R-PAM; an extended-release injectable aqueous suspension formulation of brexanolone; a single-injection therapy in development for the treatment of PPD

- The completed open-label, Phase 1, single ascending dose study assessed the safety, tolerability and PK of Brii-296 as a single-injection treatment option for PPD in 116 subjects enrolled across 16 cohorts. Three formulation concentrations (100 mg/mL, 200 mg/mL and 300 mg/mL) were administered via one or more IM injections to healthy adults at total dose levels of 30 mg, 75 mg, 100 mg, 200 mg, 300 mg and 600 mg.
- Oral prophylactic treatment or local steroid administration with Brii-296 were evaluated to manage local injection site reactions
- Single ascending dose phase I study in healthy subjects: single treatment with IM injection of 600mg of Brii-296 achieved dose linearity, early drug absorption, gradual and extended-release profiles without the need for dose titration or tapering
- Phase 2 clinical trails expected in the future

Additional neuroactive steroids under development for postpartum depression

**NORA520**: an oral prodrug which is hydrolyzed to Brexanolone (Allopregnanolone), the same active ingredient in the only FDA-approved drug specifically indicated for PPD.

- The prodrug contains two pro-moieties, one to enhance oral absorption and one to prolong half-life
- According to website, is in Phase I development, nearing Phase II development for PPD
- No trial listed on clinicaltrials.gov

Additional neuroactive steroids under development for postpartum depression

**LYT-300**: oral prodrug of allopregnanolone, uses a proprietary Glyph™ platform

- Topline results from a completed multi-part phase I trial showed that oral LYT-300 achieved blood levels of allopregnanolone at or above those associated with therapeutic effects
- 72 healthy volunteers were dosed; single and multiple ascending doses were evaluated along with cohorts to evaluate the effect of food on oral absorption. LYT-300 was generally well-tolerated with no treatment-related severe or serious adverse events observed. Doses have been selected to carry forward into the planned Phase 1b/2a clinical trial.
- An open-label, Phase 2a, proof-of-concept clinical trial in women with PPD is expected to initiate in the second half of 2023.
The Patient Perspective
Hope for the Future
Audience Q&A
Posttest Survey