Insights on GABAergic Mechanism of PPD From Pivotal Studies of Brexanolone Injection and Zuranolone (SAGE-217)

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Disclosures

• Samantha Meltzer-Brody reports personal fees from MedScape and grants from Sage Therapeutics, Inc., awarded to the University of Carolina (Chapel Hill, NC, USA) during the conduct of the brexanolone injection and zuranolone (SAGE-217) clinical trials and grants from Janssen, PCORI, and the NIH outside the submitted work.

• Brexanolone IV is approved by the United States Food and Drug Administration (FDA) for the treatment of postpartum depression in adults, and it is not approved in Europe or any other countries for any use.

• Zuranolone is an investigational compound in clinical development and is not approved in any country for any use.

• Sage Therapeutics, Inc. sponsored the studies of brexanolone IV and zuranolone.
**Study Designs in Postpartum Depression (PPD)**

**HUMMINGBIRD TRIALS**

Brexanolone injection (BRX)

- **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, N=247**

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

- **Primary Endpoint:** Reduction in HAMD-17 Total Score

- **Day 15 Follow-up**
- **Day 30 Follow-up**

- **60 Hour continuous IV infusion**

**ROBIN TRIAL**

Zuranolone (ZRN)

- **Women with PPD***
- Study: HAMD-17 ≥ 26

- **1:1 Randomized: 1:1, N=151**
- **Placebo**
- **ZRN 30 mg**

- **Primary Endpoint:** Reduction in HAMD-17 Total Score

- **Day 15 Follow-up**
- **Day 45 Follow-up**

- **14 Day outpatient oral treatment**

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*Women were 18-45 years old, ≤6 months postpartum, with PPD (defined as MDE onset in the 3rd trimester up to 4 weeks postpartum)
BRX: Pivotal Studies in PPD (Hummingbird)

Efficacy

- Patients treated with BRX90 met the primary efficacy endpoint at Hour 60, by achieving significantly greater HAMD-17 total score change from baseline vs patients receiving placebo (p<0.0001).

**TEAEs**

- BRX common TEAEs (≥5% of BRX and ≥2x placebo rate included sedation and/or somnolence, dry mouth, flushing/hot flush and loss of consciousness).
  - BRX caused sedation/somnolence requiring dose interruption/reduction in some patients (5% of BRX compared with 0% of placebo-treated patients).
  - Some patients also had loss/altered state of consciousness (4% of BRX compared with 0% of placebo-treated patients).
  - Time to recovery from loss/altered state of consciousness, after dose interruption, ranged from 15 to 60 minutes. All patients recovered with dose interruption.

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ZRN: Pivotal Study in PPD (ROBIN)

**Efficacy**

- Patients treated with ZRN met the primary efficacy endpoint at Day 15, by achieving a significantly greater HAMD-17 total score change from baseline vs those who received placebo (p=0.0028).\(^1,2\)

**TEAEs**

- The most common TEAEs occurring in ≥5% of patients who received ZRN were somnolence, headache, dizziness, upper respiratory tract infection, diarrhea, and sedation.\(^1,2\)
  - A similar proportion of patients reported TEAEs in the ZRN group compared with the placebo group.\(^1\)
  - One patient experienced a serious adverse event (SAE) in the ZRN arm that resolved after dose reduction, and one patient experienced an SAE in the placebo arm.\(^1\)
  - Three patients in the ZRN arm, and three patients in the placebo arm experienced severe AEs.\(^1\)
  - One ZRN-treated patient experienced a TEAE leading to drug discontinuation.
  - Two patients randomized to placebo received at least one dose of ZRN and were included in the ZRN safety population.\(^1\)
  - There was no increased signal for suicidality compared with baseline, as measured by the Columbia-Suicide Severity Rating Scale.\(^1\)

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

Neuroactive Steroid GABA$_A$ Receptor PAMs in PPD

**Summary and Conclusions**

- BRX and ZRN achieved their primary endpoints of a statistically significant reduction in HAMD-17 total score at Hour 60 and Day 15, respectively.
  - Significant reductions in HAMD-17 total score vs placebo were achieved rapidly (BRX90: Hour 24; ZRN: Day 3) and were sustained through Day 30 (BRX90) or Day 45 (ZRN).
- BRX and ZRN were generally well tolerated relative to placebo across all studies.
  - AEs occurring in ≥5% of all BRX patients, and ≥2x the rate of placebo, were sedation/somnolence, dry mouth, loss of consciousness, and flushing/hot flush.
  - AEs occurring in ≥5% of ZRN patients were somnolence, headache, dizziness, upper respiratory tract infection, diarrhea, and sedation.
- Neuroactive steroid GABA$_A$ receptor PAMs are in ongoing clinical development for both PPD and MDD.
  - These findings supported the first approved pharmacotherapy for PPD in the US and more generally, the potential utility of neuroactive GABA$_A$ receptor PAMs in the treatment of depressive episodes.
Seeing the brain differently makes a world of difference