Onset of Reduction in Depressive Symptoms in Postpartum Depression (PPD): Pivotal Studies of Two Neuroactive Steroid GABA Receptor Positive Allosteric Modulators, Brexanolone Injection and Zuranolone

Savannah Mathis-Brindley, MD, MPH, Andres M. Gilanes-Pena, MD, Colleen Thompson, MD, MBB, Stephen J. Kanes, MD, PhD, Handan Gunduz-Bruce, MD, MBA

Introduction

Postpartum depression (PPD) is one of the most frequent mental health conditions affecting new mothers. In the United States, estimates of new mothers experiencing PPD vary by state (10-24%), with an average of 13.2%. PPD can negatively impact the mother, her family, and partners.1,2

Material and methods are a leading cause of mortality in maternal peripartum mood and depression symptoms, extend beyond the woman, and impact her partner, children of mothers with PPD exhibit poorer health-related outcomes, and can manifest in various domains, including physical and mental health.3-6

Synthesis of the findings and discussion of implications are provided for future research, and potential applications, with recommendations for future clinical practice.

Conclusions

Brexanolone and zuranolone have previously been shown to provide rapid improvement (BRX: Hour 0; ZRN: Day 3) and sustained improvement in depressive symptoms from Day 45 to Day 80 in women with PPD as measured by HAMD-17 total score. These results support BRX and the development of zuranolone as treatments with rapid onset for adult women with PDD.

Methods

- Three BRX RCTs enrolled women ages 18-45, 6 months postpartum, with PPD defined as a PHQ-9 score (≥15) at least once in the 3 days before randomization or ≥14 on 2 prior assessments, and a HAMD-17 total score ≥26 (HUMMINGBIRD studies). For approval, efficacy was based on analyses from Studies A and C only, whereas safety was based on Study A. An unblinded, independent, data monitoring committee (DMC) facilitated pre-planned analyses of an integrated study database for the HUMMINGBIRD studies to assess BRX in women with PPD.

- Zuranolone was in a Phase 3 trial in PPD. A preplanned analysis of the integrated BRX dataset examined reductions in depressive symptoms over the first 24-48 hours, with a focus on HAMD-17 total score reduction from baseline to Hour 60. Secondary endpoints included HAMD-17 total score at all other time points and categorical assessment of HAMD-17 responses (reduction ≥50%, remission ≤7, and CGI-I total score reduction of ≥5 very much improved to 2 much improved). Secondary endpoints were not adjusted for multiplicity.

- Safety and tolerability were assessed in the total population of Studies A-C by treatment emergent adverse event (TEAE) reporting and standard clinical assessments.

Results

- The BRX pooled, BRX90, BRX60, and placebo arms included 140, 102, 38, and 107 patients who were randomized and evaluable for the efficacy analyses, respectively.

- Baseline demographics and patient characteristics were well balanced between the treatment arms, as was previously described in detail previously.7

- BRX common TEAEs (≥5% of BRX and ≥2x placebo rate included sedation and/or somnolence, dry mouth, flushing/hot flush, and/or nausea) were consistent with those reported in previous clinical trials.8

- Time to recovery from loss of antidepressant effect was ≥15 minutes and ≥30 minutes for BRX90 and BRX60, respectively.9,10

- Patients with ≥5% of BRX and ≥2x placebo rate included sedation and/or somnolence, dry mouth, flushing/hot flush, and/or nausea were consistent with those reported in previous clinical trials.8

- Two patients randomized to placebo experienced an SAE in the placebo arm. One patient experienced a transient myocardial infarction (MI) (p=0.0027).11

- A similar proportion of patients reported at least 1 TEAE in the BRX90 group compared with placebo (p=0.013).12

- As previously presented, patients treated with BRX90 met the primary efficacy endpoint at Hour 6, by achieving significantly greater HAMD-17 total score improvement vs placebo at Hour 6 (p=0.005).13

- As previously presented, patients treated with BRX90 met the primary efficacy endpoint at Hour 6, by achieving statistically significantly greater improvement vs placebo at Hour 6 (p=0.005); †p<0.001 vs placebo.

- The ZRN and placebo arms included 76 and 74 patients, respectively, that were evaluable for the efficacy analyses, respectively.14 Baseline demographic and patient characteristics were well balanced between the treatment arms, as measured by the Hamilton State Scale for Depression (HAMD-17) total score in the BRX90 group, and CGI-I (0-7) response at baseline, as measured by the Hamilton State Scale for Depression (HAMD-17) total score in the BRX90 group.

- The most common TEAEs occurring in ≥5% of patients who received ZRN were somnolence, headache, dizziness, upper respiratory tract infection, diarrhea, and nausea.15

- A similar proportion of patients reported TEAEs in the ZRN group compared with placebo also occurred at Days 3 (20%, 20%, and 20%, respectively; p=0.014; †p<0.001 vs placebo).

- Three patients in the ZRN arm, and three patients in the placebo arm experienced serious adverse events (SAE).16

- Two patients randomized to placebo experienced an SAE in the placebo arm. One patient experienced a transient MI (p=0.0027).11

- As previously presented, patients treated with ZRN met the primary efficacy endpoint at Hour 6, by achieving statistically significantly greater improvement vs placebo at Hour 6 (p=0.005).13

- As previously presented, patients treated with ZRN met the primary efficacy endpoint at Hour 6, by achieving statistically significantly greater improvement vs placebo at Hour 6 (p=0.005); †p<0.001 vs placebo.

- The ZRN total in PPD enrolled women ages 18-45, ≥6 months postpartum, with PPD defined as a PHQ-9 score (≥15) at least once in the 3 days before randomization or ≥14 on 2 prior assessments, and a HAMD-17 total score ≥26 (HUMMINGBIRD studies).17

- Patients were randomized 1:1 to receive oral ZRN 30 mg or placebo daily for 24 days as an outpatients.18

- As previously presented, patients treated with ZRN met the primary efficacy endpoint at Hour 6, by achieving statistically significantly greater improvement vs placebo at Hour 6 (p=0.005); †p<0.001 vs placebo.

- The ZRN in HAMD-17 total score response evaluated using the least-squares mean difference vs placebo at 72 hours (p=0.012; †p<0.001 vs placebo).19

- As previously presented, patients treated with ZRN met the primary efficacy endpoint at Hour 6, by achieving statistically significantly greater improvement vs placebo at Hour 6 (p=0.005); †p<0.001 vs placebo.

- As previously presented, patients treated with ZRN met the primary efficacy endpoint at Hour 6, by achieving statistically significantly greater improvement vs placebo at Hour 6 (p=0.005); †p<0.001 vs placebo.

- As previously presented, patients treated with ZRN met the primary efficacy endpoint at Hour 6, by achieving statistically significantly greater improvement vs placebo at Hour 6 (p=0.005); †p<0.001 vs placebo.