Effect of Zuranolone on Anxiety Outcomes in Postpartum Depression in a Randomized, Placebo-Controlled Trial

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Introduction

In the United States, estimates of new mothers identified with postpartum depression (PPD) each year vary by state from 8% to 20%, with an average of 11.5%.5

PPD is associated with significant impairments in mother-infant bonding1 and maternal functioning,4 including breastfeeding,5 and caring for the child.6,7 with implications for the child's health and development.8,9

Dysfunctional signaling of y-amino butyric acid (GABA) has been implicated in some studies in the etiology of PPD.10,11

Women with PPD may have intense feelings of sadness, anxiety, irritability, and rage as well as a range of cognitive, social, and somatic symptoms.3,12

Anxiety is a prominent symptom of PPD13-16 and has been associated with more severe disease.17,18

Zuranolone (SAGE-217), an investigational oral neuroactive steroid GABA receptor positive allosteric modulator,19 demonstrated improvements in depressive symptoms versus placebo as measured by HAMD-17 total score in a Phase 3 trial (NCT02978326) in women with PPD.20

Secondary and post-hoc analyses were performed to further understand the effects of zuranolone on anxiety in women with PPD.

Conclusions

Zuranolone previously demonstrated statistically significant reductions in depressive symptoms in women with PPD as measured by HAMD-17 total score.17

- Zuranolone was generally well tolerated.17 The most common TEAEs occurring in ≥5% of patients who received zuranolone were somnolence, headache, dizziness, upper respiratory tract infection, diarrhea, and sedation.17

In this analysis of secondary and post-hoc anxiety endpoints in women with PPD, patients who received zuranolone had:

- Significantly greater improvements in HAM-A, and HAMD-17 A/S LSM change from baseline scores at all time points measured and in EPDS-3A LSM change from baseline score at all time points measured starting at Day 8.

- Numerically greater rates of HAM-A remission and response, HAMD-17 A/S response at all time points compared to those receiving placebo. EPDS-3A response rates were numerically greater at all time points measured starting at Day 8. Statistical significance of these categorical endpoints varied by scale and time point.

- These data support the potential for neuroactive steroids in the treatment of anxiety in patients with PPD.

Methods

- Patients were women (N=151), ages 18-45, ≤6 months postpartum, diagnosed with PPD (defined as a major depressive episode with onset in the 3rd trimester or ≤4 weeks postpartum), and a baseline ≥7-item Hamilton Rating Scale for Depression (HAMD-17) total score ≥28.

- Patients were randomized 1:1 to receive either zuranolone 30 mg or placebo for 2 weeks, with follow-up through Day 45.

- Patients were not permitted to breastfeed from just prior to receiving study drug until 7 days after the last dose.

- Psychotropic medications were permitted if initiated ≥30 days prior to Day 1 and taken at a stable dose until after Day 15 assessments.

The primary endpoint of the study was the change from baseline in HAMD-17 total score at Day 15 compared to placebo. Secondary endpoints included change from baseline in the Hamilton Rating Scale for Anxiety (HAM-A) and the Edinburg Postnatal Depression Scale (EPDS).

Results

- Treatment emergent adverse events (TEAEs) were assessed throughout the study.

- Post-hoc analyses were conducted using the change from baseline in the HAMD-17 Anxiety/Somatization (A/S) Subscale and EPDS Anxiety Subscale (EPDS-3A), rates of HAMD-17 A/S and HAM-A response (≥50% reduction in score) and rate of HAM-A remission (score ≤7).

- Change from baseline data were analyzed using a mixed effects model for repeated measures, and categorical response/remission data were analyzed using generalized estimating equation models, both adjusting for baseline antidepressant use, assessment time point, and time point-by-treatment interaction.

- Least-squares means (LSM) and adjusted odds ratios are reported by treatment arm.

- Secondary and post-hoc endpoints were not adjusted for multiplicity.

- State anxiety was measured by HAMD-17 total score and HAM-A, and somnolence, headache and diarrhea were measured by EPDS-3A.

- Serious Adverse Events (SAEs): Zuranolone group (1 patient), confusional state, Day 3, resolved after 24 hours. Dose interrupted, reduced to 50% for 3 days, then discontinued.

- Placebo group (1 patient) Cholelithiasis/pancraticitis on Day 32, resolved on Day 35 with cholecystectomy.

- Statistically significant differences occurred at Day 3 (-1.2 versus -1.5; p=0.0037)

- Statistically significant differences were also sustained at all measured time points through Day 45 (-3.6 versus -2.1; p=0.001)

- Statistically significant differences were also sustained at all measured time points starting at Day 3 (2.7 versus 2.2; p=0.0015)