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

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Introduction

- Across eight European countries*, approximately 11% of mothers experience symptoms of postpartum depression (PPD) [1] each year [2-10].
- PPD is associated with significant impairments in mother-infant bonding [11] and maternal function [12], including breastfeeding [13], and caring for the child [14,15], with implications for the child’s health and development [16-19].
- Dysfunctional signaling of γ-aminobutyric acid (GABA) has been implicated in some studies in the etiology of PPD [20,21].
- Women with PPD may have intense feelings of sadness, anxiety, irritability, and/or rage as well as a range of cognitive, social, and somatic symptoms [1, 22].
- Anxiety is a prominent symptom of PPD [23-25] and has been associated with more severe disease [23, 26].
- Only about one-third of patients remit after first-line treatment, and subsequent remission rates decrease with each trial of antidepressant [27, 28].
- Zuranolone (ZRN, SAGE-217) is an investigational, oral neuroactive steroid GABA-A receptor positive allosteric modulator not approved for use by any regulatory agency in any country [29].
- Previously presented in detail, from the Phase 3 ROBIN trial (NCT02978326) in women with PPD, ZRN demonstrated improvements in depressive symptoms and met its primary endpoint of a significant change from baseline (CFB) vs placebo in the 17-item Hamilton rating scale for depression total score (HAMD-17) at Day 15 [30, 31].
  - ZRN also showed significant improvements vs placebo in the Bech-6 subscale of HAMD-17 at Day 15, highlighting its benefit on core symptoms of depression [32, 33].
- Secondary, exploratory, and post hoc analyses were performed to further understand the effects of zuranolone on the symptoms of anxiety in women with PPD.

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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 HAMD-17 total score ≥26.
- Patients were randomized 1:1 to receive either ZRN 30 mg or placebo for two weeks, with follow-up through Day 45.
- The primary endpoint of the study was the change from baseline (CFB) in HAMD-17 total score at Day 15 compared with placebo.
- The CFB in the Hamilton Rating Scale for Anxiety (HAM-A) was a secondary endpoint, and the CFB in the Edinburgh Postnatal Depression Scale (EPDS) was an exploratory endpoint.
- Post hoc analyses included the CFB in the HAMD-17 Anxiety/Somatization (A/S) Subscale and EPDS Anxiety Subscale (EPDS-3A), rates of HAMD-17 A/S, HAM-A, and EPDS-3A improvement (defined as a ≥50% reduction in score), and HAM-A improvement (defined as a score ≤7).
  - Secondary endpoints, exploratory endpoints, and post hoc analyses were not adjusted for multiplicity.
- Statistics are from a mixed effect model for repeated measures including the least-squares mean CFB at each visit as the dependent variable, and categorical response/remission data were analyzed using generalized estimating equation models, both adjusting for baseline total score, the treatment effect for baseline antidepressant use, assessment time point, and time point-by-treatment interaction.
Results

• There were 76 and 74 patients, respectively, who were randomized into the ZRN and placebo arms, and included in the efficacy analyses.

• Baseline demographics and patient characteristics were well balanced between the two treatment arms and have been described in detail previously [30, 31].

• The most common TEAEs occurring in ≥5% of patients who received ZRN were somnolence, headache, dizziness, upper respiratory tract infection, diarrhea, and sedation [30, 31].
  • A similar proportion of patients reported TEAEs in the ZRN group compared with the placebo group [30].
  • 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 [31].
  • Three patients in the ZRN arm, and three patients in the placebo arm experienced severe AEs [31].
  • One ZRN-treated patient experienced a TEAE leading to drug discontinuation [31].
  • Two patients randomized to placebo received at least one dose of ZRN and were included in the ZRN safety population [31].
• There was no increased signal for suicidality compared with baseline, as measured by the Columbia-Suicide Severity Rating Scale [30,31].
Significantly Greater Improvement in Depressive Symptoms Achieved With ZRN vs Placebo

- Patients treated with ZRN met the primary efficacy endpoint at Day 15 by achieving a significantly greater HAMD-17 total score CFB vs those who received placebo (p=0.0028) [30, 31].

- Statistically significant differences occurred at Day 3 (p=0.0252) and were sustained at all measured time points through Day 45 (p=0.0027).
In Addition to Improving Depressive Symptoms, Significantly Greater Improvement in Anxiety Symptoms Were Achieved With ZRN vs Placebo in Women with PPD
Patients treated with ZRN achieved significantly greater reductions in HAM-A CFB vs placebo starting at Day 3 (p=0.0169) and at all other time points measured during the study, including up to Day 45 (30 days after cessation of treatment: p=0.0002).
HAMD-17-A/S Total Score CFB: Post Hoc Endpoint

- Patients treated with ZRN achieved significantly greater reductions in HAMD-17 A/S CFB vs placebo starting at Day 3 (p=0.0073) and at all other time points measured during the study, including up to Day 45 (30 days after cessation of treatment: p=0.0033).
Patients treated with ZRN achieved significantly greater reductions in EPDS-3A CFB vs placebo starting at Day 8 (p=0.0315) and at all other time points measured during the study, including up to Day 45 (30 days after cessation of treatment: p=0.0001).
Significantly Greater Rates of Improvement in Anxiety Symptoms Were Achieved with ZRN vs Placebo in Women With PPD
HAM-A Improvement Rates (HAM-A Total Score ≤7): Post Hoc Endpoint

• ZRN demonstrated a significantly higher rate of HAM-A improvement compared with placebo at Day 3 (27.0% vs 12.2%).

• Significantly higher rates compared with placebo were also observed on Day 8 (41.3% vs 23.0%), Day 15 (51.4% vs 24.7%), and Day 45 (56.2% vs 30.4%).

*p=0.0340; †p=0.0264; ‡p=0.0019; §p=0.0030 vs placebo; p-values compare adjusted rates from the models (not the raw rates presented in the charts).
HAM-A Improvement Rates (≥50% Reduction in Score): Post Hoc Endpoint

- ZRN demonstrated significantly higher rates of HAM-A improvement compared with placebo at Day 8 (69.3% vs 43.2%).

- Significantly higher rates compared with placebo were also observed on Day 15 (71.6% vs 49.3%), Day 21 (71.6% vs 54.8%), and Day 45 (72.6% vs 52.2%).

*p=0.0016; †p=0.0099; ‡p=0.0431; §p=0.0153 vs placebo; p-values compare adjusted rates from the models (not the raw rates presented in the charts).
HAMD-17 A/S Improvement Rates (≥50% Reduction in Score): Post Hoc Endpoint

• ZRN demonstrated significantly higher rates of HAMD-17 A/S improvement compared with placebo at Day 15 (68.9% vs 46.6%).

• Significantly higher rates compared with placebo were also observed on Day 21 (67.6% vs 49.3%) and Day 45 (68.5% vs 47.8%).

*\(p=0.0086\); †\(p=0.0285\); ‡\(p=0.0137\) vs placebo; p-values compare adjusted rates from the models (not the raw rates presented in the charts).
EPDS-3A Improvement Rates (≥50% Reduction in Score): Post Hoc Endpoint

- ZRN demonstrated a significantly higher rate of EPDS-3A improvement compared with placebo at Day 45 (56.2% vs 26.1%).

* p=0.0004 vs placebo; p-values compare adjusted rates from the models (not the raw rates presented in the charts).
Conclusions

• ZRN treatment in PPD patients has previously been shown to provide rapid (Day 3 HAMD-17 total score CFB) and sustained (HAMD-17 total score CFB) at all measured time points up to Day 45) improvement in depressive symptoms [30, 31].

• In addition to its effects on core symptoms of depression in this trial, these secondary endpoints, exploratory endpoints, and post hoc analyses showed that ZRN treatment also resulted in significantly greater reductions in symptoms of anxiety and higher proportions of PPD patients who achieved an anxiety symptom improvement compared with placebo (as measured by the HAM-A, HAMD-17-A/S and EPDS-3A).

• These data support the continued development of ZRN in the treatment of PPD and suggests it may provide potential benefits in addressing anxiety symptoms with PPD.
References

Disclosures

Brian Werneburg and the authors AM, MH, ES, SL, HGB, RL, VB, PH, and SJK are employees of Sage Therapeutics, Inc., with stock/stock options. KMD serves as a consultant to Sage Therapeutics, Inc., receives NIMH support and royalties from an NIH employee invention, and reports funding from Sage Therapeutics, Inc. awarded to Zucker Hillside Hospital during the conduct of the brexanolone injection and zuranolone clinical trials. SA is an employee at Acaster Lloyd Consulting Ltd., London. MF is an employee at MF Consulting, Los Angeles, CA. This study and medical writing support were funded by Sage Therapeutics, Inc. Writing and editorial support was provided by Elizabeth Wheatley of Boston Strategic Partners.
Notes for MRC:

- ECNP 2020 is a fully virtual meeting and the organizers have opted to use a poster interface known as iPosterSessions.

- Poster presenters cannot upload their posters in PDF or PPT format, but must use the iPoster interface which contains only a small number of poster templates for presenters to choose from.

- As such, this interface has limited formatting capabilities relative to PPT or Adobe InDesign. Unfortunately, iPosters do not resemble nor reflect the typical caliber of Sage posters. For now, we compiled data into a PPT for annotation purposes, and for ease of your review.

General Notes:

- The title cannot be edited using the interface.
- Data (e.g. graphs and tables) can be uploaded as images.
- Wording can be copy and pasted or uploaded as an image.

For a preview of an example poster on the iPoster interface: https://ecnp33-ecnp.ipostersessions.com/default.aspx?s=5D-24-C1-CB-91-4C-E2-F-36-D0-22-F7-FD-48-52-85&guestview=true

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