

It is illegal to post this copyrighted PDF on any website.

Effect of Zuranolone on Concurrent Anxiety and Insomnia Symptoms in Women With Postpartum Depression

Kristina M. Deligiannidis, MD^{a,b,*}; Leslie Citrome, MD, MPH^c; Ming-Yi Huang, PhD^d; Sarah Acaster, MSc^e; Moshe Fridman, PhD^f; Vijayveer Bonthapally, PhD^d; Robert Lasser, MD, MBA^d; and Stephen J. Kaness, MD, PhD^d

ABSTRACT

Objective: Concurrent anxiety and/or insomnia symptoms in women with postpartum depression (PPD) are common and associated with more severe PPD. The effects of zuranolone on concurrent anxiety and/or insomnia symptoms and on patient-perceived functional health in women with PPD in the ROBIN study are reported.

Methods: The phase 3, double-blind, randomized, placebo-controlled trial (conducted January 2017–December 2018) included women aged 18–45 years, ≤ 6 months postpartum, with PPD (onset of DSM-5–defined major depressive episode in the third trimester or ≤ 4 weeks postpartum) and baseline 17-item Hamilton Depression Rating Scale (HDRS-17) total score ≥ 26. Women were randomized 1:1 to once-daily oral zuranolone 30 mg (n = 77) or placebo (n = 76) for 14 days with follow-up through day 45. Concurrent remission of depressive and anxiety symptoms (Hamilton Anxiety Rating Scale total score ≤ 7 plus HDRS-17 total score ≤ 7 or Montgomery-Asberg Depression Rating Scale total score ≤ 10), improvement in insomnia symptoms, patient-perceived functional health, and treatment effect sizes described by number needed to treat (NNT) were assessed. Analyses were exploratory; *P* values are nominal.

Results: Rates of concurrent remission of depressive and anxiety symptoms were higher with zuranolone versus placebo (*P* < .05) at days 3, 15, and 45; the rate of sustained concurrent remission (ie, at both days 15 and 45) was also higher with zuranolone (*P* < .05). Anxiety symptoms (assessed by HDRS-17 anxiety/somatization subscale and Edinburgh Postnatal Depression Scale anxiety subscale) improved with zuranolone versus placebo (*P* < .05) at days 3 through 45. Potential benefits on insomnia symptoms and patient-perceived functional health were observed. Day 15 NNTs were 5 for both HDRS-17 response and remission.

Conclusions: Zuranolone was associated with concurrent improvements in depressive and anxiety symptoms, with beneficial effects on insomnia symptoms and patient-perceived functional health in adults with PPD.

Trial Registration: ClinicalTrials.gov identifier: NCT02978326

J Clin Psychiatry 2023;84(1):22m14475

To cite: Deligiannidis KM, Citrome L, Huang M-Y, et al. Effect of zuranolone on concurrent anxiety and insomnia symptoms in women with postpartum depression. *J Clin Psychiatry*. 2023;84(1):22m14475.

To share: <https://doi.org/10.4088/JCP.22m14475>

© 2023 Physicians Postgraduate Press, Inc.

^aZucker Hillside Hospital, Northwell Health, Glen Oaks, New York

^bFeinstein Institutes for Medical Research, Northwell Health, Manhasset, New York

^cNew York Medical College, Valhalla, New York

^dSage Therapeutics, Inc., Cambridge, Massachusetts

^eAcaster Lloyd Consulting Ltd., London, United Kingdom

^fAMF Consulting, Los Angeles, California

*Corresponding author: Kristina M. Deligiannidis, MD, Zucker Hillside Hospital, Division of Psychiatry Research, Women's Behavioral Health, 75-59 263rd St, Glen Oaks, NY 11004 (kdeligian1@northwell.edu).

Postpartum depression (PPD), defined as a major depressive episode with peripartum onset occurring during pregnancy or within 4 weeks postpartum, is one of the most common medical complications associated with pregnancy.^{1–4} Many women with PPD experience significantly impaired functioning and well-being, with more severe depression resulting in worse mental functional health.^{5–7} Symptoms of PPD can be associated with significant impairment in mother-infant bonding and maternal function,^{8–11} including breastfeeding^{9,12} and caring for the child.^{13,14} In addition to depressive symptoms, women with PPD often experience other symptoms/comorbidities that can adversely affect their psychological well-being and overall functioning. For example, anxiety symptoms may be prominent in women with PPD, with prevalence estimates as high as approximately 70% of patients.^{10,15–17} In women with PPD, anxiety symptoms have been associated with more severe depression,^{18–20} longer time to treatment response,¹⁶ and an increased risk of self-harm ideation.²¹ Similarly, sleep problems are also common in women during the peripartum period.²² Insomnia (difficulty falling asleep when baby is sleeping or returning to sleep after waking to care for baby) can be both a risk factor for and a symptom of PPD, and its presence may predict both the development and severity of PPD.^{9,23,24} Sleep disturbance and poor sleep quality are also associated with frequent self-harm thoughts and poor mental health status in women with PPD.^{5,21} Furthermore, poor sleep quality has been associated with postpartum anxiety symptoms.²⁵ Therefore, it is important to address anxiety symptoms, as well as insomnia and other symptoms of depression, to improve the function and psychological health of women with PPD.

Multiple factors may contribute to the pathophysiology of PPD.^{26,27} Altered neuroactive steroid (NAS) levels^{28–30} and dysregulation of γ -aminobutyric acid (GABA) signaling and, thus, disruption of excitatory-inhibitory balance in key brain networks (eg, those controlling mood)^{31–35} are implicated in PPD. Endogenous NASs such as allopregnanolone are important regulators of the hypothalamic-pituitary-adrenal (HPA) axis in response to stress, acting via interactions with GABA_A receptors.³⁶ Administration of allopregnanolone has been shown to exert anxiolytic and antidepressant effects in mice, likely through enhancement of GABA_A receptor-mediated tonic inhibition.³⁷ Zuranolone is an investigational NAS

You are prohibited from making this PDF publicly available.

Clinical Points

- Postpartum depression with anxiety symptoms or symptoms of sleep disturbance/insomnia is associated with more severe depression, longer time to treatment response, increased of self-harm ideation, and poor mental health status.
- A once-daily, 14-day treatment course of oral zuranolone was associated with concurrent improvements in depressive and anxiety symptoms, with beneficial effects on insomnia and self-reported functional health in women with postpartum depression.

and a positive allosteric modulator of GABA_A receptors in clinical development as an oral, once-daily, 14-day treatment course for adults with PPD.^{38–41} Zuranolone binds to both synaptic (containing γ subunit) and extrasynaptic (containing δ subunit) GABA_A receptors in vitro, leading to potentiation of phasic and tonic postsynaptic currents, respectively, which is hypothesized to play a role in restoring brain network function in regions thought to be involved in depression.^{39,40} By increasing phasic and tonic inhibitory GABAergic signaling, zuranolone may rapidly restore and maintain excitatory-inhibitory balance in brain networks, thereby improving depressive and anxiety symptoms in women with PPD.

The phase 3 ROBIN study (NCT02978326) was a randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of zuranolone in adult women with PPD. The study demonstrated a statistically significant and clinically meaningful improvement in depressive symptoms (defined in adults with PPD as a minimal important difference [MID] in 17-item Hamilton Depression Rating Scale [HDRS-17]⁴² total score of -2.1)⁴³ at day 15 with a once-daily, 14-day course of zuranolone versus placebo.⁴¹ Greater and nominally significant improvement in anxiety symptoms as assessed by Hamilton Anxiety Rating Scale (HARS) was also observed at day 15 with zuranolone versus placebo.⁴¹ The present report describes prespecified exploratory and post hoc analyses assessing concurrent remission of depressive and anxiety symptoms, anxiety symptoms, insomnia symptoms, and patient-perceived functional health from the ROBIN study. For an indirect comparison with standard-of-care (SOC) antidepressant therapy (ADT), treatment benefits and risks with zuranolone versus placebo are described by the number needed to treat (NNT) for HDRS-17 response and remission and the number needed to harm (NNH) for adverse events (AEs), respectively.

METHODS

Trial Design and Clinical Analyses

The trial design and patient inclusion/exclusion criteria have been described previously.⁴¹ Briefly, the study enrolled women aged 18–45 years, ≤ 6 months postpartum, with a diagnosis of PPD (onset of DSM-5–defined major depressive

episode in the third trimester or ≤ 4 weeks postpartum) and a HDRS-17 total score ≥ 26 at baseline (N = 153).⁴¹ Use of psychotropic medications intended to treat depressive symptoms was permitted, provided that patients were on a stable dose for ≥ 30 days prior to day 1 with intent to remain at the same dose until completion of the day 15 assessments. A new ADT could be initiated during the follow-up period based on the patient's clinical needs as per investigator judgment. The first informed consent was received on January 4, 2017, and the final poststudy observation was on December 11, 2018. Women were randomized 1:1 to receive oral zuranolone 30 mg (n = 77) or placebo (n = 76) once daily for 14 days as outpatients, with follow-up through day 45 (30 days after cessation of treatment). The trial received institutional review board approval and was performed in compliance with the Declaration of Helsinki, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use, and Good Clinical Practice guidelines and all applicable regulatory requirements. All patients provided written informed consent prior to enrollment.

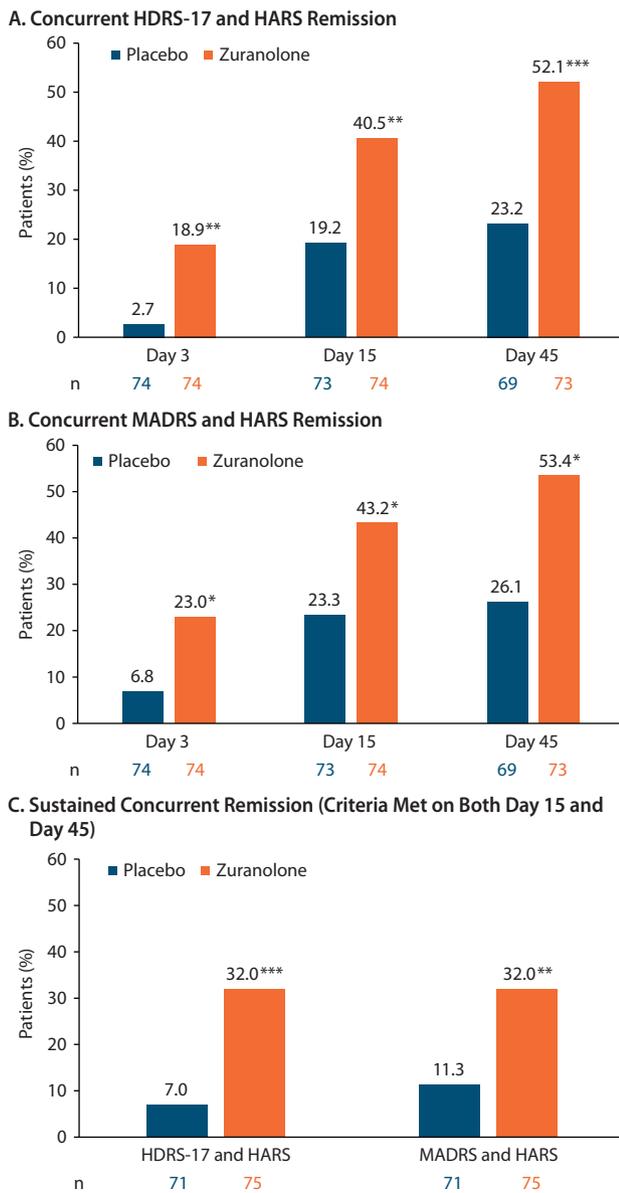
The primary and secondary endpoints have been reported previously.⁴¹ The primary endpoint was the change from baseline (CFB) in HDRS-17 total score at day 15. Secondary endpoints included CFB in HDRS-17 total score at days 3, 8, 21, and 45; CFB in the HARS⁴⁴ and the Montgomery-Asberg Depression Rating Scale (MADRS)⁴⁵ total scores; and rates of HDRS-17 response and remission at all measured time points. Safety and tolerability, reported previously, were evaluated by AEs, vital signs, clinical laboratory evaluations, electrocardiogram parameters, and the Columbia-Suicide Severity Rating Scale.^{41,46}

Concurrent remission of depressive and anxiety symptoms (defined as HARS total score ≤ 7 plus either HDRS-17 total score ≤ 7 or MADRS total score ≤ 10) was analyzed post hoc. Results are reported as percentage of patients achieving concurrent remission of depressive and anxiety symptoms.

The effect of zuranolone on anxiety symptoms was evaluated using CFB in the HDRS-17 Anxiety/Somatization (A/S) subscale score^{47,48} and the patient-reported Edinburgh Postnatal Depression Scale anxiety (EPDS-3A) subscale score over time⁴⁹; the rate of HARS, HDRS-17 A/S, and EPDS-3A response (defined as $\geq 50\%$ reduction from baseline in total scores); and the rate of sustained HARS, HDRS-17 A/S, and EPDS-3A response (defined as achievement of response at both days 15 and 45). The HDRS-17 A/S subscale, which reflects the severity of anxiety symptoms in patients with depression, includes HDRS-17 items 10 (psychic anxiety), 11 (somatic anxiety), 12 (gastrointestinal somatic symptoms), 13 (general somatic symptoms), 15 (hypochondriasis), and 17 (insight).^{47,48} The EPDS-3A includes the EPDS items 3 (self-blame), 4 (anxious/worried), and 5 (scared/panicky).⁴⁹ Insomnia was evaluated using CFB in HDRS-17 insomnia subscale (HDRS-17 Ins), MADRS item 4 (reduced sleep), and EPDS item 7 (difficulty sleeping) over time. These analyses were conducted post hoc.

It is illegal to post this copyrighted PDF on any website.

Figure 1. Proportion of Patients Achieving Concurrent Remission in Depressive and Anxiety Symptoms by Outcomes and Assessment Time Points^a



^aConcurrent remission of depressive and anxiety symptoms was defined as achieving both HDRS-17 and HARS remission or both MADRS and HARS remission. HDRS-17 remission was defined as total score ≤ 7 , HARS remission was defined as total score ≤ 7 , and MADRS remission was defined as total score ≤ 10 .

* $P < .05$ vs placebo. ** $P < .01$ vs placebo. *** $P < .001$ vs placebo. P values have not been adjusted for multiplicity and are nominal.

Abbreviations: HARS = Hamilton Anxiety Rating Scale, HDRS-17 = 17-item Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, n = number of patients at that visit.

Improvements in general health status were assessed in a prespecified analysis using the 36-item Short-Form Health Survey, version 2 (SF-36v2), which measures adult patients' perceptions of their own functional health and well-being that are not directly reflected in HDRS-17, HARS, or other metrics.^{50,51} The survey evaluates the person's functioning in 8 domains, including Physical Functioning, Role Limitations due to Physical Problems, Role Limitations

due to Emotional Problems, Bodily Pain, General Health Perceptions, Vitality, Social Functioning, and General Mental Health.⁵⁰

Clinical benefits and risks were evaluated post hoc by assessing NNT, NNH, and the likelihood to be helped or harmed (LHH).^{52,53} NNTs were estimated for response, remission, sustained response, and sustained remission and NNHs for discontinuation due to an AE, experiencing ≥ 1 treatment-emergent AE (TEAE), and AEs with an incidence $\geq 2\%$ with zuranolone and higher than with placebo. LHH, defined as the NNH-to-NNT ratio, was calculated if both NNT and NNH were significant for a specific event.

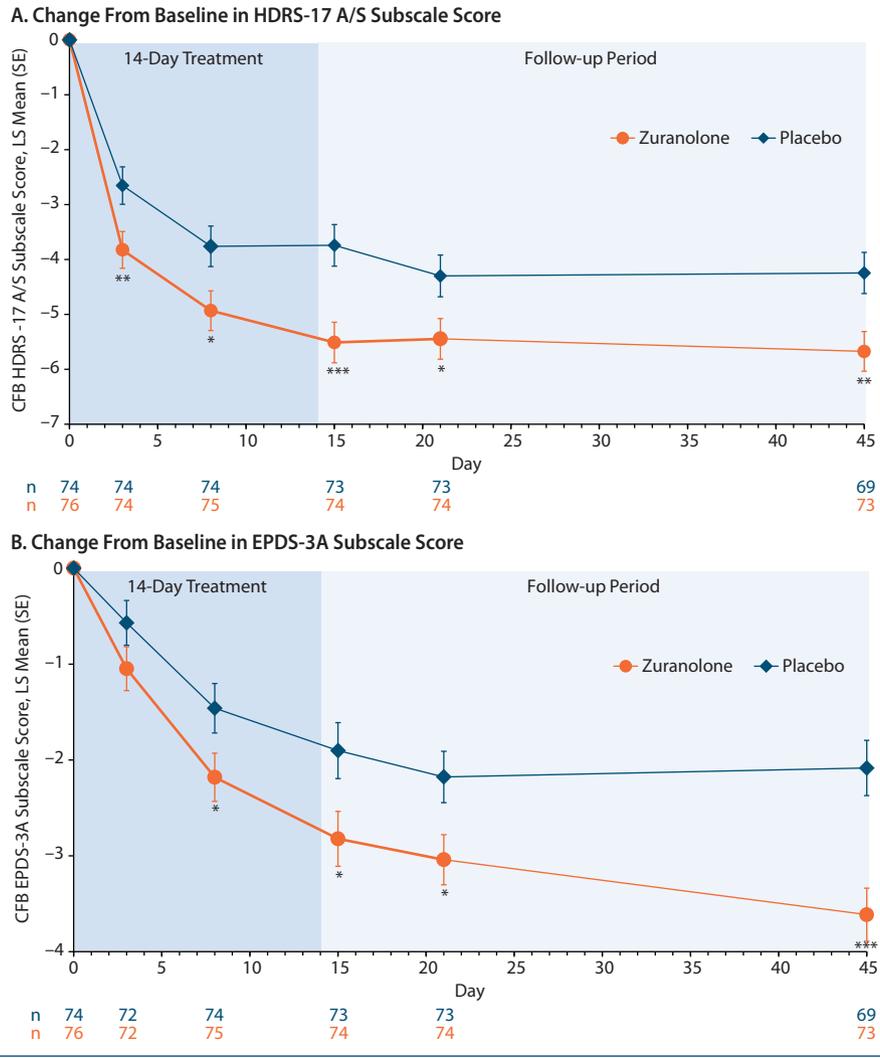
Statistical Analysis

The CFB at each time point was evaluated using the least squares (LS) mean from a mixed model for repeated measures (MMRM). Concurrent remission rates were derived using the generalized estimating equation models for repeated measures, adjusting for baseline covariates. Secondary, exploratory, and post hoc endpoints were evaluated using an MMRM and were not adjusted for multiplicity. SF-36v2 domain or summary scores of 50 represent the normative level of the general population.⁵¹ In line with the SF-36v2 manual,⁵¹ the MIDs for SF-36v2 domain and summary scores are 2 points for Vitality, General Health, and Physical Component Summary; 3 points for Role Physical, Physical Functioning, Bodily Pain, Social Functioning, Mental Health, and Mental Component Summary; and 4 points for Role Emotional. NNT and NNH were calculated based on the proportions of patients (P) for a specific outcome ($1/[P_{\text{treatment}} - P_{\text{placebo}}]$). The 95% confidence intervals (CIs) for NNT and NNH were calculated based on Wilson score intervals. The analyses are exploratory. All P values are nominal, with $P < .05$ indicating statistical significance. Analyses were conducted using SAS, version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Of 153 women randomized, 150 were evaluable and included in the efficacy analyses (zuranolone, $N = 76$; placebo, $N = 74$) as previously described.⁴¹ Demographic and baseline patient characteristics (ie, age, race, ADT use, HDRS-17 total score) were well balanced between the 2 treatment arms.⁴¹ At baseline, 16/76 (21.1%) and 13/74 (17.6%) patients in the zuranolone and placebo groups, respectively, were receiving stable doses of ADTs.⁴¹ In the zuranolone group, 12 patients were receiving a selective serotonin reuptake inhibitor (SSRI), 3 were receiving a norepinephrine/dopamine-reuptake inhibitor (NDRI), and 1 was receiving a serotonin and norepinephrine reuptake inhibitor. In the placebo group, 12 patients were receiving an SSRI and 1 patient was receiving an NDRI. A small proportion (6 patients [7.9%] and 4 patients [5.4%] in the zuranolone and placebo groups, respectively) initiated ADT during the follow-up period.⁴¹

Figure 2. Rapid and Sustained Improvement in Symptoms of Anxiety



* $P < .05$ vs placebo. ** $P < .01$ vs placebo. *** $P < .001$ vs placebo. P values have not been adjusted for multiplicity and are nominal.

Abbreviations: CFB= change from baseline, EPDS-3A=Edinburgh Postnatal Depression Scale anxiety subscale, HARS=Hamilton Anxiety Rating Scale, HDRS-17=17-item Hamilton Depression Rating Scale, HDRS-17 A/S=HDRS-17 Anxiety/Somatization, LS=least squares, n=number of patients that day, SE=standard error.

Concurrent Remission of Depressive and Anxiety Symptoms

As assessed by the combined criteria of HDRS-17 total score ≤ 7 and HARS total score ≤ 7 , a greater proportion of women receiving zuranolone achieved concurrent remission of depressive and anxiety symptoms compared with those receiving placebo as early as day 3 (18.9% vs 2.7%; $P = .003$) and at day 15 (40.5% vs 19.2%; $P = .007$) and day 45 (52.1% vs 23.2%; $P < .001$; Figure 1A). Similarly, as assessed by the combined criteria of MADRS total score ≤ 10 and HARS total score ≤ 7 , a higher rate of concurrent remission was achieved with zuranolone versus placebo at day 3 (23.0% vs 6.8%; $P = .010$), day 15 (43.2% vs 23.3%; $P = .014$), and day 45 (53.4% vs 26.1%; $P = .001$; Figure 1B). The rate of sustained concurrent remission of depressive and anxiety symptoms

(ie, at both days 15 and 45) was higher with zuranolone versus placebo using the criteria of either the combined HDRS-17/HARS ($P < .001$; odds ratio [OR; 95% CI], 6.2 [2.2 to 17.4]) or the combined MADRS/HARS ($P = .003$; OR [95% CI], 3.7 [1.5 to 8.9]; Figure 1C).

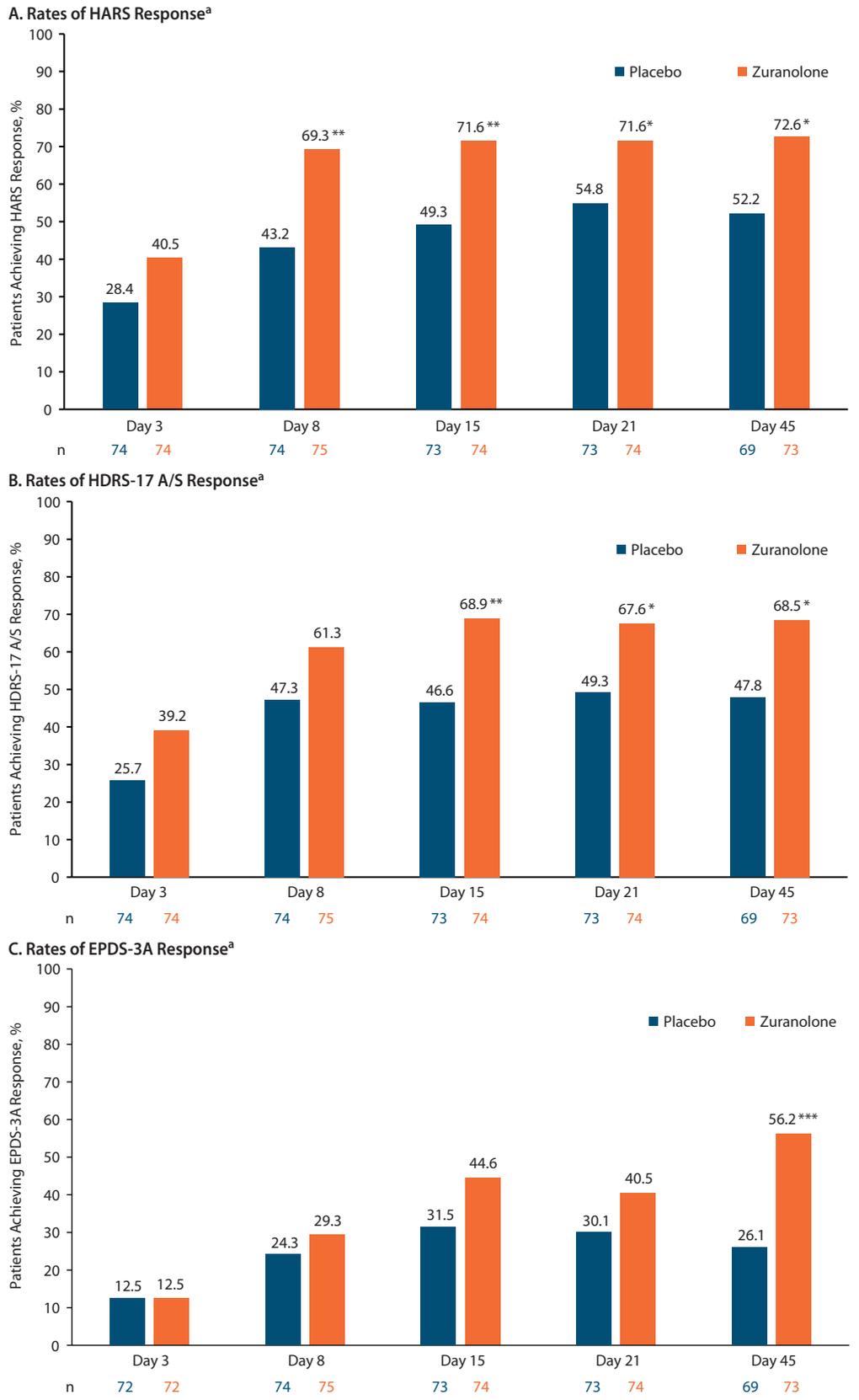
Anxiety Symptoms

Greater CFB in HARS score at days 3 through 45 with zuranolone versus placebo ($P < .05$ at all measured time points) in this population has been reported previously.⁴¹ At baseline, mean (SD) HDRS-17 A/S subscale total score was 9.0 (1.5) and 9.4 (1.7) for women receiving zuranolone and placebo, respectively. Women demonstrated an improvement in anxiety/somatization symptoms as assessed by CFB in HDRS-17 A/S subscale score (LS mean [SE; 95% CI]) with

You are prohibited from making this PDF publicly available.

It is illegal to post this copyrighted PDF on any website.

Figure 3. Proportions of Patients Achieving Responses in Symptoms of Anxiety



^aResponse is defined as $\geq 50\%$ reduction from baseline on respective assessment scale.
 * $P < .05$ vs placebo. ** $P < .01$ vs placebo. P values have not been adjusted for multiplicity and are nominal.
 Abbreviations: EPDS-3A = Edinburgh Postnatal Depression Scale anxiety subscale, HARS = Hamilton Anxiety Rating Scale, HDRS-17 = 17-item Hamilton Depression Rating Scale, HDRS-17 A/S = HDRS-17 Anxiety/Somatization, n = number of patients that day.

You are prohibited from making this PDF publicly available.

zuranolone versus placebo starting at day 3 (-3.8 [0.3; -4.5 to -3.2] vs -2.7 [0.3; -3.3 to -2.0]; $P = .007$) and continuing at all measured time points through day 45 (-5.7 [0.4; -6.4 to -5.0] vs -4.3 [0.4; -5.0 to -3.5]; $P = .003$; Figure 2A). Reductions in EPDS-3A score were greater with zuranolone versus placebo at day 8 (-2.2 [0.3] vs -1.5 [0.3]; $P = .032$) through day 45 (-3.6 [0.3] vs -2.1 [0.3]; $P < .001$; Figure 2B).

Higher rates of HARS response (71.6% vs 49.3%, $P = .007$; Figure 3A) and HDRS-17 A/S response (68.9% vs 46.6%, $P = .008$; Figure 3B) were observed in women treated with zuranolone versus placebo at day 15 and continued at all measured timepoints through day 45. EPDS-3A response rates were numerically higher with zuranolone versus placebo at all measured time points from day 8 through day 45, with a nominally significant difference at day 45 (56.2% vs 26.1%, $P < .001$; Figure 3C). Rates of sustained response (ie, at both days 15 and 45) on HARS (58.7% vs 42.3%, $P = .068$), HDRS-17 A/S (53.3% vs 34.3%, $P = .029$), and EPDS-3A (29.3% vs 16.9%, $P = .082$) were numerically higher with zuranolone versus placebo (Figure 4).

Insomnia Symptoms

Numerically greater improvement in symptoms of insomnia was achieved by women receiving zuranolone versus placebo as assessed by HDRS-17 Ins (Figure 5A), MADRS reduced sleep item (Figure 5B), and EPDS difficulty sleeping item (Figure 5C); nominally significant benefits were observed for zuranolone versus placebo at all measured time points on HDRS-17 Ins, all time points except day 21 on MADRS reduced sleep item, and at day 45 on EPDS difficulty sleeping item.

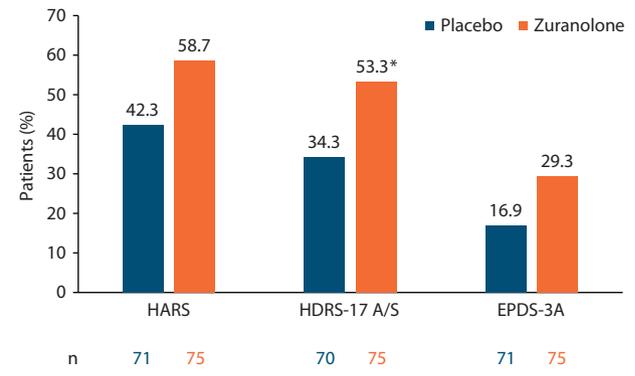
Patient-Reported Functional Health and Well-Being

At day 45, women receiving zuranolone achieved improvements compared with placebo across 5 domains of the SF-36v2, including Social Functioning (LS mean [SE; 95% CI], 18.27 [1.37; 15.56 to 21.0] vs 13.53 [1.44; 10.69 to 16.37]; $P = .008$), Mental Health (19.39 [1.58; 16.27 to 22.51] vs 13.93 [1.64; 10.69 to 17.17]; $P = .008$), Physical Functioning (6.38 [0.95; 4.51 to 8.26] vs 3.8 [0.99; 1.85 to 5.74]; $P = .038$), Role Physical (11.75 [1.11; 9.56 to 13.94] vs 8.85 [1.16; 6.56 to 11.13]; $P = .045$), and Bodily Pain (8.19 [1.17; 5.87 to 10.51] vs 4.0 [1.23; 1.56 to 6.40]; $P = .007$), and in the Mental Component Summary score (23.59 [1.83; 19.97 to 27.21] vs 18.45 [1.90; 14.68 to 22.21]; $P = .030$); CFB in other SF-36v2 domains was numerically greater with zuranolone versus placebo (Supplementary Figure 1A). In women receiving zuranolone, mean scores at day 45 for Physical Functioning, Bodily Pain, and General Health domains and for Physical Component Summary reached the US population normative levels; mean Role Physical domain score was within 1 MID from population normative levels (Supplementary Figure 1B).

NNT and NNH Estimates

A greater proportion of women achieved sustained HDRS-17 response (59% vs 39%; $P = .020$) and sustained

Figure 4. Rates of Sustained Response in Symptoms of Anxiety as Assessed by HARS, HDRS-17 A/S, and EPDS-3A^a



^aSustained response is defined as $\geq 50\%$ reduction from baseline on respective assessment scale at both day 15 and day 45.

* $P < .05$ vs placebo. ** $P < .01$ vs placebo. P values have not been adjusted for multiplicity and are nominal.

Abbreviations: EPDS-3A = Edinburgh Postnatal Depression Scale anxiety subscale, HARS = Hamilton Anxiety Rating Scale, HDRS-17 = 17-item Hamilton Depression Rating Scale, HDRS-17 A/S = HDRS-17 Anxiety/Somatization, n = number of patients that day.

HDRS-17 remission (37% vs 13%, $P < .001$) with zuranolone versus placebo. The NNT estimates (95% CI) were similar for HDRS-17 response (5 [3 to 13]) and remission (5 [3 to 17]) at day 15, sustained response (5 [3 to 27]), and sustained remission (5 [3 to 10]; Supplementary Table 1). The NNH estimates were ≥ 10 for incidence of TEAEs and discontinuation due to an AE (Supplementary Table 1). LHH estimates were not calculated for this population as the NNH estimates were nonsignificant.

DISCUSSION

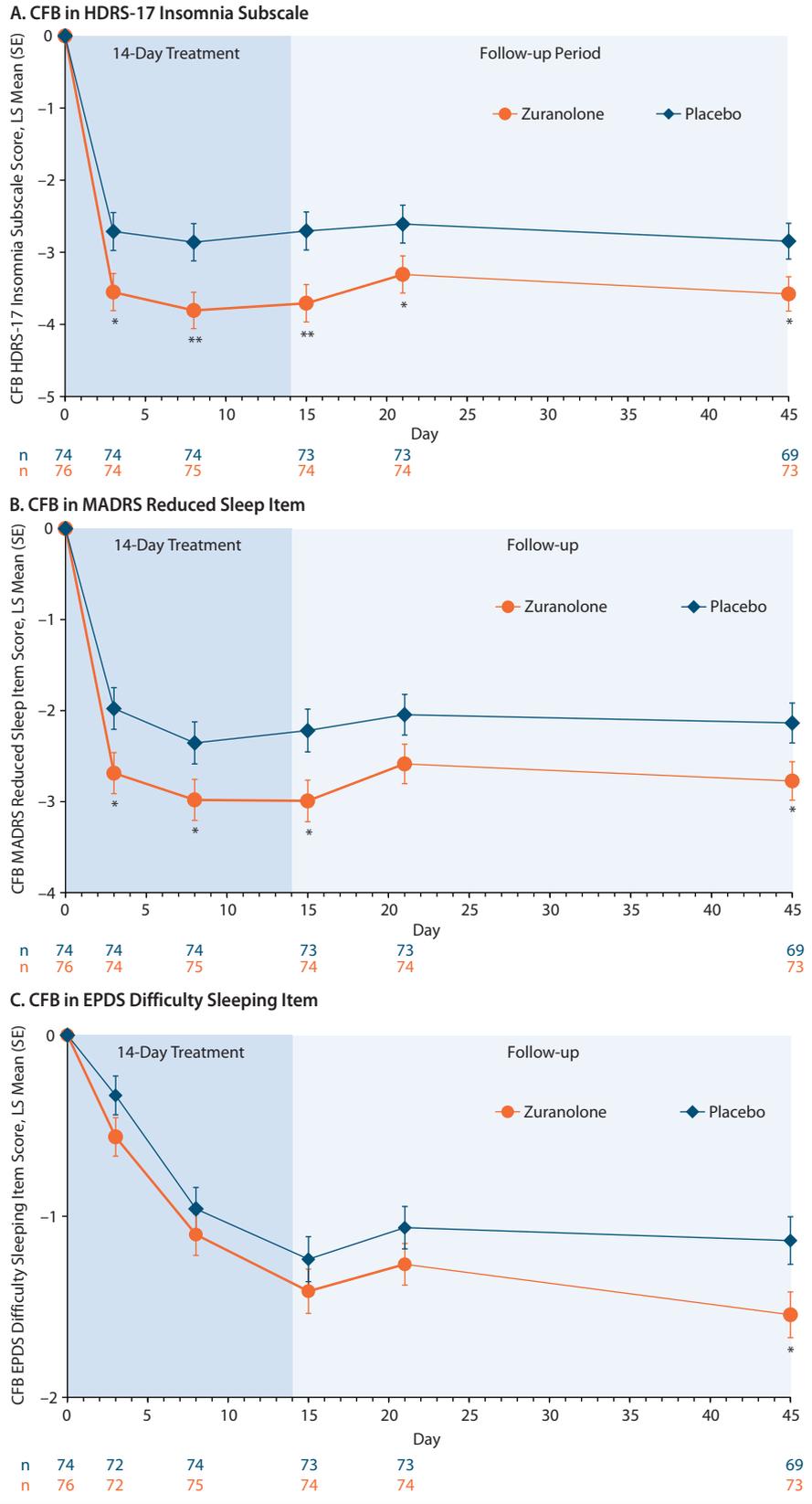
Results from ROBIN prespecified exploratory and post hoc analyses presented here show that women with PPD achieved concurrent improvements in both depressive and anxiety symptoms with zuranolone; the proportion of women achieving concurrent remission of both symptoms was greater with zuranolone versus placebo as early as day 3, and the benefit was maintained at days 15 and 45. Sustained (at both days 15 and 45) concurrent remission was observed in approximately 30% of women receiving zuranolone based on either the HDRS-17/HARS or the MADRS/HARS criteria; the rate was higher than that of women receiving placebo (7% on HDRS-17/HARS criteria and 11% on MADRS/HARS criteria). Improvements in anxiety symptoms as assessed by HDRS-17 A/S and EPDS-3A with zuranolone versus placebo are consistent with previous similar findings based on HARS assessments.⁴¹ Beneficial effects of zuranolone on insomnia symptoms and patient-perceived functional health were also observed.

Given the high rate of concurrent anxiety and/or insomnia symptoms in women with PPD, these findings are potentially clinically impactful, as rapid improvements in depressive, anxiety, and insomnia symptoms may be

You are prohibited from making this PDF publicly available.

It is illegal to post this copyrighted PDF on any website.

Figure 5. Improvement in Symptoms of Insomnia



* $P < .05$ vs placebo. ** $P < .01$ vs placebo. P values have not been adjusted for multiplicity and are nominal. Abbreviations: CFB = change from baseline, EPDS-3A = Edinburgh Postnatal Depression Scale anxiety subscale, HDRS-17 = 17-item Hamilton Depression Rating Scale, LS = least squares, MADRS = Montgomery-Asberg Depression Rating Scale, n = number of patients that day, SE = standard error.

You are prohibited from making this PDF publicly available.

achieved without a need for polypharmacy. In clinical practice, pharmacotherapies targeting anxiety and/or insomnia symptoms are often used in addition to SOC ADT, increasing risk for adverse effects, drug-drug interactions, and poor adherence,⁵⁴ as only a few SOC ADTs have been shown to improve both depressive and anxiety symptoms in clinical studies of women with PPD.^{55–58} Additionally, it often takes 4 to 6 weeks for SOC ADTs to demonstrate clinical benefit,^{59–61} with women experiencing transient increases in jitteriness/anxiety during the early treatment period⁶² at greater rates than men.⁶³

Women with PPD experience significant impairments in physical functioning and psychosocial well-being beyond the mood and neurovegetative symptoms associated with PPD.^{5,7,64} Patient-reported outcome measures such as SF-36v2 are increasingly incorporated into clinical trials to evaluate how treatment impacts the overall functioning and well-being of patients.^{65,66} The present results of nominally significant improvements in 5 domains of the SF-36v2 (including 3 of the 4 physical health domains) and in the Mental Component Summary score suggest that women receiving zuranolone as treatment for their PPD perceive improvements in their own functional health and well-being.

When medications are compared with placebo, the resultant NNT and NNH estimates can serve as a basis of indirect comparisons within a class of agents, as recently demonstrated for ADTs.⁶⁷ In general, NNT values < 10 for efficacy measures suggest that the intervention is potentially clinically beneficial.⁶⁸ NNTs of 6–9 are commonly reported when comparing SOC ADTs with placebo. In addition, NNH values ≥ 10 are desirable for AE outcomes.⁶⁸ Our analyses found an NNT of 5 for response and remission at

day 15 and NNH estimates ≥ 10 for both incidence of AEs and discontinuation due to an AE.

Study Limitations

The analyses were for non-primary endpoints in the study and therefore were not controlled for multiplicity. Additionally, results may not be generalizable to patients outside the confines of a clinical trial because of the strict inclusion/exclusion criteria used in this registrational study. Furthermore, reasons for clinical trial discontinuation can be complex, so the NNH for discontinuation due to AEs in this study may not always generalize to overall tolerability in clinical practice. The brief duration of the study limits the sensitivity of calculating NNH for delayed AEs, and the relatively small sample sizes limit sensitivity of calculating NNH for uncommon AEs and subpopulation effects. Finally, the NNH results for zuranolone were nonsignificant, likely because of the small sample size. Estimates for LHH were therefore not calculated for this population.

CONCLUSIONS

Adult women with PPD receiving zuranolone experienced improvements in both depressive and anxiety symptoms, with a higher rate of concurrent remission at days 3, 15, and 45 compared with those receiving placebo. Beneficial effects of zuranolone versus placebo on insomnia and patient-reported functional health and well-being were also observed. Together, these findings support further development of zuranolone as a potentially rapid-acting pharmacotherapy for adults with PPD, including those with anxiety and/or insomnia symptoms, potentially without the need for polypharmacy.

Submitted: March 31, 2022; accepted October 31, 2022.

Published online: January 30, 2023.

Relevant financial relationships: Dr Deligiannidis serves as a consultant to Sage Therapeutics, Inc., Bria Biosciences, and GH Research and reports grants awarded to Zucker Hillside Hospital/Feinstein Institutes for Medical Research during the conduct of the brexanolone injection and zuranolone clinical trials. Dr Deligiannidis received grants from National Institutes of Health (NIH) and Vorso Corporation and royalties from an NIH employee invention outside of the submitted work. Dr Citrome serves as a consultant to AbbVie/Allergan, Acadia, Adamas, Alkermes, Angelini, Astellas, Avanir, Axsome, BioXcel, Boehringer Ingelheim, Cadent Therapeutics, Eisai, Enteris BioPharma, HLS Therapeutics, Impel, Intra-Cellular Therapies, Janssen, Karuna, Lundbeck, Lyndra, Medavante-ProPhase, Merck, Neurocrine, Novartis, Noven, Otsuka, Ovid, Relmada, Reviva, Sage, Sunovion, Teva, University of Arizona, and one-off ad hoc consulting for individuals/entities conducting marketing, commercial, or scientific scoping research; speaker for AbbVie/Allergan, Acadia, Alkermes, Angelini, Eisai, Intra-Cellular Therapies, Janssen, Lundbeck, Neurocrine, Noven, Otsuka, Sage, Sunovion, Takeda, and Teva; and CME activities organized by medical education companies such as Medscape, NACCME, NEI, Vindico, and Universities and

Professional Organizations/Societies; owns stocks (small number of shares of common stock) in Bristol Myers Squibb, Eli Lilly, J & J, Merck, and Pfizer purchased > 10 years ago; and receives royalties from Wiley (Editor in Chief, *International Journal of Clinical Practice*, through end 2019), UpToDate (reviewer), Springer Healthcare (book), Elsevier (Topic Editor, Psychiatry, Clinical Therapeutics). Drs Huang, Bonthapally, and Lasser are employees of Sage Therapeutics, Inc., and may hold stock and/or stock options. Ms Acaster is an employee of Acaster Lloyd Consulting Ltd, which was paid by Sage Therapeutics, Inc., to conduct the research reported in this work. Dr Fridman is an employee of AMF Consulting, which was paid by Sage Therapeutics, Inc., to conduct the research reported in this work. Dr Kanis is a former employee of Sage Therapeutics, Inc., and may hold stock and/or stock options.

Funding/support: The ROBIN Study was funded by Sage Therapeutics, Inc., Cambridge, MA.

Role of the sponsor: Sage Therapeutics, Inc. was involved in the ROBIN Study design; both Sage Therapeutics, Inc., and Biogen Inc. were involved in the post-hoc analyses, interpretation, and writing of this report. During the development process, both Sage Therapeutics, Inc., and Biogen Inc., had the opportunity to review and comment on the manuscript; however, the authors retained full editorial control and provided final approval on all

content. All authors had full access to all data, and the corresponding author had final responsibility for the decision to submit for publication.

Previous presentations: Aspects of this post hoc analysis have been presented at the Society for Maternal-Fetal Medicine, 40th Annual Pregnancy Meeting, February 3–8, 2020, Grapevine, TX; the Society of Biological Psychiatry, Virtual Annual Meeting, April 30–May 2, 2020; Psych Congress 2020, Virtual Annual Meeting, September 10–13, 2020; the European College of Neuropsychopharmacology, Annual Virtual Meeting, September 12–15, 2020; the American Society of Clinical Psychopharmacology, Annual Virtual Meeting, 2020; the American College of Neuropsychopharmacology, Annual Virtual Meeting, 2020; and the Society of Biological Psychiatry, Annual Virtual Meeting, April 29–May 1, 2021.

Acknowledgments: Medical writing and editorial assistance were provided by Symbiotix, LLC (Linda M. Ritter, PhD, Medical Director [no conflicts of interest to disclose]), and funded by Sage Therapeutics, Inc., and Biogen Inc. The authors also thank Brian Werneburg, PhD, and Handan Gunduz-Bruce, MD, MBA, for their contributions to earlier versions of the manuscript. Drs Werneburg and Gunduz-Bruce are former employees of Sage Therapeutics, Inc., and may hold stock and/or stock options.

Supplementary material: Available at Psychiatrist.com.

It is illegal to post this copyrighted PDF on any website.

REFERENCES

- Bauman BL, Ko JY, Cox S, et al. *Vital signs: postpartum depressive symptoms and provider discussions about perinatal depression - United States, 2018. MMWR Morb Mortal Wkly Rep.* 2020;69(19):575–581.
- Martin JA, Hamilton BE, Osterman MJK, et al. Births: final data for 2017. *Natl Vital Stat Rep.* 2018;67(8):1–50.
- DeSisto CL, Kim SY, Sharma AJ. Prevalence estimates of gestational diabetes mellitus in the United States, Pregnancy Risk Assessment Monitoring System (PRAMS), 2007–2010. *Prev Chronic Dis.* 2014;11:130415.
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*. 5th ed. Arlington, VA: American Psychiatric Association; 2013.
- Da Costa D, Dritsa M, Rippen N, et al. Health-related quality of life in postpartum depressed women. *Arch Women Ment Health.* 2006;9(2):95–102.
- Sadat Z, Abedzadeh-Kalahroudi M, Kafaei Atrian M, et al. The impact of postpartum depression on quality of life in women after child's birth. *Iran Red Crescent Med J.* 2014;16(2):e14995.
- Gerbasi ME, Kosinski M, Meltzer-Brody S, et al. Achieving clinical response in postpartum depression leads to improvement in health-related quality of life. *Curr Med Res Opin.* 2021;37(7):1221–1231.
- Kerstis B, Aarts C, Tillman C, et al. Association between parental depressive symptoms and impaired bonding with the infant. *Arch Women Ment Health.* 2016;19(1):87–94.
- Pearlstein T, Howard M, Salisbury A, et al. Postpartum depression. *Am J Obstet Gynecol.* 2009;200(4):357–364.
- Bobo WV, Yawn BP. Concise review for physicians and other clinicians: postpartum depression. *Mayo Clin Proc.* 2014;89(6):835–844.
- Sloman J, Honvo G, Emonts P, et al. Consequences of maternal postpartum depression: a systematic review of maternal and infant outcomes. *Womens Health (Lond).* 2019;15:1745506519844044.
- Wouk K, Stuebe AM, Meltzer-Brody S. Postpartum mental health and breastfeeding practices: an analysis using the 2010–2011 pregnancy risk assessment monitoring system. *Matern Child Health J.* 2017;21(3):636–647.
- Barkin JL, Wisner KL, Bromberger JT, et al. Factors associated with postpartum maternal functioning in women with positive screens for depression. *J Womens Health (Larchmt).* 2016;25(7):707–713.
- McLearn KT, Minkovitz CS, Strobino DM, et al. Maternal depressive symptoms at 2 to 4 months post partum and early parenting practices. *Arch Pediatr Adolesc Med.* 2006;160(3):279–284.
- Ross LE, Gilbert Evans SE, Sellers EM, et al. Measurement issues in postpartum depression part 1: anxiety as a feature of postpartum depression. *Arch Women Ment Health.* 2003;6(1):51–57.
- Hendrick V, Altshuler L, Strouse T, et al. Postpartum and nonpostpartum depression: differences in presentation and response to pharmacologic treatment. *Depress Anxiety.* 2000;11(2):66–72.
- Nakić Radoš S, Tadinac M, Herman R. Anxiety during pregnancy and postpartum: course, predictors and comorbidity with postpartum depression. *Acta Clin Croat.* 2018;57(1):39–51.
- Fox M, Sandman CA, Davis EP, et al. A longitudinal study of women's depression symptom profiles during and after the postpartum phase. *Depress Anxiety.* 2018;35(4):292–304.
- Postpartum Depression: Action Towards Causes and Treatment (PACT) Consortium. Heterogeneity of postpartum depression: a latent class analysis. *Lancet Psychiatry.* 2015;2(1):59–67.
- Farr SL, Dietz PM, O'Hara MW, et al. Postpartum anxiety and comorbid depression in a population-based sample of women. *J Womens Health (Larchmt).* 2014;23(2):120–128.
- Sit D, Luther J, Buysse D, et al. Suicidal ideation in depressed postpartum women: associations with childhood trauma, sleep disturbance and anxiety. *J Psychiatr Res.* 2015;66–67:95–104.
- Sivertsen B, Hysing M, Dørheim SK, et al. Trajectories of maternal sleep problems before and after childbirth: a longitudinal population-based study. *BMC Pregnancy Childbirth.* 2015;15(1):129.
- Dørheim SK, Bjorvatn B, Eberhard-Gran M. Can insomnia in pregnancy predict postpartum depression? a longitudinal, population-based study. *PLoS One.* 2014;9(4):e94674.
- Okun ML. Sleep and postpartum depression. *Curr Opin Psychiatry.* 2015;28(6):490–496.
- Okun ML, Mancuso RA, Hobel CJ, et al. Poor sleep quality increases symptoms of depression and anxiety in postpartum women. *J Behav Med.* 2018;41(5):703–710.
- Yim IS, Tanner Stapleton LR, Guardino CM, et al. Biological and psychosocial predictors of postpartum depression: systematic review and call for integration. *Annu Rev Clin Psychol.* 2015;11(1):99–137.
- Payne JL, Maguire J. Pathophysiological mechanisms implicated in postpartum depression. *Front Neuroendocrinol.* 2019;52:165–180.
- Deligiannidis KM, Kroll-Desrosiers AR, Mo S, et al. Peripartum neuroactive steroid and γ -aminobutyric acid profiles in women at-risk for postpartum depression. *Psychoneuroendocrinology.* 2016;70:98–107.
- Hellgren C, Åkerud H, Skalkidou A, et al. Low serum allopregnanolone is associated with symptoms of depression in late pregnancy. *Neuropsychobiology.* 2014;69(3):147–153.
- Osborne LM, Gispén F, Sanyal A, et al. Lower allopregnanolone during pregnancy predicts postpartum depression: an exploratory study. *Psychoneuroendocrinology.* 2017;79:116–121.
- Maguire J. Neuroactive steroids and GABAergic involvement in the neuroendocrine dysfunction associated with major depressive disorder and postpartum depression. *Front Cell Neurosci.* 2019;13:83.
- Fogaça MV, Duman RS. Cortical GABAergic dysfunction in stress and depression: new insights for therapeutic interventions. *Front Cell Neurosci.* 2019;13:87.
- Northoff G, Sibille E. Why are cortical GABA neurons relevant to internal focus in depression? a cross-level model linking cellular, biochemical and neural network findings. *Mol Psychiatry.* 2014;19(9):966–977.
- Mederos S, Perea G. GABAergic-astrocyte signaling: a refinement of inhibitory brain networks. *Glia.* 2019;67(10):1842–1851.
- Duman RS, Sanacora G, Krystal JH. Altered connectivity in depression: GABA and glutamate neurotransmitter deficits and reversal by novel treatments. *Neuron.* 2019;102(1):75–90.
- Crowley SK, Girdler SS. Neurosteroid, GABAergic and hypothalamic pituitary adrenal (HPA) axis regulation: what is the current state of knowledge in humans? *Psychopharmacology (Berl).* 2014;231(17):3619–3634.
- Antonoudiou P, Colmers PLW, Walton NL, et al. Allopregnanolone mediates affective switching through modulation of oscillatory states in the basolateral amygdala. *Biol Psychiatry.* 2022;91:283–293.
- Hoffmann E, Nomikos GG, Kaul I, et al. SAGE-217, a novel GABAA receptor positive allosteric modulator: clinical pharmacology and tolerability in randomized phase I dose-finding studies. *Clin Pharmacokinet.* 2020;59(1):111–120.
- Martinez Botella G, Salituro FG, Harrison BL, et al. Neuroactive steroids. 2. 3 α -hydroxy-3 β -methyl-21-(4-cyano-1H-pyrazol-1'-yl)-19-nor-5 β -pregnan-20-one (SAGE-217): a clinical next generation neuroactive steroid positive allosteric modulator of the (gamma-aminobutyric acid) A receptor. *J Med Chem.* 2017;60(18):7810–7819.
- Althaus AL, Ackley MA, Belfort GM, et al. Preclinical characterization of zuranolone (SAGE-217), a selective neuroactive steroid GABA_A receptor positive allosteric modulator. *Neuropharmacology.* 2020;181:108333.
- Deligiannidis KM, Meltzer-Brody S, Gunduz-Bruce H, et al. Effect of zuranolone vs placebo in postpartum depression: a randomized clinical trial. *JAMA Psychiatry.* 2021;78(9):951–959.
- Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* 1960;23(1):56–62.
- Gerbasi ME, Meltzer-Brody S, Acaster S, et al. Brexanolone in postpartum depression: post hoc analyses to help inform clinical decision-making. *J Womens Health (Larchmt).* 2021;30(3):385–392.
- Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol.* 1959;32(1):50–55.
- Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry.* 1979;134(4):382–389.
- Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry.* 2011;168(12):1266–1277.
- Huang CJ, Lin CH, Wu JI, et al. The Relationship Between Depression Symptoms and Anxiety Symptoms During Acute ECT for Patients With Major Depressive Disorder. *Int J Neuropsychopharmacol.* 2019;22(10):609–615.
- McClintock SM, Husain MM, Bernstein IH, et al. Assessing anxious features in depressed outpatients. *Int J Methods Psychiatr Res.* 2011;20(4):e69–e82.
- Tuohy A, McVey C. Subscales measuring symptoms of non-specific depression, anhedonia, and anxiety in the Edinburgh Postnatal Depression Scale. *Br J Clin Psychol.* 2008;47(Pt 2):153–169.
- Ware JE, Kosinski M, Turner-Bowker DM, et al. *User's Manual for the SF-12v2 Health Survey*. Lincoln, RI: QualityMetric; 2009.
- Maruish ME. *User's Manual for the SF-36v2 Health Survey*. Quality Metric Incorporated; 2011.
- Citrome L. Compelling or irrelevant? using number needed to treat can help decide. *Acta Psychiatr Scand.* 2008;117(6):412–419.
- Citrome L, Ketter TA. When does a difference make a difference? interpretation of number needed to treat, number needed to harm, and likelihood to be helped or harmed. *Int J Clin Pract.* 2013;67(5):407–411.
- Amodeo G, Laurenzi PF, Santucci A, et al. Advances in treatment for postpartum major depressive disorder. *Expert Opin Pharmacother.* 2020;21(14):1685–1698.

You are prohibited from making this PDF publicly available.

It is illegal to post this copyrighted PDF on any website.

55. Cohen LS, Viguera AC, Bouffard SM, et al. Venlafaxine in the treatment of postpartum depression. *J Clin Psychiatry*. 2001;62(8):592–596.
56. Misri S, Swift E, Abizadeh J, et al. Overcoming functional impairment in postpartum depressed or anxious women: a pilot trial of desvenlafaxine with flexible dosing. *Ther Adv Psychopharmacol*. 2016;6(4):269–276.
57. Misri S, Reebye P, Corral M, et al. The use of paroxetine and cognitive-behavioral therapy in postpartum depression and anxiety: a randomized controlled trial. *J Clin Psychiatry*. 2004;65(9):1236–1241.
58. Misri S, Abizadeh J, Albert G, et al. Restoration of functionality in postpartum depressed mothers: an open-label study with escitalopram. *J Clin Psychopharmacol*. 2012;32(5):729–732.
59. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. 2006;163(11):1905–1917.
60. Trivedi MH, Rush AJ, Wisniewski SR, et al; STAR*D Study Team. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry*. 2006;163(1):28–40.
61. De Crescenzo F, Perelli F, Armando M, et al. Selective serotonin reuptake inhibitors (SSRIs) for post-partum depression (PPD): a systematic review of randomized clinical trials. *J Affect Disord*. 2014;152-154:39–44.
62. Sinclair LI, Christmas DM, Hood SD, et al. Antidepressant-induced jitteriness/anxiety syndrome: systematic review. *Br J Psychiatry*. 2009;194(6):483–490.
63. Li Z, Pfeiffer PN, Hoggatt KJ, et al. Emergent anxiety after antidepressant initiation: a retrospective cohort study of Veterans Affairs Health System patients with depression. *Clin Ther*. 2011;33(12):1985–1992.e1.
64. Boyce PM, Johnstone SJ, Hickey AR, et al. Functioning and well-being at 24 weeks postpartum of women with postnatal depression. *Arch Women Ment Health*. 2000;3(3):91–97.
65. Mercieca-Bebber R, King MT, Calvert MJ, et al. The importance of patient-reported outcomes in clinical trials and strategies for future optimization. *Patient Relat Outcome Meas*. 2018;9:353–367.
66. Scoggins JF, Patrick DL. The use of patient-reported outcomes instruments in registered clinical trials: evidence from ClinicalTrials.gov. *Contemp Clin Trials*. 2009;30(4):289–292.
67. Citrome L, DiBernardo A, Singh J. Appraising esketamine nasal spray for the management of treatment-resistant depression in adults: number needed to treat, number needed to harm, and likelihood to be helped or harmed. *J Affect Disord*. 2020;271:228–238.
68. Citrome L. Quantifying clinical relevance. *Innov Clin Neurosci*. 2014;11(5–6):26–30.

Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Women's Mental Health section. Please contact Marlene P. Freeman, MD, at mfreeman@psychiatrist.com.

See supplementary material for this article at PSYCHIATRIST.COM.

You are prohibited from making this PDF publicly available.



THE JOURNAL OF CLINICAL PSYCHIATRY

THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Article Title: Effect of Zuranolone on Concurrent Anxiety and Insomnia Symptoms in Women With Postpartum Depression

Authors: Kristina M. Deligiannidis, MD; Leslie Citrome, MD, MPH; Ming-Yi Huang, PhD; Sarah Acaster, MSc; Moshe Fridman, PhD; Vijayveer Bonthapally, PhD; Robert Lasser, MD, MBA; and Stephen J. Kanes, MD, PhD

DOI Number: 10.4088/JCP.22m14475

List of Supplementary Material for the article

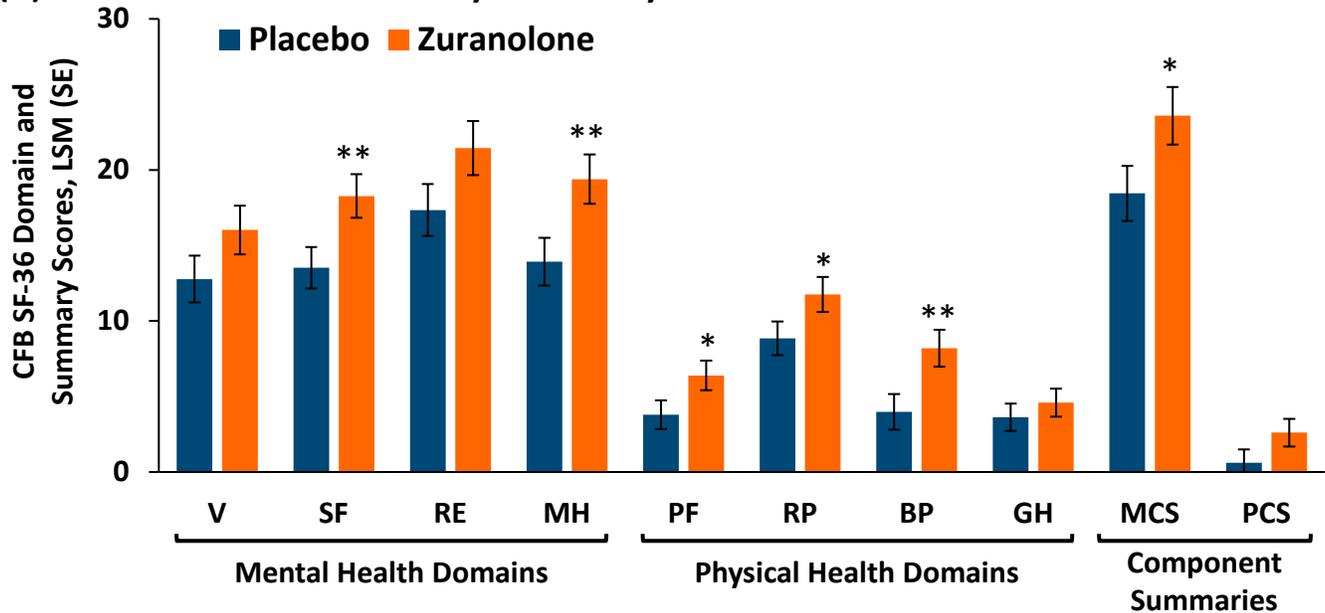
1. [Figure 1](#) Patients' Perceptions of Their Own Functional Health and Well-being as Reported on the SF-36v2
2. [Table 1](#) Summary of NNT Estimates for HRDS-17 Response, Remission, and Sustained Response and Remission and NNH Estimates for Discontinuation Due to AE and Specific TEAEs ($\geq 2\%$ Incidence With Zuranolone and Greater Than That With Placebo).

Disclaimer

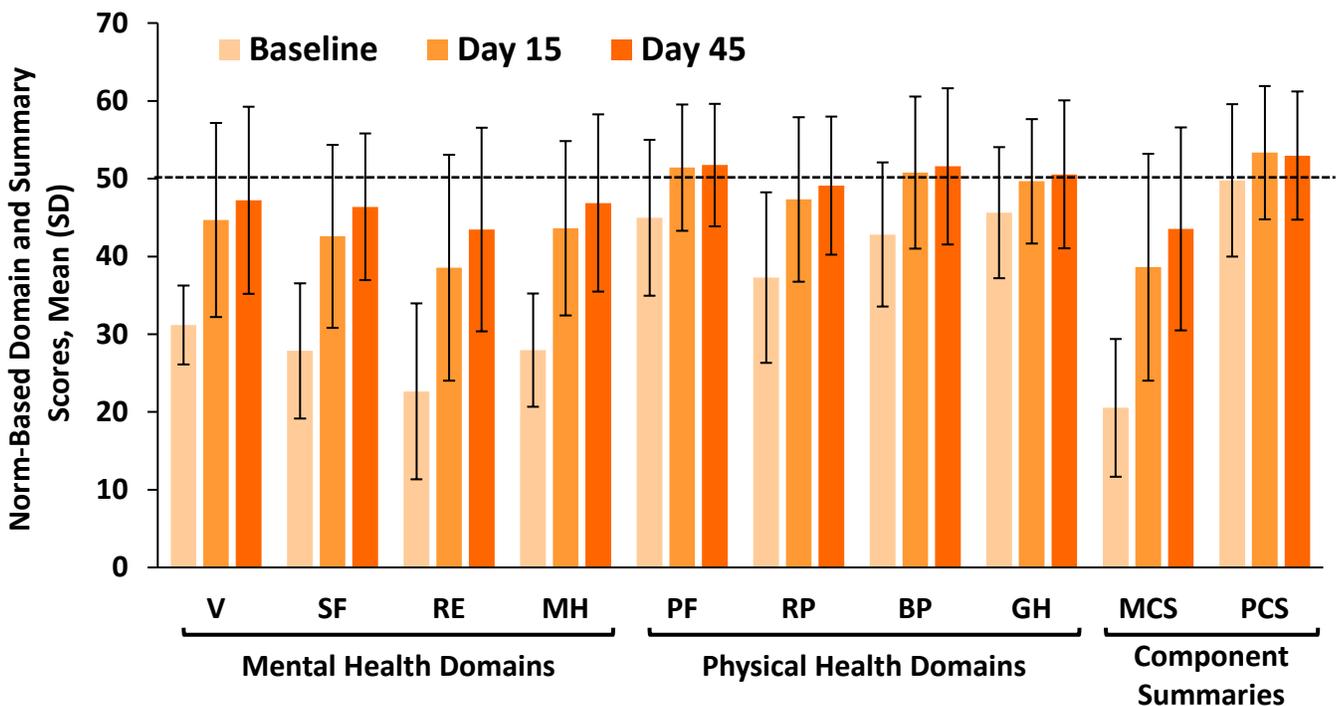
This Supplementary Material has been provided by the authors as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Figure 1. Patients' Perceptions of Their Own Functional Health and Well-being as Reported on the SF-36v2. (A) Change From Baseline in Domain and Summary Scores at Day 45. (B) Mean Domain and Component Summary Scores at Baseline, Day 15, and Day 45 (in Patients Receiving Zuranolone Only).

(A) SF-36 Domain and Summary Scores Day 45



(B) Norm-Based SF-36 Domain and Summary Scores



* $P < .05$; ** $P < .01$ vs placebo. P values have not been adjusted for multiplicity and are nominal.

Abbreviations: BP = Bodily Pain; CFB = change from baseline; GH = General Health; LSM = least squares mean; MCS = Mental Component Score; MH = Mental Health; PCS = Physical Component Score; PF = Physical Functioning; RE = Role Emotional; RP = Role Physical; SD = standard deviation; SE = standard error; SF = Social Functioning; SF-36v2 = 36-Item Short Form Health Survey Instrument version 2; V = Vitality.

Supplementary Table 1. Summary of NNT Estimates for HDRS-17 Response, Remission, and Sustained Response and Remission and NNH Estimates for Discontinuation Due to AE and Specific TEAEs (≥2% Incidence With Zuranolone and Greater Than That With Placebo).

(A) NNT Estimates			
Outcome, n (%) ^a	Placebo (N = 74)	Zuranolone (N = 76)	Associated NNT (95% CI)
HDRS-17 response (day 15)	35 (47.9)	53 (71.6)	5 (3 to 13)
HDRS-17 remission (day 15)	17 (23.3)	33 (44.6)	5 (3 to 17)
Sustained HDRS-17 response (days 15/45)	27 (38.6)	44 (58.7)	5 (3 to 27)
Sustained HDRS-17 remission (days 15/45)	9 (12.7)	28 (37.3)	5 (3 to 10)
(B) NNH Estimates			
Outcome, n (%)	Placebo (N = 73)	Zuranolone (N = 78)	Associated NNH ^b
Treatment discontinuation due to AE	0	1 (1.3)	78
TEAE			
Somnolence	8 (11.0)	12 (15.4)	23
Dizziness	4 (5.5)	6 (7.7)	46
Sedation	0	4 (5.1)	20
Diarrhea	2 (2.7)	5 (6.4)	28
Dry mouth	0	3 (3.8)	26
Upper respiratory infection	1 (1.4)	6 (7.7)	16
Nasopharyngitis	1 (1.4)	3 (3.8)	41
Pain in extremity	1 (1.4)	2 (2.6)	84
Fatigue	1 (1.4)	3 (3.8)	41

^aPercentages were calculated using the numbers of patients with data evaluable at that day as denominator: N = 73 (placebo) and N = 74 (zuranolone) for HDRS-17 response and remission at day 15; N = 70 (placebo) and N = 75 (zuranolone) for sustained HDRS-17 response; and N = 71 (placebo) and N = 75 (zuranolone) for sustained HDRS-17 remission.

^bNot statistically significant versus placebo at the p<0.05 threshold.

Abbreviations: AE = adverse events; CI = confidence interval; HDRS-17 = 17-item Hamilton Depression Rating Scale; NNT = number needed to treat; NNH = number needed to harm; TEAE = treatment-emergent adverse event.