

# Effect of Zuranolone vs Placebo in Postpartum Depression A Randomized Clinical Trial

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**IMPORTANCE** Postpartum depression (PPD) is one of the most common medical complications during and after pregnancy, negatively affecting both mother and child.

**OBJECTIVE** To demonstrate the efficacy and safety of zuranolone, a neuroactive steroid  $\gamma$ -aminobutyric acid receptor-positive allosteric modulator, in PPD.

**DESIGN, SETTING, AND PARTICIPANTS** This phase 3, double-blind, randomized, outpatient, placebo-controlled clinical trial was conducted between January 2017 and December 2018 in 27 enrolling US sites. Participant were women aged 18 to 45 years, 6 months or fewer post partum, with PPD (major depressive episode beginning third trimester or  $\leq 4$  weeks postdelivery), and baseline 17-item Hamilton Rating Scale for Depression (HAM-D-17) score of 26 or higher. Analysis was intention to treat and began December 2018 and ended March 2019.

**INTERVENTIONS** Randomization 1:1 to placebo:zuranolone, 30 mg, administered orally each evening for 2 weeks.

**MAIN OUTCOMES AND MEASURES** Primary end point was change from baseline in HAM-D-17 score for zuranolone vs placebo at day 15. Secondary end points included changes from baseline in HAM-D-17 total score at other time points, HAM-D-17 response ( $\geq 50\%$  score reduction) and remission (score  $\leq 7$ ) rates, Montgomery-Åsberg Depression Rating Scale score, and Hamilton Rating Scale for Anxiety score. Safety was assessed by adverse events and clinical assessments.

**RESULTS** Of 153 randomized patients, the efficacy set comprised 150 patients (mean [SD] age, 28.3 [5.4] years), and 148 (98.7%) completed treatment. A total of 76 patients were randomized to placebo, and 77 were randomized to zuranolone, 30 mg. Zuranolone demonstrated significant day 15 HAM-D-17 score improvements from baseline vs placebo ( $-17.8$  vs  $-13.6$ ; difference,  $-4.2$ ; 95% CI,  $-6.9$  to  $-1.5$ ;  $P = .003$ ). Sustained differences in HAM-D-17 scores favoring zuranolone were observed from day 3 (difference,  $-2.7$ ; 95% CI,  $-5.1$  to  $-0.3$ ;  $P = .03$ ) through day 45 (difference,  $-4.1$ ; 95% CI,  $-6.7$  to  $-1.4$ ;  $P = .003$ ). Sustained differences at day 15 favoring zuranolone were observed in HAM-D-17 response (odds ratio, 2.63; 95% CI, 1.34-5.16;  $P = .005$ ), HAM-D-17 score remission (odds ratio, 2.53; 95% CI, 1.24-5.17;  $P = .01$ ), change from baseline for Montgomery-Åsberg Depression Rating Scale score (difference,  $-4.6$ ; 95% CI,  $-8.3$  to  $-0.8$ ;  $P = .02$ ), and Hamilton Rating Scale for Anxiety score (difference,  $-3.9$ ; 95% CI,  $-6.7$  to  $-1.1$ ;  $P = .006$ ). One patient per group experienced a serious adverse event (confusional state in the zuranolone group and pancreatitis in the placebo group). One patient in the zuranolone group discontinued because of an adverse event vs none for placebo.

**CONCLUSIONS AND RELEVANCE** In this randomized clinical trial, zuranolone improved the core symptoms of depression as measured by HAM-D-17 scores in women with PPD and was generally well tolerated, supporting further development of zuranolone in the treatment of PPD.

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Postpartum depression (PPD) is a perinatal major depressive episode that negatively affects new female parents and their families.<sup>1,2</sup> Although symptoms of PPD affects around 13.2% of new female parents across the US<sup>3</sup> and is among the most common medical complications during and after pregnancy,<sup>3-9</sup> it is underdiagnosed and undertreated<sup>10,11</sup> and can persist for years.<sup>12,13</sup> Complications of untreated PPD include maternal suicide,<sup>14-16</sup> lasting negative effects on infant and child development,<sup>12,17-22</sup> and depression in partners.<sup>23-25</sup>

The pathophysiology of PPD is likely multifactorial,<sup>26,27</sup> with evidence supporting a role for disruption of perinatal  $\gamma$ -aminobutyric acid (GABA) signaling, the major inhibitory signaling pathway of the central nervous system.<sup>28</sup> One potential factor affecting GABAergic signaling and PPD development are dramatic perinatal changes in circulating levels of allopregnanolone, a neuroactive steroid (NAS) GABA<sub>A</sub> receptor (GABA<sub>A</sub>R)-positive allosteric modulator (PAM).<sup>29-32</sup> In brain regions associated with emotion and self-perception, neural network connectivity, supported by GABAergic signaling, is positively correlated with plasma allopregnanolone concentrations in individuals with PPD vs healthy postpartum female individuals.<sup>33</sup> The role of GABAergic signaling is further supported by animal model studies demonstrating PPD-like behaviors in mice lacking the extrasynaptic GABA<sub>A</sub>R  $\delta$  subunit or potassium/chloride cotransporter KCC2, and these PPD models also functionally link GABA with the hypothalamic-pituitary axis, a stress pathway implicated in PPD.<sup>34,35</sup> Administration of a preclinical NAS GABA<sub>A</sub>R PAM that targets both synaptic and extrasynaptic receptors (SAGE-516; Sage Therapeutics, Inc) in late pregnancy reduced PPD-like behaviors in these mouse models, supporting the development of NAS GABA<sub>A</sub>R PAMs in PPD treatment.<sup>36</sup>

Clinical research in the treatment of PPD supports a role for NAS GABA<sub>A</sub>R PAMs. Brexanolone injection, a NAS GABA<sub>A</sub>R PAM, demonstrated reductions in depressive symptoms in 3 double-blind, randomized, placebo-controlled trials and was approved by the US Food and Drug Administration for treatment of adults with PPD.<sup>37,38</sup> Zuranolone (SAGE-217; Sage Therapeutics, Inc) is an investigational NAS GABA<sub>A</sub>R PAM with a similar mechanism of action and a pharmacokinetic profile suitable for once-daily oral dosing.<sup>39</sup> NAS GABA<sub>A</sub>R PAMs have pharmacological profiles and binding sites distinct from benzodiazepines,<sup>40,41</sup> with the ability to modulate the activity of both synaptic and extrasynaptic GABA<sub>A</sub>Rs.<sup>39,42</sup> Therefore, we performed a phase 3, double-blind, randomized, placebo-controlled clinical trial comparing the efficacy and safety of zuranolone vs placebo in the outpatient treatment of adult women with PPD.

## Methods

### Study Design and Participants

Patients were screened at 33 centers in the US (first informed consent, January 4, 2017; final poststudy observation, December 11, 2018), with 27 sites randomizing and dosing at least 1 patient. The trial received institutional review board ap-

### Key Points

**Question** Does treatment with zuranolone reduce depressive symptoms in female individuals experiencing postpartum depression?

**Findings** In this phase 3, double-blind, randomized, placebo-controlled trial of 151 adult women with postpartum depression, patients taking daily zuranolone for 2 weeks displayed greater statistically significant reductions in depressive symptoms compared with placebo at day 15, assessed by change from baseline in the 17-item Hamilton Rating Scale for Depression. Reductions in depressive symptoms were observed by day 3 and sustained at all measured time points through day 45.

**Meaning** Zuranolone provided significant reductions in depressive symptoms and was generally well tolerated, supporting its further development in the treatment of postpartum depression.

proval and was performed in accordance with ethical principles originating in the Declaration of Helsinki<sup>43</sup> and are consistent with International Council for Harmonisation 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 trial was completed on reaching predetermined target enrollment numbers.

### Inclusion/Exclusion Criteria

Adult ambulatory female patients, aged 18 to 45 years old, 6 months or less post partum, with a major depressive episode without psychosis (diagnosed by the Structured Clinical Interview for DSM-5 Axis I Disorders for clinical trials)<sup>1</sup> that began no earlier than the third trimester and no later than the first 4 weeks following delivery, were enrolled. This PPD definition was used in previous clinical trials.<sup>37,38</sup> A baseline 17-item Hamilton Rating Scale for Depression (HAM-D-17) score of 26 or higher was required.<sup>44</sup> Patients taking psychotropic medications used to treat depressive symptoms were required to have been taking a stable dose for more than 30 days prior to day 1 and delay the start/alteration of psychotropic treatment regimens until after the treatment period and day 15 assessments were completed. Patients must have ceased lactating at screening or agreed to cease breastfeeding from just prior to receiving the study drug until 7 days after the last dose. Race/ethnicity was self-reported by patients, or the data were pulled from external medical records, if available. The principal investigator at each site was responsible for recruitment and enrollment of patients. The trial protocol, which contains additional inclusion and full exclusion criteria, is available in [Supplement 1](#).

### Randomization/Masking

Patients were randomized 1:1 to receive zuranolone, 30 mg, or matching placebo capsules for 2 weeks, based on previous studies.<sup>39,45</sup> Randomization codes were generated with a block size of 4 by an independent statistical vendor not affiliated with

Sage Therapeutics, Inc. The randomization scheme was initially performed manually using SAS statistical software version 9.3 (SAS Institute); a decision was then made to contract randomization to an interactive response technology system vendor using SAS statistical software version 9.4 (SAS Institute). Of 153 total randomized patients, 80 were randomized manually and 73 were randomized by interactive response technology implementation. Study site-designated pharmacy staff, responsible for dispensing the study drug, were the only study personnel unblinded to the randomization scheme. All other site personnel were blinded to treatment assignments during the study. In the event of a medical emergency, the clinic pharmacist could reveal the study drug assignment to the investigator, after which the patient could be unmasked and terminated from the study.

### Procedures

The study drug (placebo or zuranolone, 30 mg) was administered once each evening with food. Four initial patients were administered the study drug by a health care professional in a clinic, and the rest of the patients self-administered the study drug at home. Patients unable to tolerate 30 mg of the study drug once daily could be administered 20 mg for the remainder of the treatment period. All assessments were conducted via outpatient clinic visits. Posttreatment follow-up was through day 45.

### Outcome Measures

The primary efficacy end point was the change from baseline in HAMD-17<sup>44</sup> total score at day 15. Secondary efficacy end points included the change from baseline in HAMD-17 total score at all other time points (days 3, 8, 21, and 45) with no modifications, Montgomery-Åsberg Depression Rating Scale (MADRS) score with no modifications,<sup>46</sup> Hamilton Rating Scale for Anxiety (HAM-A) score,<sup>47</sup> HAMD-17 response ( $\geq 50\%$  reduction in score from baseline), HAMD-17 remission (score  $\leq 7$ , which is widely adopted as criteria for remission using this clinician-rated scale of depressive symptoms<sup>48,49</sup>), and Clinical Global Impression Improvement (CGI-I) response (1 indicated very much improved or 2, much improved).<sup>50</sup> Other end points included change from baseline in the Barkin Index of Maternal Functioning (BIMF), a validated measure of patient-reported maternal function within the first year of childbirth that may be used in clinical settings.<sup>51</sup>

Safety and tolerability were evaluated by adverse events (AEs), vital signs, clinical laboratory evaluations, electrocardiogram parameters, and the Columbia-Suicide Severity Rating Scale.<sup>52</sup> Serious AEs were defined as any untoward medical occurrence that resulted in death, was life threatening (at the time of event), required inpatient hospitalization, resulted in persistent or significant disability, or was a congenital anomaly.

### Statistical Analysis

By 2-sided *t* test ( $\alpha$  level of .05), a sample size of approximately 65 evaluable patients per treatment group provided 90% power to detect a placebo-adjusted treatment difference of approximately 4 points in the primary end point as-

suming an SD of 7 points. Assuming a 10% dropout rate and 1:1 randomization ratio, approximately 72 randomized patients per treatment group were required to obtain 130 evaluable patients. The safety set included all patients who received at least 1 dose of the double-blind study drug. The efficacy set, based on intention to treat, included all patients in the safety set who had a valid baseline and at least 1 post-baseline efficacy assessment.

A mixed-effects model for repeated measures including treatment, baseline HAMD-17 total score, baseline antidepressant use, assessment time point, and time point by treatment as explanatory variables was used for analysis of the primary end point. An unstructured covariance structure was used to model the within-patient errors. Secondary (HAMD-17, MADRS, HAM-A scores change from baseline) and other end points (BIMF score) were assessed using the same mixed-effects model for repeated measures as the primary end point. Model-based point estimates (ie, least-squares means), 95% CIs, and *P* values were reported. Treatment comparisons were made between placebo and treatment groups. Categorical secondary end points (HAMD-17 response and remission and CGI-I response) were analyzed by a generalized estimating equations approach. Odds ratios (ORs), 95% CIs, and *P* values were reported. *P* values and 95% CIs for secondary end points, which are highly associated with the primary end point, were not adjusted for multiplicity, and therefore reported as point estimates. Statistical analyses used SAS statistical software version 9.4 (SAS Institute). No imputation was used to estimate missing data (Supplement 1). Analysis began December 2018 and ended March 2019.

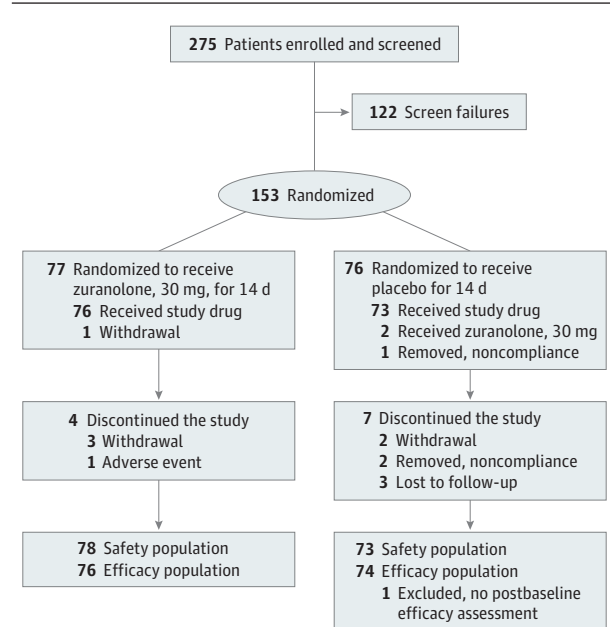
## Results

### Disposition and Demographics

A total of 275 women were screened and enrolled; 153 were randomized (placebo, *n* = 76; zuranolone, *n* = 77; Figure 1). Two patients were randomized but did not receive dosing (zuranolone, *n* = 1 [withdrawal]; placebo, *n* = 1 [noncompliance]). The safety set included 78 patients treated with zuranolone and 73 patients treated with placebo, as 2 patients were randomized to placebo but received at least 1 dose of zuranolone. In the safety set, 76 of 78 patients in the zuranolone group (97%) completed treatment. Reasons for treatment discontinuation in the zuranolone group were AE (*n* = 1) and non-compliance (*n* = 1). Of patients in the zuranolone group who completed treatment, 3 patients' study drug doses were reduced to 20 mg. Of 73 patients receiving placebo, 72 (99%) completed treatment, with no dose reductions and 1 patient was lost to follow-up. One patient in the placebo group did not complete a postbaseline efficacy assessment, resulting in 150 evaluable patients (placebo, *n* = 74; zuranolone, *n* = 76).

Baseline characteristics and demographics were well balanced between treatment groups (efficacy set, Table 1; safety set, eTables 1-5 in Supplement 2). The mean (SD) age was 29.3 (5.4) years in the zuranolone group and 27.4 (5.3) years in the placebo group (range, 18-44 years). Most patients identified as White (placebo group, 54% [40 of 74]; zuranolone group, 58%

Figure 1. CONSORT Diagram



The 122 patients who were considered screen failures were screened but deemed ineligible for the study. Two patients randomized to placebo each received in error 1 dose of zuranolone, 30 mg (1 patient on day 1 and the other on day 3). Both were logged as such for safety analysis, but the patients received placebo at all other time points. Therefore, the safety population included 78 patients treated with zuranolone and 73 patients treated with placebo. Two patients were randomized but did not receive dosing (zuranolone, n = 1 [withdrawal]; placebo, n = 1 [noncompliance]), and 1 patient in the placebo group did not complete a postbaseline efficacy assessment, resulting in an efficacy population of 76 patients in the zuranolone group and 74 patients in the placebo group.

[44 of 76]) or Black/African American (placebo group, 42% [31 of 74]; zuranolone group, 41% [31 of 76]). More than 20% of patients in the placebo (24% [18 of 74]) and zuranolone groups (21% [16 of 76]) identified as Hispanic or Latina. At baseline, 21% (16 of 76) and 18% (13 of 74) of patients in the zuranolone and placebo groups, respectively, were taking stable doses of antidepressant medications.

**Efficacy Outcomes**

**Primary End Point**

The primary end point was achieved. There was a significantly greater reduction from baseline in HAMD-17 total score with zuranolone compared with placebo at day 15 (least-squares mean, -17.8 points vs -13.6 points; 95% CI, -6.9 to -1.5; *P* = .003; effect size, 0.53; **Figure 2**).

**Secondary End Points**

Greater reductions from baseline in HAMD-17 score favoring zuranolone compared with placebo were observed at all measured time points from day 3 through day 45, 4 weeks after treatment cessation (day 3: least-squares means difference, -2.7; 95% CI, -5.1 to -0.3; *P* = .03; day 45: least-squares means difference, -4.1; 95% CI, -6.7 to -1.4; *P* = .003) (**Figure 2**; eTable 6 in **Supplement 2**).

Table 1. Baseline Characteristics of the Efficacy Population

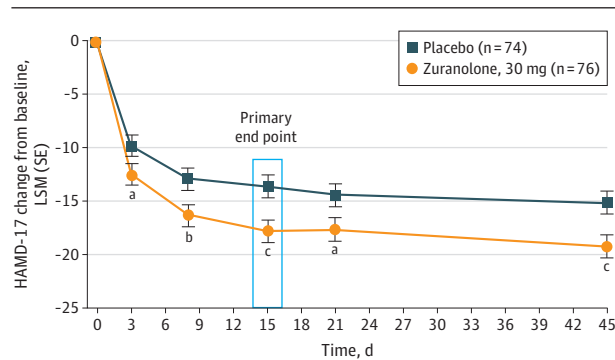
Characteristic	No. (%)	
	Zuranolone, 30 mg (n = 76)	Placebo (n = 74)
Age, mean (SD), y	29.3 (5.4)	27.4 (5.3)
Hispanic/Latina ethnicity	16 (21)	18 (24)
Race		
African American	31 (41)	31 (42)
White	44 (58)	40 (54)
Other <sup>a</sup>	1 (1)	3 (4)
Weight, mean (SD), kg	85.1 (19)	80.2 (24)
BMI, mean (SD)	31.1 (6)	30.3 (8)
Baseline antidepressant use	16 (21)	13 (18)
Onset of PPD		
Third trimester	32 (42)	31 (42)
≤4 wk After delivery	44 (58)	43 (58)
Family history of PPD	10 (13)	10 (14)
Baseline HAMD-17 total score, mean (SD) <sup>b</sup>	28.4 (2)	28.8 (2)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HAMD-17, 17-item Hamilton Rating Scale for Depression; PPD, postpartum depression.

<sup>a</sup> Other includes Asian, Native Hawaiian or Other Pacific Islander, and more than 1 race.

<sup>b</sup> The HAMD-17 scale ranges from 0 to 52, and a higher score indicates increased depression severity.

Figure 2. Least-Squares Mean (LSM) Change From Baseline in the 17-Item Hamilton Rating Scale for Depression (HAMD-17) Score



Treatment with zuranolone, 30 mg, achieved the primary end point of a significant change from baseline HAMD-17 total score at day 15 compared with placebo using mixed-effects model for repeated measures. HAMD-17 total score at time points other than day 15 were secondary end points, not adjusted for multiplicity and therefore reported as point estimates, which also showed sustained improvements for the zuranolone group compared with the placebo group.

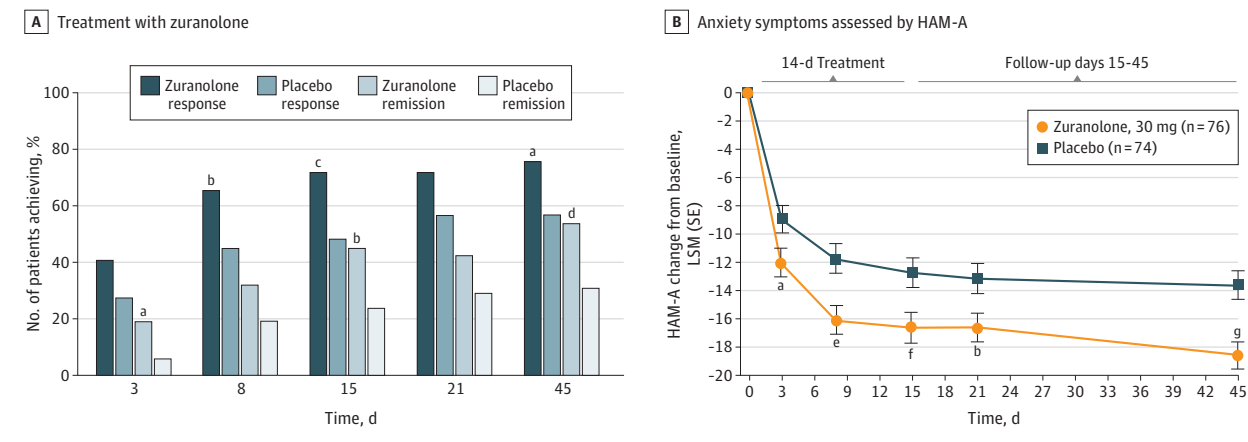
<sup>a</sup> *P* = .03.

<sup>b</sup> *P* = .01.

<sup>c</sup> *P* = .003.

Day 15 secondary end points supported the primary end point, including a sustained greater proportion of patients achieving HAMD-17 response and remission with zuranolone compared with placebo (response: 72% [53 of 74] in the zuranolone group vs 48% [35 of 73] in the placebo group; OR, 2.6;

Figure 3. HAMD-17 Response, HAMD-17 Remission, and LSM Change From Baseline in HAM-A Scores



Key secondary end points were not adjusted for multiplicity, and *P* values are reported as point estimates. A, Treatment with zuranolone, 30 mg, resulted in a greater percentage of patients achieving 17-item Hamilton Rating Scale for Depression (HAMD-17) response (days 8, 15, and 45) and HAMD-17 remission (days 3, 15, and 45) compared with placebo. HAMD-17 response is defined as a 50% or greater reduction in total score from baseline, and HAMD-17 remission is defined as total score of 7 or less. B, Sustained improvements in anxiety symptoms as assessed by Hamilton Rating Scale for Anxiety (HAM-A) were observed across the treatment and follow-up periods in the zuranolone group compared with the placebo group. LSM indicates least-squares mean.

<sup>a</sup> *P* = .02.

<sup>b</sup> *P* = .01.

<sup>c</sup> *P* = .005.

<sup>d</sup> *P* = .009.

<sup>e</sup> *P* = .001.

<sup>f</sup> *P* = .006.

<sup>g</sup> *P* < .001.

95% CI, 1.3-5.2; *P* = .005; remission: 45% [33 of 74] in the zuranolone group vs 23% [17 of 73] in the placebo group; OR, 2.5; 95% CI, 1.2-5.2; *P* = .01 (Figure 3A; eTables 7 and 8 in Supplement 2). HAMD-17 score change from baseline by predefined baseline subgroups at day 15 were similar to overall HAMD-17 score analyses (race, age, stable concomitant antidepressant use, body mass index, onset of PPD, and family history of PPD; eFigure 1 in Supplement 2). There was also a sustained larger reduction from baseline in MADRS score with zuranolone vs placebo at day 15 (least-squares means difference, -4.6; 95% CI, -8.3 to -0.8; *P* = .02) (eFigure 2 in Supplement 2). Improvements in anxiety (HAM-A) and global functioning (CGI-I response) were observed at day 15. A sustained larger reduction from baseline in HAM-A score favored zuranolone compared with placebo at day 15 (least-squares means difference, -3.9; 95% CI, -6.7 to -1.1; *P* = .006) (Figure 3B). Sustained greater increase in CGI-I response rate was observed for zuranolone compared with placebo at day 15 (72% [53 of 74] in the zuranolone group vs 52% [38 of 73] in the placebo group; OR, 2.2; 95% CI, 1.1-4.3; *P* = .03) (eFigure 3 in Supplement 2).

At day 3, a higher percentage of patients in the zuranolone group achieved HAMD-17 remission vs the placebo group (19% [14 of 74] in the zuranolone group vs 5% [4 of 74] in the placebo group; OR, 3.9; 95% CI, 1.2-12.2; *P* = .02; eTable 8 in Supplement 2). The change from baseline in HAM-A score favoring zuranolone vs placebo was also apparent at day 3 (least-squares means difference, -3.1; 95% CI, -5.7 to -0.6; *P* = .02; Figure 3B).

At day 45, 4 weeks after study drug cessation, HAMD-17 response (75% [55 of 73] in the zuranolone group vs 57% [39 of 69] in the placebo group; OR, 2.3; 95% CI, 1.1-4.6; *P* = .02)

and HAMD-17 remission (53% [39 of 73] in the zuranolone group vs 30% [21 of 69] in the placebo group; OR, 2.5; 95% CI, 1.3-5.0; *P* = .009) were sustained in the zuranolone vs placebo group (Figure 3; eTables 7 and 8 in Supplement 2). During the follow-up period, only a small proportion (6 patients [7.9%] and 4 patients [5.4%] in the zuranolone and placebo groups, respectively) had new antidepressant medication treatment initiated by investigators. There were sustained larger reductions from baseline in MADRS and HAM-A scores in the zuranolone group vs placebo at day 45 (MADRS: least-squares means difference, -5.8; 95% CI, -9.4 to -2.2; *P* = .002; HAM-A: least-squares means difference, -5.0; 95% CI, -7.5 to -2.4; *P* < .001) (eFigure 3 in Supplement 2; Figure 3).

In addition to assessing clinician-rated measures of depression, anxiety, and global function, the patient-reported BIMF scores were assessed for maternal function. Numerically greater increases in BIMF scores were observed for zuranolone vs placebo at all time points, with statistical significance at day 45 (least-squares means difference, 7.2; 95% CI, 1.3-13.0; *P* = .02) (eTable 9 in Supplement 2).

### Safety and Tolerability

Zuranolone was generally well tolerated (Table 2). The most common treatment-emergent AEs in the zuranolone group ( $\geq 5\%$ ) were somnolence (15% [12 of 78]), headache (9% [7 of 78]), dizziness (8% [6 of 78]), upper respiratory tract infection (8% [6 of 78]), diarrhea (6% [5 of 78]), and sedation (5% [4 of 78]). The most common treatment-emergent AEs in the placebo group ( $\geq 5\%$ ) were headache (12% [9 of 73]), somnolence (11% [8 of 73]), nausea (8% [6 of 73]), dizziness (6% [4 of

Table 2. Treatment-Emergent Adverse Events (TEAEs)<sup>a</sup>

Patients reporting TEAE	No. (%)	
	Zuranolone, 30 mg (n = 78)	Placebo (n = 73)
Any AE	47 (60)	38 (52)
Severe AE	3 (4)	3 (4)
Serious AE	1 (1)	1 (1)
AE drug discontinuation	1 (1)	0
Death	0	0
Most common TEAEs, ≥5% patients occurring in either study arm		
Somnolence	12 (15)	8 (11)
Headache	7 (9)	9 (12)
Dizziness	6 (8)	4 (6)
Upper respiratory tract infection	6 (8)	1 (1)
Diarrhea	5 (6)	2 (3)
Sedation	4 (5)	0
Nausea	3 (4)	6 (8)
Vomiting	1 (1)	4 (6)
Abnormal dreams	0	4 (6)
Hyperhidrosis	0	4 (6)

Abbreviation: AE, adverse event.

<sup>a</sup> A TEAE is an AE with onset after the start of study drug or worsening of preexisting medical condition or AE with onset after the start of study drug. Severe AEs were defined as AEs that were incapacitating, with inability to perform normal activities. Serious AEs were defined as any untoward medical occurrence resulting in death, was life threatening (at time of event), required inpatient hospitalization, resulted in persistent or significant disability, or was a congenital anomaly. Data shown are from the safety population.

73]), vomiting (6% [4 of 73]), abnormal dreams (6% [4 of 73]), and hyperhidrosis (6% [4 of 73]).

In both treatment groups, most treatment-emergent AEs were mild or moderate. Three patients in the zuranolone group experienced severe treatment-emergent AEs (sedation, n = 1; confusional state, n = 1; migraine, n = 1), and 3 patients in the placebo group experienced severe treatment-emergent AEs (back pain/muscle spasms, n = 1; headache/oropharyngeal pain, n = 1; menorrhagia, n = 1). Two patients experienced serious AEs. One patient in the zuranolone group, with no record of other medical or psychiatric conditions except for PPD, experienced a confusional state on day 3, involving inability to remember the exact sequence of the day's events, along with sedation, which resolved within 7 hours. Following dose interruption on the day of the serious AE and reduction to 20 mg the following day (day 4), the patient continued treatment and completed the study without further incident. One patient in the placebo group experienced pancreatitis on day 32 of the follow-up period that was resolved on day 36 with cholecystectomy. In the zuranolone group, 1 patient discontinued because of an AE (intermittent sedation).

No notable or clinically significant changes in vital signals, electrocardiograms, or clinical laboratory parameters associated with any clinical findings were reported or resulted in study drug dose adjustment or discontinuation. No evidence for increased suicidal ideation or suicidal behavior was observed compared with baseline, measured by the Columbia-

Suicide Severity Rating Scale. There were no medical emergencies requiring unblinding of any patient's study drug and no evidence of withdrawal based on adverse events and vital signs.

## Discussion

In this first phase 3, randomized, placebo-controlled outpatient trial in women with PPD, zuranolone demonstrated rapid (by day 3), clinically meaningful, and sustained (at all measured time points through day 45) antidepressant effects, as well as rapid and sustained improvements in anxiety and improved global and maternal functioning compared with placebo, despite the relatively high placebo response observed in this trial.

The rapid antidepressant effects, along with previous bexanalone injection clinical trials, support the development of NAS GABA<sub>A</sub>R PAMs as PPD therapies and potential fast-acting antidepressants.<sup>37,38,53</sup> The mechanism of rapid antidepressant onset has yet to be completely elucidated.<sup>54</sup> Currently, none of the monoaminergic antidepressants (eg, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, or atypical antidepressants) have specific indications for PPD. A recent meta-analysis of controlled clinical trials of selective serotonin reuptake inhibitors in PPD reported that the strength of available evidence was low and inconclusive of whether selective serotonin reuptake inhibitors were more effective than psychosocial intervention, while demonstrating higher response and remission rates than placebo.<sup>55</sup> Despite these limitations, current PPD standard-of-care pharmacotherapies are antidepressants approved for major depressive disorder treatment, which are often associated with delayed onset of response and/or failure to achieve remission.<sup>56-58</sup> Even with dosing cessation after 2 weeks, zuranolone demonstrated sustained depressive symptom reduction over all measured time points during the 45-day study period, a high proportion of patients remained in remission over the study period, and a small proportion of patients initiated new antidepressant medications during the follow-up period. This sustained effect is clinically meaningful and similar to the effects observed in bexanalone injection studies.<sup>38</sup> Improvements in anxiety, a common PPD symptom/comorbidity,<sup>59</sup> and in clinician-measured global functioning (CGI-I) were also sustained through day 45. Notably, although PPD diagnosis requires that symptoms cause impaired functioning,<sup>1</sup> standard clinician-rated trial instruments may only measure reductions in depressive symptoms, not functioning.<sup>44,46,60</sup> Zuranolone was associated with clinically meaningful improvements in postpartum maternal functioning at day 45 using the patient-reported BIMF score, suggesting an overall treatment effect.<sup>51</sup> Although the persistence of the zuranolone effect beyond 45 days is currently unknown, it suggests the potential for short-term, outpatient utility of zuranolone in PPD.

Zuranolone was generally well tolerated. No loss of consciousness events or AEs related to drug discontinuation after treatment/withdrawal syndrome or worsening of depres-

sion were reported. The results of this double-blind, randomized, placebo-controlled clinical trial with zuranolone suggest the potential for an oral NAS GABA<sub>A</sub>R PAM in the treatment of PPD. The need for rapid and effective resolution of PPD symptoms cannot be overstated, given the prevalence of PPD and the negative effect untreated PPD can have on mothers, children, and partners.

### Limitations

The study population represents a US population that may not be generalizable to broader global populations of women with PPD, although the study did enroll a higher proportion of African American and Hispanic individuals than generally observed in clinical trials. Since the follow-up period ended at day 45, the sustainability of any treatment response beyond this period is unknown. An ongoing open-label study with zuranolone will investigate the sustainability of effects and need for retreatment in major depressive disorder as a secondary end point (NCT03864614). Finally, patients were not permitted to

breastfeed during the treatment period and for 1 week after treatment ended (21 days), so the safety of breastfeeding while being treated with zuranolone is currently unknown.

### Conclusions

In this phase 3 randomized clinical trial of women with PPD, zuranolone achieved its primary end point of a statistically significant change from baseline in HAM-D-17 total score compared with placebo at day 15. Zuranolone showed rapid (by day 3), sustained (all measured time points through day 45), and clinically meaningful improvements in depressive symptoms, anxiety, and global and maternal functioning and was generally well tolerated. Zuranolone has the potential to become a novel treatment for patients with PPD. Moreover, the findings of this study, along with prior PPD studies,<sup>37,38</sup> support the potential for the development and therapeutic use of NAS GABA<sub>A</sub>R PAMs in the treatment of PPD.

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**Correction:** This article was corrected on May 11, 2022, to fix an error in Figure 3 and on November 30, 2022, to fix an error in the Results section.

**Author Contributions:** Drs Deligiannidis and Gunduz-Bruce had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Concept and design:** Gunduz-Bruce, Doherty, Jonas, Li, Sankoh, Campbell, Kanes.

**Acquisition, analysis, or interpretation of data:** Deligiannidis, Meltzer-Brody, Gunduz-Bruce, Jonas, Li, Sankoh, Silber, Werneburg, Kanes, Lasser.

**Drafting of the manuscript:** Deligiannidis, Meltzer-Brody, Doherty, Sankoh, Campbell, Werneburg, Kanes, Lasser.

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**Obtained funding:** Campbell.

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**Supervision:** Gunduz-Bruce, Doherty, Jonas, Sankoh, Silber, Campbell, Kanes, Lasser.

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Neuropsychopharmacology; December 10 and 11, 2019; Orlando, Florida; Congrès de l'Encéphale 2020; January 23, 2020; Paris, France; 40th Annual Society for Maternal-Fetal Medicine Meeting; February 6, 2020; Grapevine, Texas; joint congress of the Working Group on Neuropsychopharmacology and Pharmacopsychiatry and the German Society for Biological Psychiatry; March 4, 2020; Berlin, Germany; American Society of Clinical Psychopharmacology Annual Meeting; May 29, 2020; virtual; Society of Biological Psychiatry Annual Meeting; May 1, 2020; virtual; European College of Neuropsychopharmacology Annual Meeting; September 12, 2020; virtual; Psych Congress Annual Meeting; September 10, 2020; virtual.

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