Improvement in HAMD-17 Subscale Scores With 14-Day Treatment Course of Zuranolone in Postpartum Depression: Results From the SKYLARK Study

J-06

Kristina M. Deligiannidis,[1,2] Bassem Maximos,[3] Mona Kotecha,[4] Sigui Li,[5] Theresa Vera,[5] Amy Bullock[5]

[1]Zucker Hillside Hospital, Northwell Health, Glen Oaks, NY, USA; [2]Feinstein Institutes for Medical Research, Northwell Health, Manhasset, NY, USA; [3]Maximos OB/GYN, League City, TX, USA; [4]Biogen Inc., Cambridge, MA, USA; [5]Sage Therapeutics, Inc., Cambridge, MA, USA

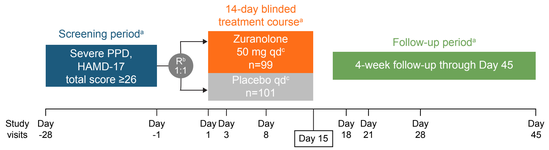
Introduction

- Postpartum depression (PPD) is a serious perinatal complication; symptomatic PPD has an overall global prevalence of 17.2% and can negatively affect maternal and infant health.[1,2]
- The Hamilton Depression Rating Scale, also known as the HAMD-17, is a 17-item scale that assesses the severity of and change in depressive symptoms.[3]
- Zuranolone is an investigational neuroactive steroid and positive allosteric modulator of synaptic and extrasynaptic $GABA_A$ receptors in clinical development as an oral, once-daily, 14-day treatment course for adults with PPD (NEST clinical development program) or major depressive disorder (LANDSCAPE development program).[4]
- In the previously published ROBIN study, which is a part of the NEST program, zuranolone improved symptoms of depression as measured by HAMD-17 scores in women with severe PPD and was generally well tolerated.[5]
- SKYLARK is a phase 3, randomized, double-blind, placebo-controlled trial (NCT04442503) that evaluated zuranolone 50 mg in adult patients with severe PPD.[6]
  - The primary endpoint, change from baseline (CFB) in HAMD-17 total score at Day 15, was met and zuranolone was generally well tolerated.[6]
- In this poster, we present HAMD-17 subscale data from the SKYLARK study to illustrate the effect of zuranolone 50 mg on depressive symptoms across multiple domains in adult patients with PPD.

Methods

- Eligible adults aged 18-45 years with severe PPD (as assessed by HAMD-17 total score of >26) were randomized 1:1 to oral, once-daily zuranolone 50 mg or placebo for 14 days (Figure 1).[4]
- Patients on baseline antidepressant therapy were permitted to continue if they were on a stable dose ≥30 days prior to Day 1 and agreed to continue on a stable dose through the completion of Day 45 assessments.
- Individual items from the HAMD-17 are grouped in subscales (Bech-6, Maier, Core Depression, Anxiety), which measure different aspects of depression presentation (Table 1).[7,8]
- Primary and secondary endpoints are shown in Figure 1.
  - Primary and key secondary endpoints were controlled for multiplicity.
- Subscales were analyzed separately by a mixed model for repeated measures (MMRM).
  - The Bech-6 subscale score is the sum of the following symptom scores: depressed mood, feelings of guilt, work and activities, retardation, anxiety psychic, and somatic symptoms general/22 × 100.
  - The Maier subscale score is the sum of the following symptom scores: depressed mood, feelings of guilt, work and activities, retardation, agitation, and anxiety psychic/24 × 100.
  - The Core subscale score is the sum of the following symptom scores: depressed mood, feelings of guilt, suicide, work and activities, and retardation/20 × 100.
  - The Anxiety subscale score is the sum of the following symptom scores: anxiety (psychic and somatic), somatic symptoms (gastrointestinal [GI] and general), hypochondriasis, and insight/18 × 100.
  - Other secondary endpoints, including Core Depression, Anxiety, Bech-6, and Maier scores, were not adjusted for multiplicity and are to be interpreted with nominal p values.

FIGURE 1. SKYLARK STUDY DESIGN



Primary Endpoint
- CFB in HAMD-17 total score at Day 15

Key Secondary Endpoints
- CFB in HAMD-17 total score at Days 3, 28, and 45
- CFB in CGI-S score at Day 15

Presented Additional Secondary Endpoints
- CFB in HAMD-17 subscale scores at Day 15
- Incidence of TEAEs

Inclusion:
- Major depressive episode began between the 3rd trimester of pregnancy and 4 weeks postpartum
- Good physical health
- ≤12 months post partum at screening and Day 1

Exclusion:
- Patient was at significant risk of suicide as determined by investigator
- History of sleep apnea, nonfebrile seizures, bipolar disorder, schizophrenia, and/or schizoaffective disorder
- Active psychosis

CGI-S, Clinical Global Impression-Severity; qd, once daily; R, randomization; TEAE, treatment-emergent adverse event.
[a]Dose could be reduced to 40 mg as needed based on tolerability. [b]Randomization was stratified based on antidepressant treatment (ADT) use at baseline. [c]Zuranolone 50 mg and placebo administered in the evening with fat-containing food.

TABLE 1. INDIVIDUAL ITEMS ASSESSED IN HAMD-17 TOTAL SCORE AND UNIPOLAR DEPRESSION SUBSCALES

Individual Item	HAM-D total score	Bech-6	Maier	Core	Anxiety
Depressed mood	X	X	X	X	
Guilt	X	X	X	X	
Work and activities	X	X	X	X	
Retardation	X	X	X	X	
Suicide	X			X	
Agitation	X		X		
Anxiety, psychic	X	X	X		X
Anxiety, somatic	X				X
Somatic, general	X	X			X
Somatic, GI	X				X
Hypochondria	X				X
Loss of weight	X				
Insomnia - early	X				
Insomnia - middle	X				
Insomnia - late	X				
Genital symptoms	X				
Insight	X				X

Results

- 200 patients were randomized, 196 received study drug, and 195 had valid baseline and ≥1 postbaseline efficacy assessments (Table 2); 180 patients completed treatment.
- Demographics and baseline characteristics were generally well balanced between treatment groups. This was a diverse patient population with most patients experiencing their first episode of PPD.
- Both the zuranolone and placebo groups had the same incidence of baseline antidepressant usage and similar Hamilton Anxiety Rating Scale (HAM-A) scores.
- The full patient disposition is available in a previous publication.[6]
- In the zuranolone group, 86% of patients completed the study and 14 patients withdrew. In the placebo group, 88% of patients completed the study and 12 withdrew.

TABLE 2. BASELINE DEMOGRAPHICS

	Zuranolone 50 mg (n=98[a])	Placebo (n=97[a])
Age, mean (SD), years	30.0 (5.90)	31.0 (5.95)
Race, n (%)		
White	68 (69.4)	69 (70.4)
Black/African-American	25 (25.5)	18 (18.4)
Other[b]	5 (5.1)	11 (11.2)
Country, n (%)		
US	95 (96.9)	96 (98.0)
Spain and UK	3 (3.1)	2 (2.0)
Onset of PPD, n (%)		
Third trimester	34 (34.7)	31 (31.6)
Postpartum	64 (65.3)	67 (68.4)
History of PPD, n (%)		
First episode	81 (82.7)	87 (88.8)
Recurrent PPD episode	17 (17.3)	11 (11.2)
Baseline ADT use, n (%)	15 (15.3)	15 (15.3)
HAMD-17 at baseline, mean (SD)	28.6 (2.49)	28.8 (2.34)
HAM-A at baseline, mean (SD)	24.4 (6.01)	24.7 (5.96)

SD, standard deviation.
[a]Represents the safety set, which comprised patients who received ≥1 dose of the assigned blinded treatment (placebo or zuranolone). [b]Other included Asian, American Indian, Alaska Native, Native Hawaiian, Pacific Islander, multiple, other race, and/or not reported.

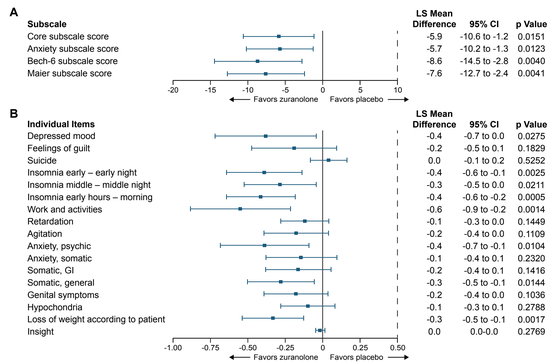
- At Day 15, patients who received zuranolone had a statistically significant and clinically meaningful improvement in depressive symptoms as assessed by CFB in HAMD-17 total score compared with patients who received placebo (least squares [LS] mean difference: -4.0; p=0.0007).[6]
- Improvement in all subscales was observed starting at Day 3 (Table 3).
- Additionally, patients receiving a 14-day treatment course of zuranolone showed significant improvements across all HAMD-17 subscales versus placebo (LS mean [standard error (SE)] CFB treatment difference) at Day 15 (Figure 2A) that were observed at all measured time points through Day 45 (Table 3).
- These improvements were observed in individual items as well, such as insomnia, work and activities, and depressed mood (Figure 2B).

TABLE 3. DIFFERENCES IN CFB IN HAMD-17 SUBSCALES FOR ZURANOLONE VERSUS PLACEBO AT DAY 3 AND DAY 45

DAY 3	Zuranolone 50 mg (n=98)	Placebo (n=97)
Core subscale score		
LS mean (95% CI)	-14.7 (-17.5 to -11.8)	-10.3 (-13.2 to -7.5)
LS mean (95% CI) [p value], ZRN-PBO	-4.4 (-8.4 to -0.3) [0.0356]	
Anxiety subscale score		
LS mean (95% CI)	-16.9 (-19.6 to -14.3)	-10.6 (-13.3 to -8.0)
LS mean (95% CI) [p value], ZRN-PBO	-6.3 (-10.1 to -2.6) [0.0010]	
Bech-6 subscale score		
LS mean (95% CI)	-18.2 (-21.5 to -14.8)	-11.9 (-15.3 to -8.5)
LS mean (95% CI) [p value], ZRN-PBO	-6.3 (-11.1 to -1.5) [0.0106]	
Maier subscale score		
LS mean (95% CI)	-16.8 (-19.8 to -13.8)	-11.3 (-14.3 to -8.2)
LS mean (95% CI) [p value], ZRN-PBO	-5.6 (-9.8 to -1.3) [0.0110]	
DAY 45		
Core subscale score		
LS mean (95% CI)	-33.3 (-36.8 to -29.9)	-25.1 (-28.5 to -21.7)
LS mean (95% CI) [p value], ZRN-PBO	-8.2 (-13.0 to -3.4) [0.0010]	
Anxiety subscale score		
LS mean (95% CI)	-31.1 (-34.6 to -27.6)	-24.4 (-27.9 to -20.9)
LS mean (95% CI) [p value], ZRN-PBO	-6.7 (-11.7 to -1.8) [0.0079]	
Bech-6 subscale score		
LS mean (95% CI)	-41.2 (-45.5 to -36.9)	-30.7 (-35.0 to -26.4)
LS mean (95% CI) [p value], ZRN-PBO	-10.5 (-16.5 to -4.4) [0.0008]	
Maier subscale score		
LS mean (95% CI)	-38.0 (-41.7 to -34.3)	-28.9 (-32.6 to -25.1)
LS mean (95% CI) [p value], ZRN-PBO	-9.2 (-14.4 to -3.9) [0.0008]	

CI, confidence interval; PBO, placebo; ZRN, zuranolone.
Model used is the MMRM with treatment (zuranolone or placebo), baseline HAM-D core subscale score, ADT use at baseline (Yes or No), assessment time point, and time point-by-treatment interaction as fixed effects with unstructured covariance structure. A negative change indicates improvement. p Values are nominal.

FIGURE 2. CFB IN HAMD-17 FOR SUBSCALES (A) AND INDIVIDUAL ITEMS (B) AT DAY 15 BY TREATMENT GROUP (FAS)



FAS, full analysis set.
The HAMD-17 total score was calculated as the sum of the 17 individual item scores. A lower score indicates better mental health; a negative change indicates improvement. Model used is the MMRM with treatment (zuranolone or placebo), baseline HAMD-17 individual score, ADT use at baseline (Yes or No), assessment time point, and time point-by-treatment interaction as fixed effects. FAS = all randomized patients in the safety set with valid baseline and at least 1 postbaseline efficacy evaluation (zuranolone, n=98; placebo, n=97). Count of 183 patients. p Values are nominal.

- The majority of TEAEs were mild or moderate in severity (Table 4) and were consistent with previous studies of zuranolone.
- Loss of consciousness was not reported during the study.
- There was no evidence of increased suicidal ideation/behavior compared with baseline as measured by the Columbia Suicide Severity Rating Scale (data not shown).
- Additionally, there was no evidence of withdrawal symptoms as assessed by the Physician Withdrawal Checklist (PWC-20; data not shown) or TEAEs.

TABLE 4. SAFETY AND TOLERABILITY

	Zuranolone 50 mg (n=98) n (%)	Placebo (n=98) n (%)
TEAEs, n (%)	65 (66.3)	52 (53.1)
Mild AE	33 (33.7)	39 (39.8)
Moderate AE	29 (29.6)	12 (12.2)
Severe AE	3 (3.1)	1 (1.0)
SAE	2 (2.0)	0
AEs leading to dose reduction[a]	16 (16.3)	1 (1.0)
AEs leading to treatment discontinuation[b]	4 (4.1)	2 (2.0)
AEs leading to withdrawal from study	1 (1.0)	1 (1.0)
TEAEs incidence (>5% in either treatment group) through Day 45, n (%)		
Somnolence	26 (26.5)	5 (5.1)
Dizziness	13 (13.3)	10 (10.2)
Sedation	11 (11.2)	1 (1.0)
Headache	9 (9.2)	13 (13.3)
Diarrhea	6 (6.1)	2 (2.0)
Nausea	5 (5.1)	6 (6.1)
Urinary tract infection	5 (5.1)	4 (4.1)
COVID-19	5 (5.1)	0

SAE, serious adverse event.
[a]No deaths occurred during the study in either the placebo or zuranolone groups. The most common AEs leading to dose reduction in the zuranolone group included somnolence (n=7), dizziness (n=6), and sedation (n=3); 14/16 patients whose dose was reduced completed the study. [b]Discontinuation of blinded treatment occurred during the 2-week treatment course. The most common AE leading to treatment discontinuation in the zuranolone group was somnolence.

Conclusions

- In SKYLARK, a 14-day treatment course of zuranolone 50 mg was associated with rapid improvements in depressive symptoms as early as Day 3 in patients with PPD across multiple HAMD-17 subscales.
  - These improvements were observed at Day 15 and were sustained through Day 45.
- Zuranolone was generally well tolerated, with most TEAEs being mild or moderate in severity.
- These results, combined with other available clinical data,[5,6] support the potential of zuranolone as an oral, novel, rapid-acting treatment option for adult patients with PPD.

References

1. Wang Z, et al. *Transl Psychiatry*. 2021; https://doi.org/10.1038/s41398-021-01663-6.
2. Shapiro AF, et al. *Early Child Dev Care*. 2020;190:1918-1930.
3. Hamilton M, et al. *J Neurol Neurosurg Psychiatr*. 1960;23:56-62.
4. Althaus AL, et al. *Neuropharmacology*. 2020;181:108333.
5. Deligiannids K, et al. *JAMA*. 2021;78(9):951-959.
6. Deligiannids K, et al. *Am J Psychiatry*. 2023. In press.
7. Bech P, et al. *Acta Psychiatr Scand*. 1981;63:290-299.
8. Maier W, Phillip M. *Pharmacopsychiatry*. 1985;18:114-115.

Acknowledgments

Medical writing and editorial support were provided by Parexel International and funded by Sage Therapeutics, Inc., and Biogen Inc. This study was sponsored by Sage Therapeutics, Inc., and Biogen Inc. We would like to thank the patients and their families for helping us reimagine brain health.

Disclosures: KD reports grants awarded to Zucker Hillside Hospital/Feinstein Institutes for Medical Research during the conduct of the zuranolone clinical trials; serves as a consultant to Sage Therapeutics, Inc., Brii Biosciences, GH Research, and BrainifyAI; and receives grants from the NIH and royalties from an NIH employee invention outside of the presented study. **BM** reports receiving research support from Sage Therapeutics, Inc., during the conduct of the zuranolone clinical trials; serves as a consultant to Sage Therapeutics, Inc.; reports speaker program compensation from Sage Therapeutics, Inc., and Evofem Biosciences; has received medical writing services from Sage Therapeutics, Inc., Evofem Biosciences, and Mycovia Pharmaceuticals; and holds stock in Sage Therapeutics, Inc., as part of his retirement account. **MK** is an employee of Biogen Inc. and may hold stock. **SL**, **TV**, and **AB** are employees of Sage Therapeutics, Inc., and may hold stock and/or stock options.

American College of Obstetricians and Gynecologists Annual Clinical & Scientific Meeting, Baltimore, MD, USA
May 19–21, 2023

drmaximos@maximosobgyn.com

MRC-217-01211