# Efficacy and Safety of Zuranolone 50 mg in Postpartum Depression: SKYLARK Study, a Double-blind, Placebo-controlled Randomised, Phase 3 Study

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# Disclosures

- **Kristina Deligiannidis, MD,** serves as a consultant to Sage Therapeutics, Inc., Brii Biosciences, Inc., and GH Research Ireland, Ltd, 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 also received grants from NIH and Vorso Corporation and royalties from an NIH employee invention outside of the submitted work.

- **Samantha Meltzer-Brody, MD, MPH,** is an investigator on the zuranolone and brexanolone trials. UNC receives research funding from Sage Therapeutics, Inc. She receives grant funding from NIH and PCORI. She is also a consultant to Modern Health, EmbarkNeuro, and WebMD.

- **Bassem Maximos, MD,** was a principal investigator of the SKYLARK clinical trial and received grants from Sage Therapeutics, Inc., to conduct the study and treat patients. Dr. Maximos is compensated for participating in advisory meetings with Sage Therapeutics, Inc., is compensated as a member of Sage Therapeutics, Inc., and Evofem speaker programs, and has retirement funds that may include limited stocks in Sage Therapeutics, Inc., and other pharmaceutical companies publicly traded.

- **E. Quinn Peeper, MD,** has no disclosures.

- **Rob Lasser, MD, MBA, Amy Bullock, PhD, Manny Garcia, MD, FAPA, Sigui Li, MS, Nilanjana Rana, MD, and James Doherty, PhD,** are employees of Sage Therapeutics, Inc., and may hold stock and/or stock options.

- **Mona Kotecha, MD, Fiona Forrestal, BSc, MSc, and Bridgette Leclair, PharmD,** are employees of Biogen Inc. and may hold stock.

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# Objective

- To present the zuranolone 50 mg efficacy and safety data from SKYLARK, a double-blind, placebo-controlled randomised, Phase 3 study in adults with postpartum depression (PPD)

# Background

- Postpartum depression (PPD) affects approximately 17.2% of women globally, with adverse effects on maternal and infant health.[1,2]
- The pathogenesis of PPD involves an interplay of genetic, biological, hormonal, environmental, and psychological factors; however, altered levels of allopregnanolone (ALLO), a neuroactive steroid (NAS), disrupted γ-aminobutyric acid (GABA) signaling, and resting-state functional connectivity are thought to be driving contributors to the etiology of PPD.[3-7]
- Psychotherapy and antidepressant therapies (ADTs) are the current standard of care for PPD.
- Zuranolone is a synthetic analogue of ALLO and positive allosteric modulator (PAM) of both synaptic and extrasynaptic $GABA_A$ receptors in clinical development as an oral, once-daily, 14-day treatment course for adults with PPD and MDD.[a]

[a] Studies included 3 MDD studies (MDD-201B, NCT03000530; MOUNTAIN, NCT03672175; WATERFALL, NCT04440490) and 2 PPD studies (ROBIN, NCT02978326; SKYLARK, NCT04442503).

1. Wang Z, et al. *Transl Psychiatry*. 2021;11(1):543. 2. Shapiro AF et al. *Early Child Dev Care*. 2020;190(12):1918-1930. 3. Deligiannidis KM, et al. *JAMA Psychiatry*. 2021;78(9):951-959. 4. Schüle C, et al. *Prog Neurobiol*. 2014;113:79-87. 5. Yim IS, et al. *Annu Rev Clin Psychol*. 2015; 11:99-137. 6. Schweizer-Schubert S, et al. *Front Med (Lausanne)*. 2021;7:479646. 7. Deligiannidis KM, et al. *Neuropsychopharmacology*. 2019;44(3):546-554.

# Zuranolone Clinical Development Program

NEST PROGRAM

**Initiation: Monotherapy or add-on to existing ADT**

LANDSCAPE DEPRESSION STUDIES

**Maintenance: Monotherapy or add-on to existing ADT**

**Co-initiation with ADT: Simultaneous start with ADT**

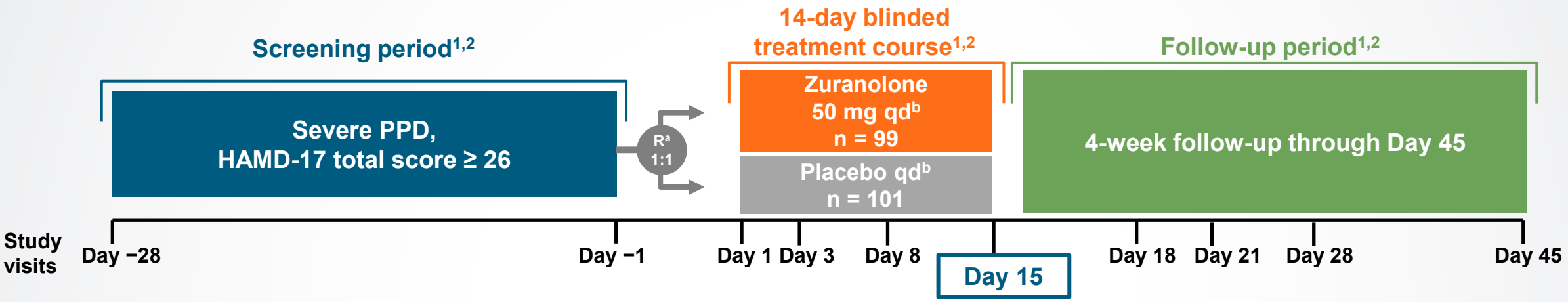
| | ROBIN STUDY | SKYLARK STUDY | | MOUNTAIN STUDY | WATERFALL STUDY | SHORELINE STUDY | CORAL STUDY |
|---|---|---|---|---|---|---|---|
| **Study No.** | **NCT02978326**[1] | **NCT04442503**[2,3] | **NCT03000530**[4] | **NCT03672175**[5] | **NCT04442490**[6] | **NCT03864614**[7] | **NCT04476030**[8,9] |
| **Design** | RCT | RCT | RCT | RCT | RCT | OL, longitudinal, maintenance | RCT |
| **Primary objective** | Efficacy: **Zuranolone 30 mg** vs placebo | Efficacy: **Zuranolone 50 mg** vs placebo | Efficacy: **Zuranolone 30 mg** vs placebo | Efficacy: **Zuranolone 30 mg** vs placebo | Efficacy: **Zuranolone 50 mg** vs placebo | Long-term safety 1-year follow-up: (**Zuranolone 30 and 50 mg**)[a] | Efficacy: **Zuranolone 50 mg** + OL ADT vs placebo + OL ADT |
| **Primary endpoint** | CFB HAMD-17 total score at Day 15 | CFB HAMD-17 total score at Day 15 | CFB HAMD-17 total score at Day 15 | CFB HAMD-17 total score at Day 15 | CFB HAMD-17 total score at Day 15 | Safety/tolerability at Week 52 | CFB HAMD-17 total score at Day 3 |
| **Population** | HAMD-17 ≥ 26 | HAMD-17 ≥ 26 | HAMD-17 ≥ 22 | HAMD-17 ≥ 22 MADRS ≥ 32 | HAMD-17 ≥ 24 | HAMD-17 ≥ 20 MADRS ≥ 28 | HAMD-17 ≥ 24 |
| **Status** | Completed | Completed | Completed | Completed | Completed | Ongoing | Completed |

ADT = antidepressant therapy; CFB = change from baseline; HAMD-17 = 17-Item Hamilton Rating Scale for Depression; MADRS = Montgomery-Åsberg Depression Rating Scale; OL = open label; PPD = postpartum depression; RCT = randomised, double-blind, placebo-controlled trial design.

[a] The SHORELINE Study initially enrolled patients using zuranolone 30 mg. The protocol was amended to allow enrolled patients to receive repeat treatment courses with zuranolone 50 mg and to add a new cohort that enrolled with zuranolone 50 mg for the initial dose and any repeat treatment courses. The new 50-mg cohort included a rollover group, in which patients co-initiated zuranolone 50 mg and an OL ADT as part of their participation in the CORAL Study and were given the opportunity to roll over into the SHORELINE Study.

1. Deligiannidis KM, et al. *JAMA Psychiatry*. 2021;78(9):951-959. 2. Sage Therapeutics. Data on file (SKYLARK Study; Protocol No. 217-PPD-301, version 2; January 2021). 3. https://clinicaltrials.gov/ct2/show/NCT04442503. Accessed 31 March 2022. 4. Gunduz-Bruce H, et al. *N Engl J Med*. 2019;381(10):903-911. 5. Mittal A, et al. Poster presented at: American Academy of Neurology Annual Meeting; 25 April-1 May 2020; Toronto, Canada. 6. Clayton A, et al. Oral presentation at: 34th ECNP Congress Hybrid; 2-5 October 2021; Lisbon, Portugal. 7. Cutler AJ, et al. Poster presented at: Society of Biological Psychiatry 2021 Virtual Annual Meeting; 29 April-1 May 2021. 8. https://clinicaltrials.gov/ct2/show/NCT04476030. Accessed 31 March 2022. 9. Sage Therapeutics. Press releases. Accessed 5 September 2022. https://investor.sagerx.com/press-releases.

# SKYLARK Study Design




## Primary Endpoint[1]

- Change from baseline (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

- HAMD-17 response/remission at Days 15 and 45
- CFB in HAM-A total score
- Incidence of TEAEs

### Inclusion Criteria Include:

- Major depressive episode that began from third trimester to ≤ 4 weeks postpartum; ≤ 12 months postpartum at Day 1[1]
- Agreed not to provide breastmilk ≤ 7 days following the last dose
- Stable ADT use ≥ 30 days prior to Day 1 was continued throughout study[2]

### Exclusion Criteria Include:

- History of nonfebrile seizures, bipolar disorder, psychotic disorder, attempted suicide, or risk of suicide in the current episode[1]
- Use of benzodiazepines, barbiturates, $GABA_A$ receptor modulators, non-GABA anti-insomnia medications, and first- or second-generation antipsychotics

ADT = antidepressant therapy; CGI-S = Clinical Global Impression-Severity; GABA = γ-aminobutyric acid; HAM-A = Hamilton Anxiety Rating Scale; HAMD-17 = 17-Item Hamilton Rating Scale for Depression; PPD = postpartum depression; qd = once daily; R = randomisation; TEAE = treatment-emergent adverse event.

[a] Randomisation was stratified based on antidepressant treatment use at baseline. [b] Zuranolone 50 mg and placebo administered in the evening with fat-containing food.[2] Dose could be reduced to 40 mg as needed based on tolerability.[2] 1. https://clinicaltrials.gov/ct2/show/NCT04442503. Accessed 31 March 2022. 2. Sage Therapeutics. Data on file (SKYLARK Study; Protocol No. 217-PPD-301, version 2. January 2021).

# Demographics and Patient Characteristics at Baseline

| | 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) |
| **Ethnicity, n (%)** | | |
| Hispanic/Latino | 33 (33.7) | 42 (42.9) |
| **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) |

**Patient characteristics were generally balanced between treatment arms**

ADT = antidepressant therapy; BMI = body mass index; HAMD-17 = 17-Item Hamilton Rating Scale for Depression; PPD = postpartum depression; 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.

# SKYLARK Study Patient Disposition

| | Zuranolone 50 mg n = 99 | Placebo n = 101 |
|---|---|---|
| **Randomised, n[a]** | 99 | 101 |
| **Dosed, n** | 98 | 98 |
| **Completed treatment, n (%)** | 89 (90.8) | 91 (92.9) |
| **Completed study, n (%)** | 84 (85.7) | 86 (87.8) |
| **Premature withdrawal from study, n (%)[b,c]** | 14 (14.3) | 12 (12.2) |
| AEs | 1 (1.0) | 1 (1.0) |
| Withdrawal by patient | 4 (4.1) | 3 (3.1) |
| Lost to follow-up | 6 (6.1) | 8 (8.2) |
| Physician decision | 2 (2.0) | 0 |
| Other[d] | 1 (1.0) | 0 |

**Majority of patients completed the study and the most common reason for premature withdrawal being lost to follow-up**

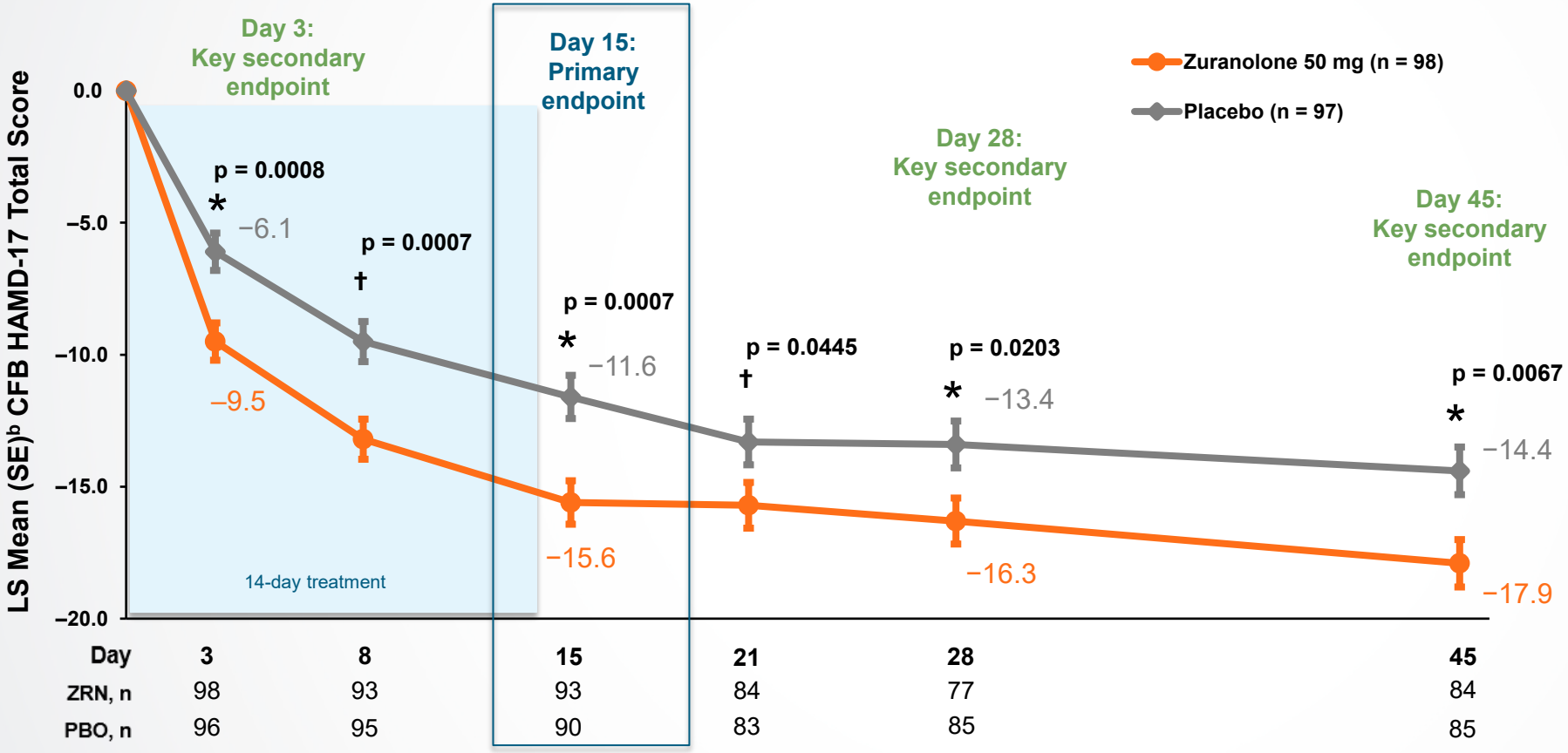
AE = adverse event.

[a] 531 women were screened. [b] Discontinuation of blinded treatment occurred during the 2-week treatment course. Participants who discontinued treatment early could complete remaining study visits through Day 45 (i.e., relative to Day 1), unless the participant withdrew consent. [c] Withdrawal from the study could occur at any time from Day 1 through 45 for any reason. 5 patients receiving placebo and 7 receiving zuranolone prematurely withdrew from the study after completing treatment. [d] Unable to complete Day 45 due to conflicting work schedule.

# Change From Baseline (CFB) in HAMD-17 Total Score on Day 15 and Days 3, 28, and 45[a]

## *Primary Endpoint and Key Secondary Endpoints*

| HAMD-17 at Baseline, Mean (SD) | |
|---|---|
| Zuranolone 50 mg | 28.6 (2.49) |
| Placebo | 28.8 (2.34) |




**The SKYLARK study met its primary endpoint and all key secondary endpoints**

**Statistically significant improvements in depressive symptoms were seen as early as Day 3 and sustained to Day 45**

CGI-S = Clinical Global Impression-Severity; FAS = full analysis set; HAMD-17 = 17-Item Hamilton Rating Scale for Depression; LS = least squares; MMRM = mixed model of repeated measures; PBO = placebo.

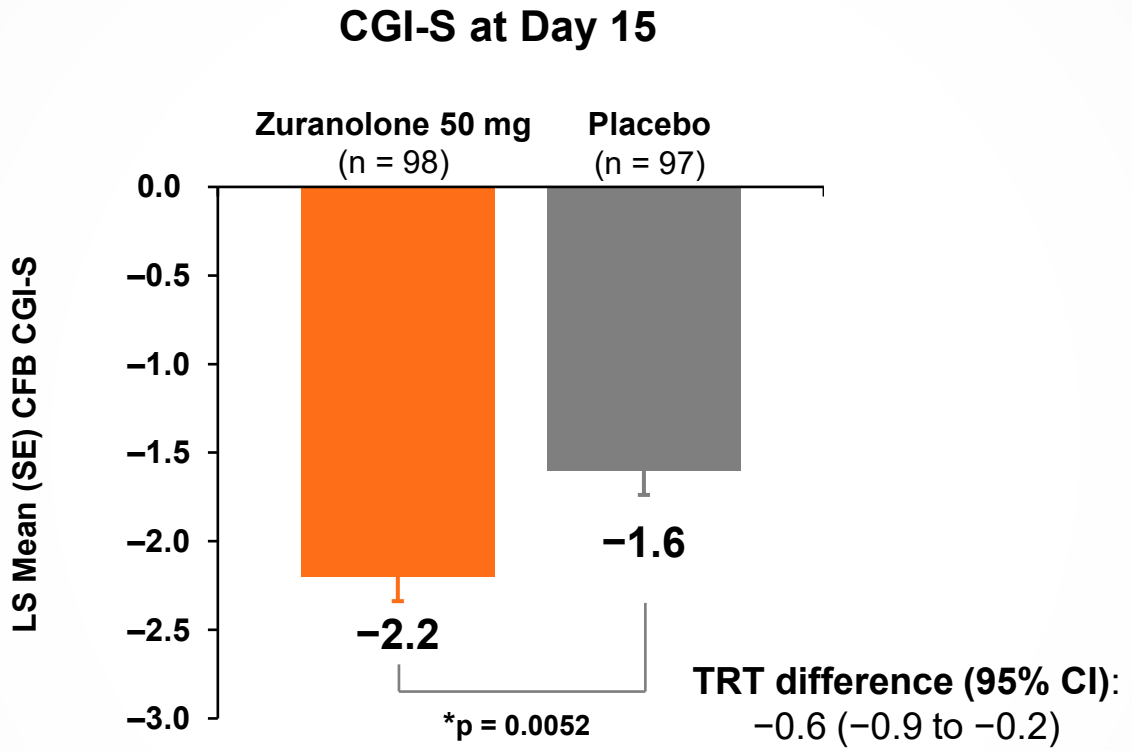
*** Statistically significant (per fixed hierarchal testing for key secondary endpoints). † Data at Days 8 and 21 were not adjusted for multiplicity, and p-values were considered nominal.**

[a] FAS was defined as all randomised participants who were administered zuranolone 50 mg or placebo with valid baseline and ≥ 1 postbaseline efficacy endpoint assessment. [b] LS mean and treatment difference along with CI and p-values were calculated using MMRM. The key secondary endpoints were tested in the following fixed sequence to control for multiplicity: CFB in HAMD-17 at Days 3, 28, and 45 followed by CFB in CGI-S on Day 15. If an endpoint was not significant at the 5% level, the following endpoints in the sequence were interpreted only with nominal p-value.

# CFB in CGI-S at Day 15[a]

## *Key Secondary Endpoint: Day 15*

| CGI-S at Baseline, Mean (SD) | |
|---|---|
| Zuranolone 50 mg | 5.0 (0.66) |
| Placebo | 4.9 (0.58) |




**Treatment with zuranolone demonstrated statistically significantly greater CFB in CGI-S at Day 15**

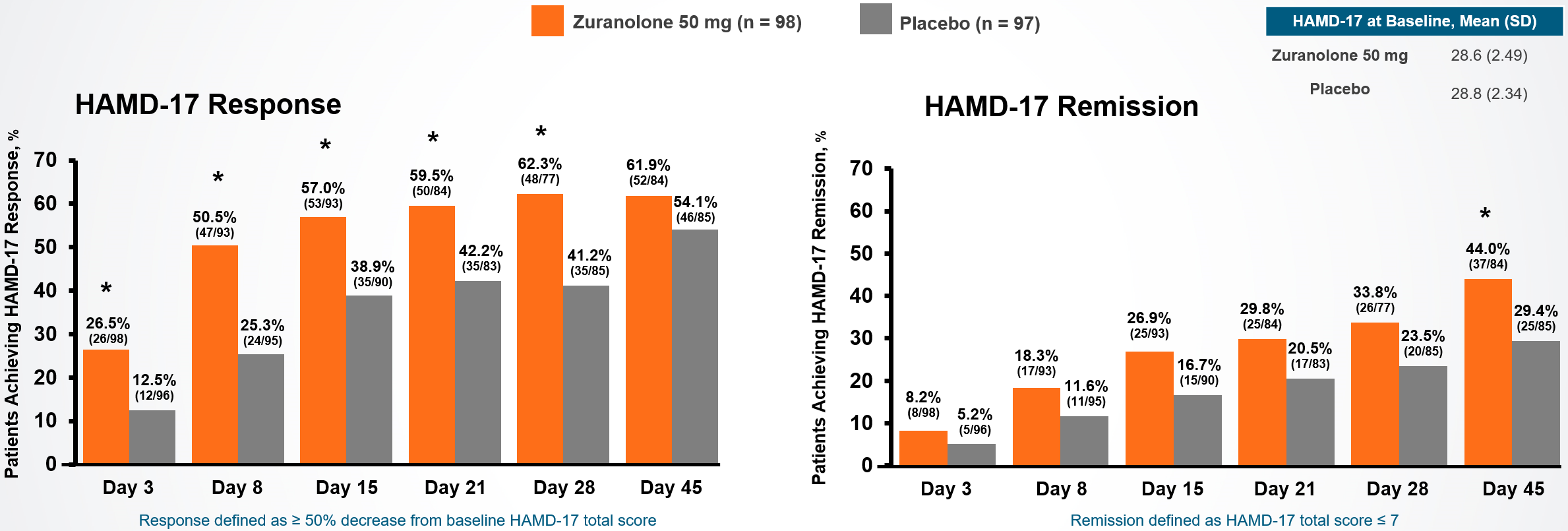
CFB = change from baseline; CGI-S = Clinical Global Impression-Severity; FAS = full analysis set; HAMD-17 = 17-Item Hamilton Rating Scale for Depression; LS = least squares; MMRM = mixed model of repeated measures; PBO = placebo; TRT = treatment.

*** Statistically significant (per fixed hierarchal testing for key secondary endpoints).**

[a] FAS was defined as all randomised participants who were administered zuranolone 50 mg or placebo with valid baseline and ≥ 1 postbaseline efficacy endpoint assessment. LS mean and treatment difference along with CI and p-values were calculated using MMRM. The key secondary endpoints were tested in the following fixed sequence to control for multiplicity: CFB in HAMD-17 at Days 3, 28, and 45 followed by CFB in CGI-S on Day 15. If an endpoint was not significant at the 5% level, the following endpoints in the sequence were interpreted only with nominal p-value.

# HAMD-17 Response and Remission Over Time[a]

## *Secondary Endpoints*




Response defined as ≥ 50% decrease from baseline HAMD-17 total score

**Treatment with zuranolone demonstrated significantly higher percentages of HAMD-17 response than placebo at Days 3, 8, 15, 21, and 28**

Remission defined as HAMD-17 total score ≤ 7

**Treatment with zuranolone demonstrated significantly higher percentage of HAMD-17 remission than placebo at Day 45**

FAS = full analysis set; HAMD-17 = 17-Item Hamilton Rating Scale for Depression.

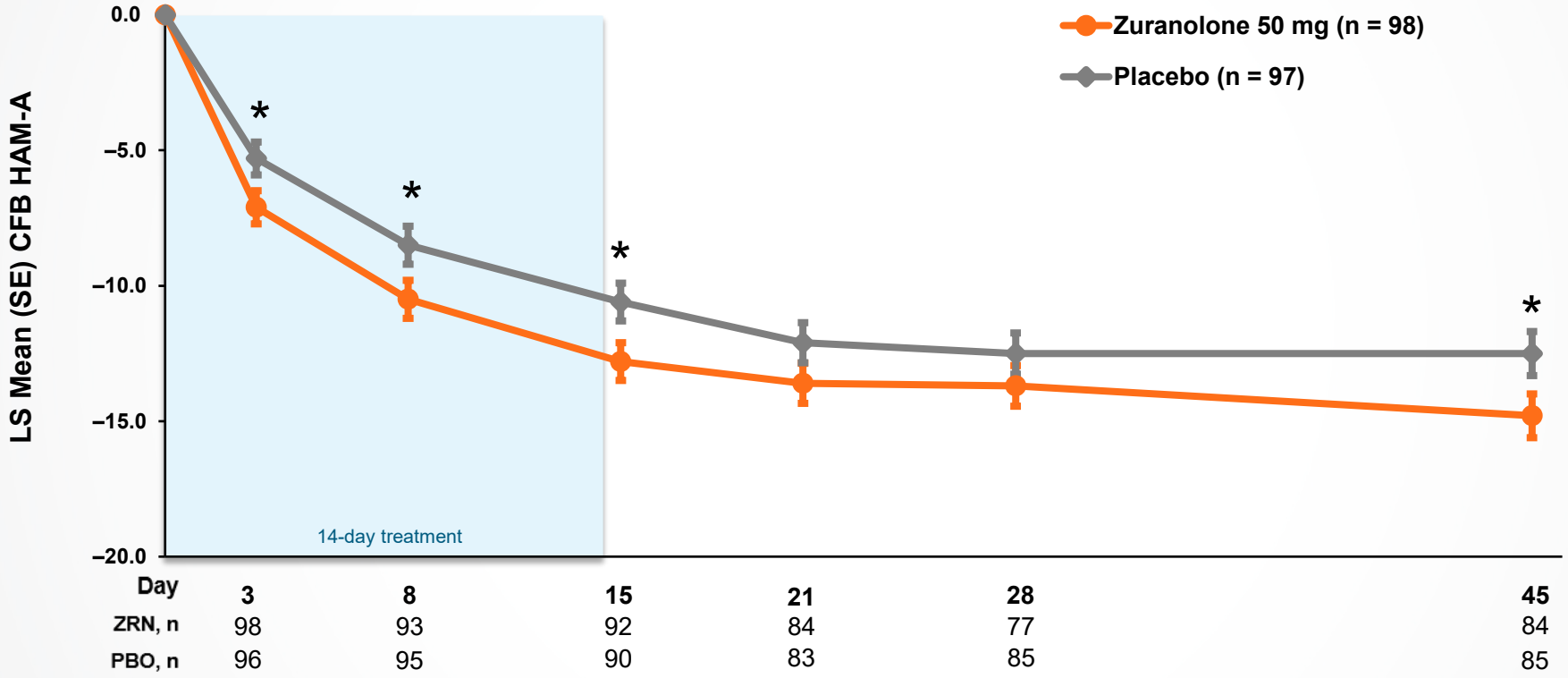
*** p < 0.05. Data were not adjusted for multiplicity, and p-values were considered nominal.**

[a] FAS was defined as all randomised participants who were administered zuranolone 50 mg or placebo with valid baseline and ≥ 1 postbaseline efficacy endpoint assessment.

# CFB in HAM-A Over Time[a]

## *Selected Secondary Endpoint*

| HAM-A at Baseline, Mean (SD) | |
|---|---|
| Zuranolone 50 mg | 24.4 (6.01) |
| Placebo | 24.7 (5.96) |




**Treatment with zuranolone demonstrated significantly greater CFB in HAM-A at Days 3, 8, 15, and 45**

CFB = change from baseline; FAS = full analysis set; HAM-A = Hamilton Anxiety Rating Scale; HAMD-17 = 17-Item Hamilton Rating Scale for Depression; LS = least squares; MMRM = mixed model of repeated measures; PBO = placebo; TRT = treatment.

*** p < 0.05. Data were not adjusted for multiplicity, and p-values were considered nominal.**

[a] FAS was defined as all randomised participants who were administered zuranolone 50 mg or placebo with valid baseline and ≥ 1 postbaseline efficacy endpoint assessment. LS mean and treatment difference along with CI and p-values were calculated using MMRM.

# SKYLARK Study: Safety/Tolerability

- Zuranolone 50 mg was generally well tolerated and demonstrated a safety profile consistent with that observed in the zuranolone clinical development program, to date.[a]
- Of the participants who had TEAEs, the majority had TEAEs that were mild or moderate in severity.
- SAEs (abdominal pain, hypertension, and peripheral oedema; acute worsening of PPD secondary to methamphetamine use) that were assessed as unrelated to zuranolone were reported in 2 patients in the zuranolone arm.

| | Zuranolone 50 mg n = 98 n (%) | Placebo n = 98 n (%) |
|---|---|---|
| **TEAE, 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[c] | 1 (1.0) | 1 (1.0) |

AE = adverse event; PPD = postpartum depression; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
[a] No deaths occurred during the study in either the placebo or zuranolone group. [b] The most common AEs leading to dose reduction in the zuranolone group included somnolence, dizziness, and sedation; 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. Participants who discontinued treatment early could complete remaining study visits through Day 45 (i.e., relative to Day 1), unless the participant withdrew consent. [c] Withdrawal from the study could occur at any time from Day 1 through 45 for any reason. AEs leading to withdrawal from the study also resulted in treatment discontinuation.

# SKYLARK Study: Safety/Tolerability (Continued)

- No AEs of loss of consciousness were reported during the study.
- No evidence of increased suicidal ideation/behavior was noted compared with baseline as measured by the C-SSRS.
- No evidence of withdrawal symptoms was observed after discontinuation of zuranolone 50 mg as assessed by PWC-20 or TEAEs.

## TEAEs Incidence (>5% in Either Treatment Group) Through Day 45

| | Zuranolone 50 mg n = 98 n (%) | Placebo n = 98 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) |
| Diarrhoea | 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 |

AE = adverse event; C-SSRS = Columbia Suicide Severity Rating Scale; PWC-20 = 20-Item Physician Withdrawal Checklist; TEAE = treatment-emergent adverse event.

# Conclusions

- The SKYLARK Study met its primary endpoint and all key secondary endpoints.
  - Patients who received zuranolone 50 mg had a statistically significant improvement in depressive symptoms (HAMD-17) at Day 15 versus placebo.
  - Statistically significant improvements in depressive symptoms compared to placebo were seen as early as Day 3 and were maintained at all timepoints assessed through Day 45.
  - Patients who received zuranolone 50 mg also showed statistically significant improvement in global functioning (CGI-S) at Day 15 compared with placebo.
- Numerical improvements in additional secondary endpoints were also observed, including CFB in HAM-A total score and HAMD-17 response and remission.
- Zuranolone was generally well tolerated, with a safety profile consistent with previous clinical trials across the PPD and MDD programs.[1-3,a]
- These data support the potential role of zuranolone as a novel, oral, rapid-acting, 14-day treatment for PPD.

CGI-S = Clinical Global Impression-Severity; HAM-A = Hamilton Anxiety Rating Scale; HAMD-17 = 17-Item Hamilton Rating Scale for Depression; MDD = major depressive disorder; PPD = postpartum depression.
[a] Clinical trials in the zuranolone clinical development program differ in sample size, entry criteria, and study sites, as well as other design elements. No direct comparison can be made across these clinical trials.
1. Sage Therapeutics. Press releases. Accessed 5 September 2022. https://investor.sagerx.com/press-releases. 2. Deligiannidis KM, et al. *JAMA Psychiatry*. 2021;78(9):951-959. 3. Cutler AJ, et al. Poster presented at: Society of Biological Psychiatry 2021 Virtual Annual Meeting; 29 April-1 May 2021.

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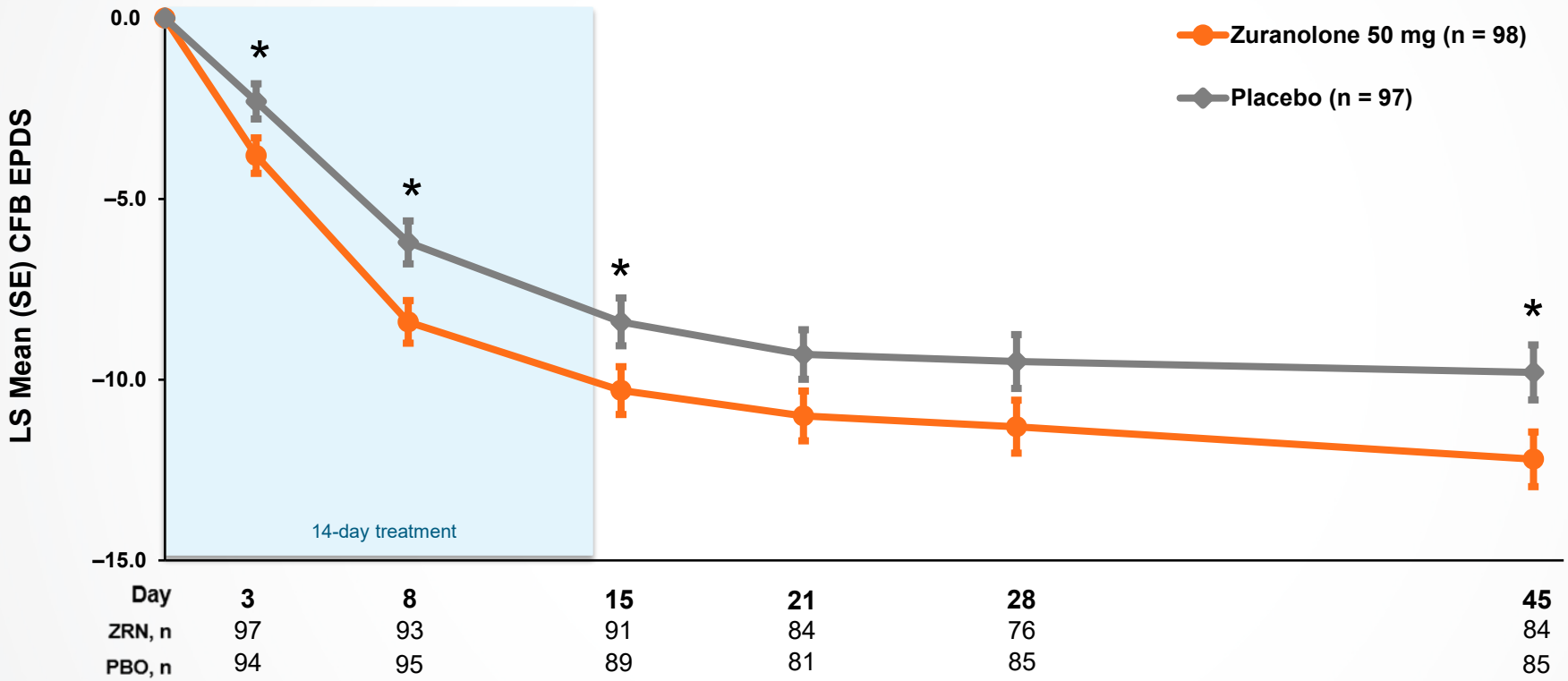
## Thank you

# CFB in Edinburgh Postnatal Depression Scale (EPDS) Over Time[a]

## *Selected Secondary Endpoint*

| EPDS at Baseline, Mean (SD) | |
|---|---|
| Zuranolone 50 mg | 21.1 (3.68) |
| Placebo | 20.0 (4.15) |




**Treatment with zuranolone demonstrated significantly greater decreases in EPDS at Days 3, 8, 15, and 45**

CFB = change from baseline; FAS = full analysis set; LS = least squares; MMRM = mixed model of repeated measures; PBO = placebo.

***p < 0.05. Data were not adjusted for multiplicity, and p-values were considered nominal.**

[a] FAS was defined as all randomised participants who were administered zuranolone 50 mg or placebo with valid baseline and ≥ 1 postbaseline efficacy endpoint assessment.