SKYLARK Study (217-PPD-301; NCT04442503) Topline Results

A Randomized, Double-blind, Placebo-controlled Study Evaluating the Efficacy and Safety of Zuranolone in the Treatment of Adults With Severe Postpartum Depression

Forward Looking Statement

The slides presented today and the accompanying oral presentations contain forward-looking statements, which may be identified by the use of words such as “may,” “might,” “will,” “should,” “can,” “expect,” “plan,” “anticipate,” “believe,” “estimate,” “project,” “intend,” “future,” “opportunity”, “goal”, “mission”, “potential,” “target”, or “continue,” and other similar expressions.

Forward-looking statements in this presentation include statements regarding: our belief in the potential benefit and profile of zuranolone in the treatment of MDD and PPD; our belief in the potential of zuranolone to be successful and to meet an unmet need in the treatment of PPD and MDD; anticipated timelines with respect to NDA filings and the potential for approval of zuranolone; the potential for commercialization of zuranolone and our commercialization plans; the goals, opportunity, mission and vision for zuranolone and our business; our estimates as to the number of patients with PPD; our belief in the unmet for new treatment options in the treatment of MDD and PPD and the potential market for zuranolone, if approved; and our vision for our company.

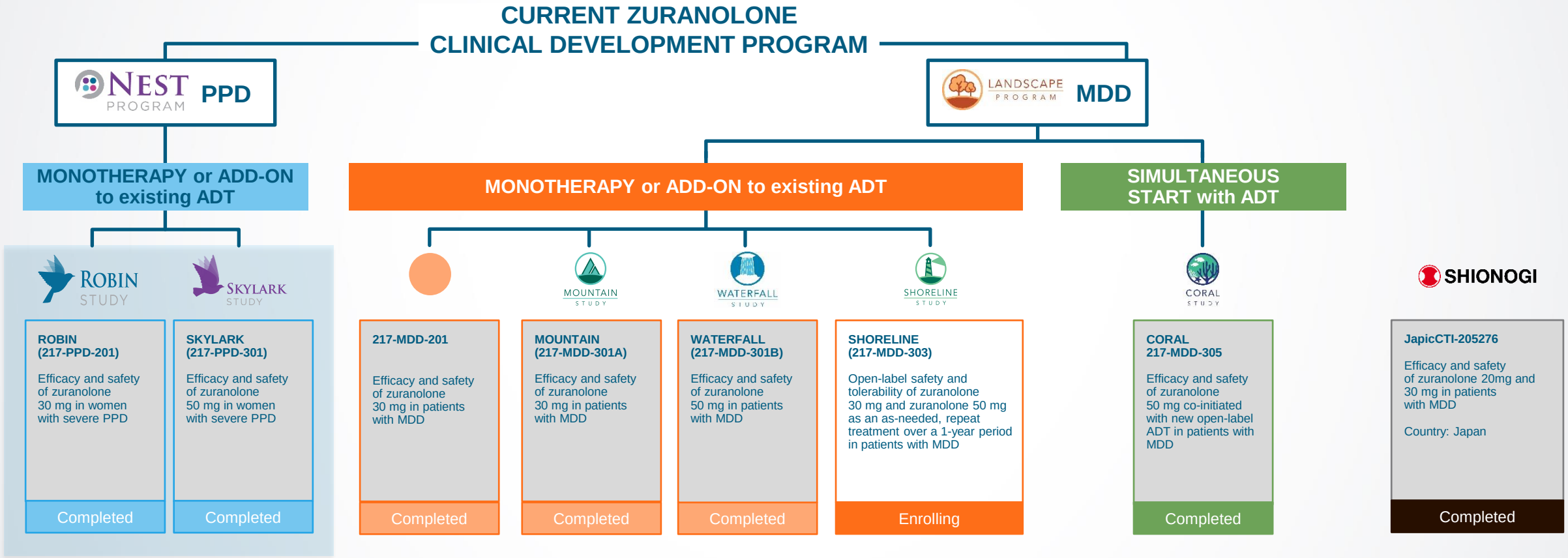
These forward-looking statements are neither promises nor guarantees of future performance, and are subject to a variety of risks and uncertainties, many of which are beyond our control, which could cause actual results to differ materially from those contemplated in these forward-looking statements, including the risk that:

- The FDA may ultimately decide that the design or results of our completed clinical trials for zuranolone are not sufficient to file for or obtain regulatory approval in MDD and PPD despite prior regulatory advice. We may not meet our expected time-lines for completion of filing of the NDA for zuranolone in MDD or for the planned filing in PPD or for approval. Even if our efforts to file an NDA are successful, the FDA may not accept the filing for review. At any stage, the FDA may ask for additional clinical trials, nonclinical studies or other data in order for us to file for or obtain regulatory approval or may find other inadequacies and deficiencies in our NDA filings. Other decisions or actions of the FDA or other regulatory authorities may affect our development efforts or our efforts to gain regulatory approval.
- We may encounter unexpected safety or tolerability issues with respect to zuranolone in ongoing or future studies that require additional studies be conducted or that impair our ability to successfully file an NDA and obtain approval.
- We may not receive FDA approval of zuranolone in the treatment of MDD or PPD, and even if we are successful in obtaining such approval, we may not be able to successfully execute our commercialization plans or to meet our commercialization goals.
- Even if zuranolone is approved, the number of patients with MDD and PPD, and the actual market for zuranolone, may be smaller than our current estimates; or the profile and benefit of zuranolone in the treatment of MDD and PPD may not be as we expect or we may not achieve market acceptance or reimbursement at acceptable levels or on the terms we expect. We may never be successful or achieve our goals with respect to commercialization of zuranolone, if approved.
- The anticipated benefits of our collaborations, including our collaboration with Biogen, may never be achieved. The need to align with our collaborators may hamper or delay our development and commercialization efforts or increase our costs; our business may be adversely affected and our costs may increase if any of our key collaborators fails to perform its obligations or terminates our collaboration.
- We may not be able to obtain and maintain adequate intellectual property protection or other forms of data and marketing exclusivity for zuranolone or any of our other products, or to defend our patent portfolio against challenges from third parties.
- We will face competition from existing marketed products, including generic SSRIs, and we may face competition from others developing products for similar uses as those for which zuranolone has been developed, and we may not successfully compete.
- We may not be successful in our development efforts with respect to our other product candidates.
- Our operating expenses may be higher than forecasted, and we may also face unexpected expenditures which could cause us to change our plans. We may need or choose to raise additional funding, which may not be available on acceptable terms, or at all.
- We may not be able to establish and maintain key business relationships with third parties on acceptable terms or we may encounter problems with the performance of such third parties.
- We may encounter technical and other unexpected hurdles in the manufacture and development of our products.
- Any of the foregoing or other factors may negatively impact our ability to achieve our goals, mission, opportunities, plans or expectations for our business.

For additional disclosure regarding these and other risks Sage faces, see the disclosure contained in the "Risk Factors" section of our most recent report, and in our other public filings, with the Securities and Exchange Commission, available on the SEC's website at http://www.sec.gov. Any forward-looking statement represent our views only as of today, and should not be relied upon as representing our views as of any subsequent date. We undertake no obligation to update or revise the information contained in this presentation, whether as a result of new information, future events or circumstances or otherwise.

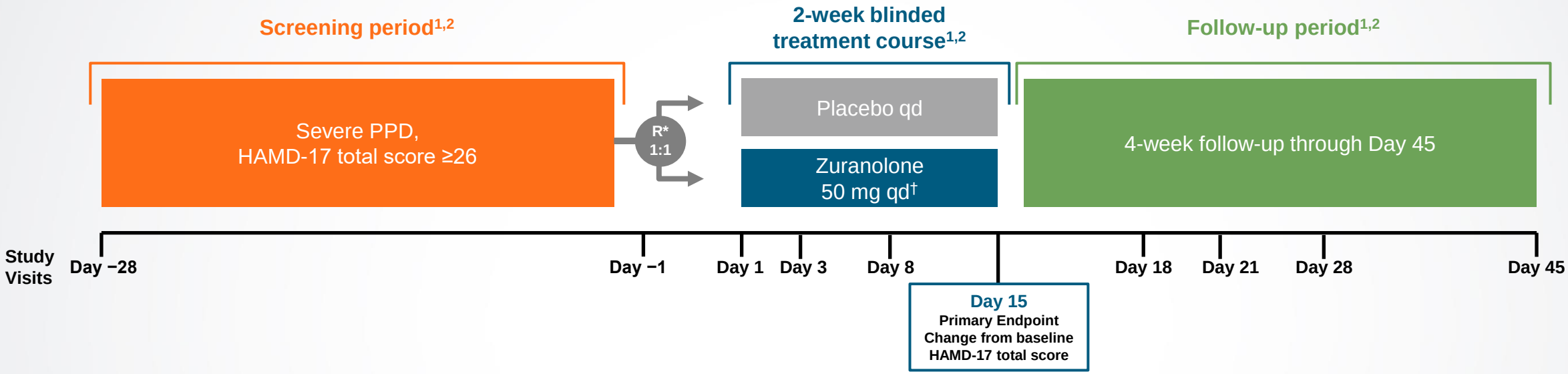
Zuranolone Clinical Development Programs

Potential to reshape the depression landscape



Abbreviations: PPD = postpartum depression, MDD = major depressive disorder, ADT = antidepressant therapy

SKYLARK Study Overview



Study Design Elements:

- Phase 3, randomized, double-blind, placebo-controlled trial.[1]
- Analysis of efficacy and safety.[1]
  - **Treatment course** = 14 days of oral dosing with zuranolone 50 mg or placebo.[2]
  - **Treatment period** = time from first dose to last dose of zuranolone 50 mg or placebo in a 2-week treatment course +1 day (Day 15).[2]
  - **Study period** = 2-week treatment course plus 4-week follow-up period through Day 45 (end of study).[2]
- NCT04442503.[1]

Study Population:

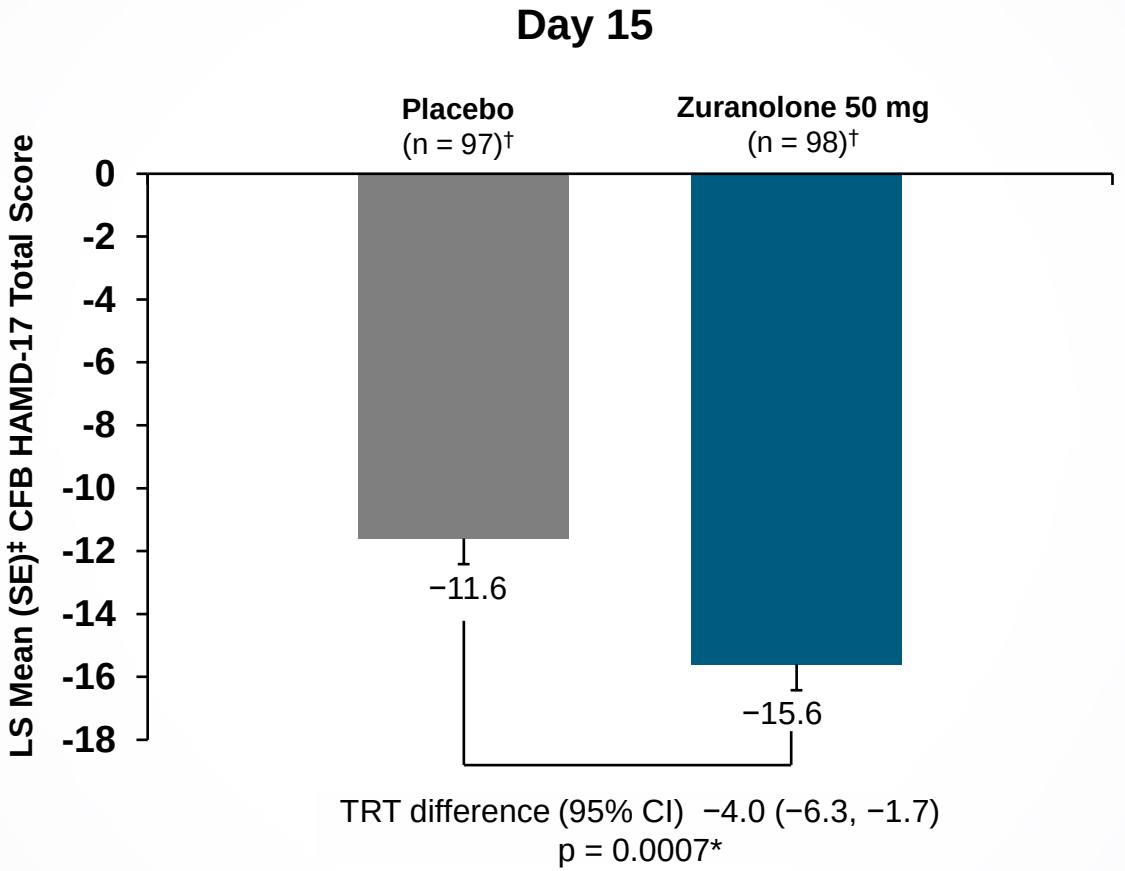
- Adult patients with severe PPD (baseline HAMD-17 total score ≥26).[1]
- 82 sites screened patients.[1,‡]
- Actual enrollment: 200.[3]
- Antidepressants were permitted as long as the patient was on a stable dose for ≥30 days prior to Day 1 and agreed to continue that stable dose through the completion of the Day 45 assessments.[2]

(See ClinicalTrials.gov NCT04442503 for inclusion/exclusion criteria.)

*Randomization was stratified based on antidepressant treatment use at baseline. †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] ‡Patients screened: N = 531.
HAMD-17 = 17-item Hamilton Rating Scale for Depression; PPD = postpartum depression; qd = once daily; R = randomization.
1. SKYLARK. ClinicalTrials.gov identifier: NCT04442503. 2. Data on file. SKYLARK Study; Protocol Number: 217-PPD-301, Version 2. Jan 2021. 3. Data on file. SAGE-217-PPD-301 Topline results memo, Version 1.0. 25 May 2022.

SKYLARK Study: Primary Endpoint Results

Change From Baseline in HAMD-17 Total Score at Day 15 (FAS†)



***Statistically significant.**

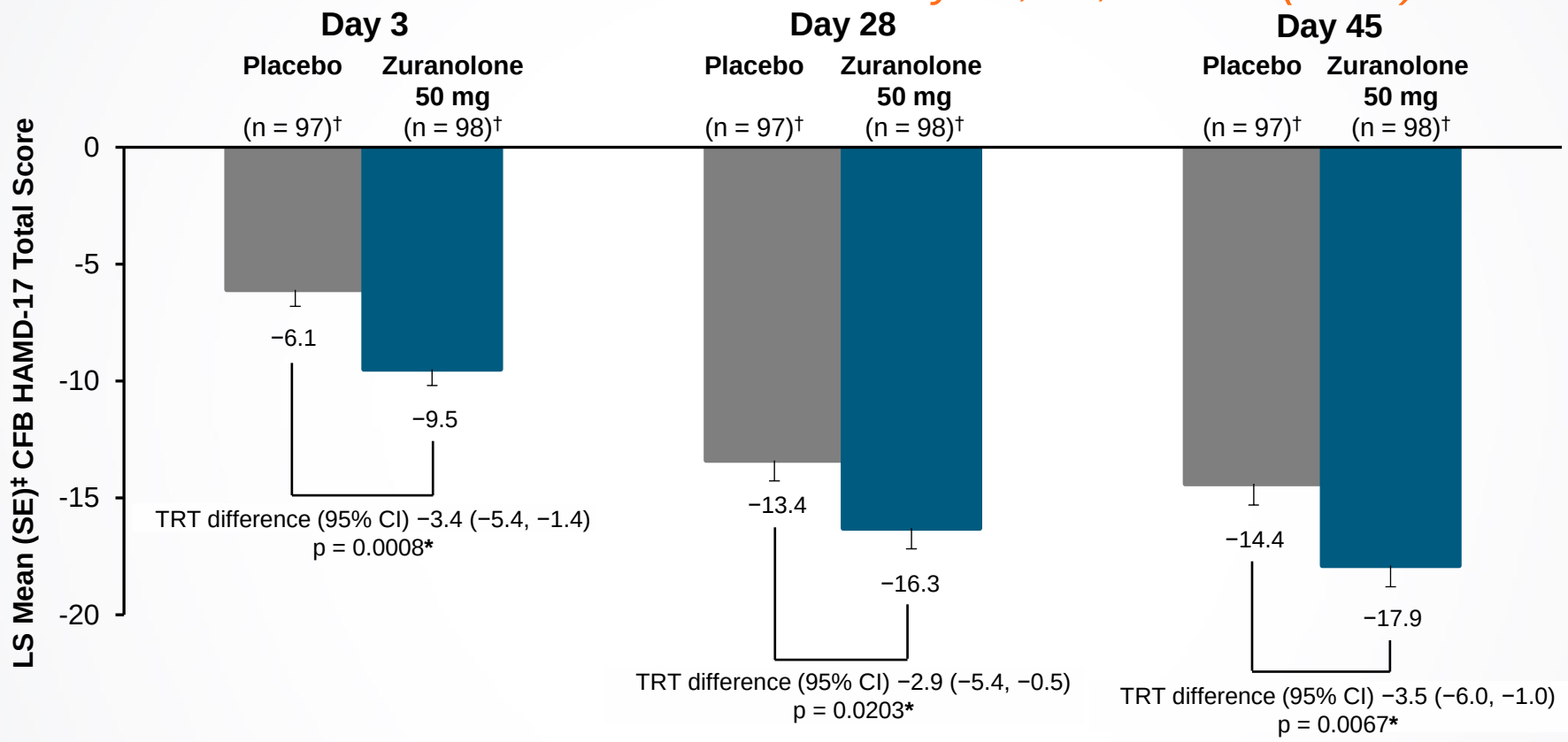
†FAS was defined as all randomized participants who were administered zuranolone 50 mg or placebo with valid baseline and ≥1 post-baseline efficacy endpoint assessment. ‡LS mean and treatment difference along with CI and p values were calculated using MMRM.

CFB = change from baseline; CI = confidence interval; FAS = Full Analysis Set; HAMD-17 = 17-item Hamilton Rating Scale for Depression; LS = least squares; MMRM = Mixed Model of Repeated Measures; SE = standard error; TRT = treatment.

Data on file. SAGE-217-PPD-301 Topline results memo, Version 1.0. 25 May 2022.

SKYLARK Study: Key Secondary Endpoint Results

Change From Baseline in HAMD-17 Total Score on Days 3, 28, and 45 (FAS†)



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

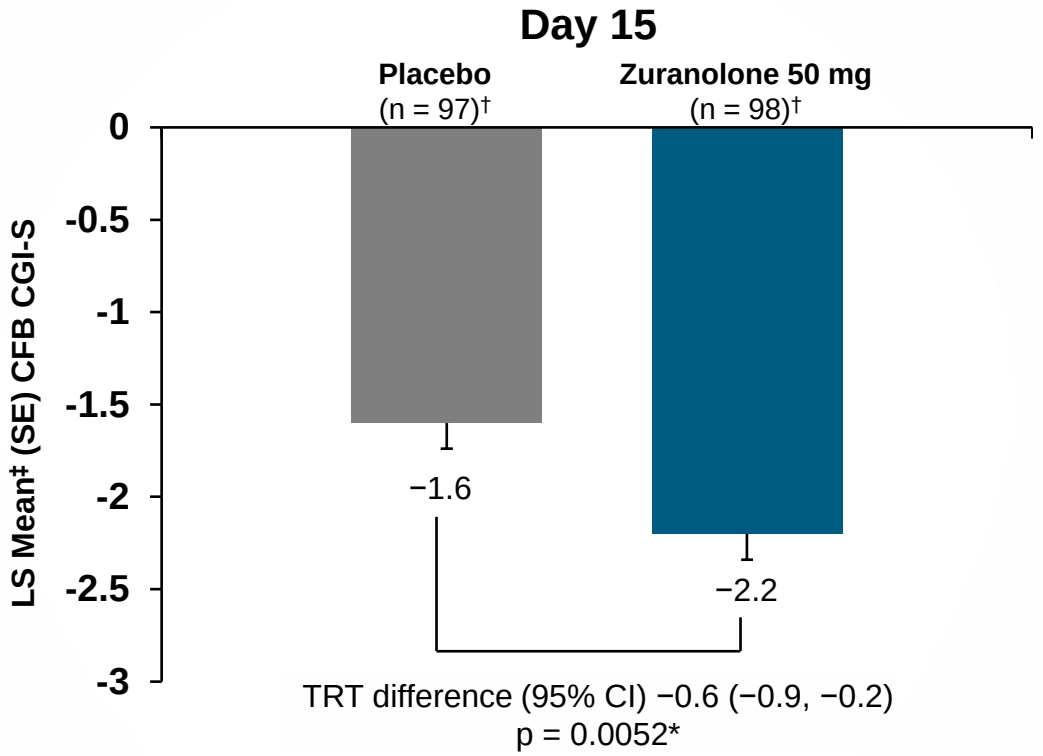
†FAS was defined as all randomized participants who were administered zuranolone 50 mg or placebo with valid baseline and ≥1 post-baseline efficacy endpoint assessment. ‡LS mean and treatment difference along with CI and p values were calculated using MMRM. The key secondary endpoints were tested in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

CFB = change from baseline; CGI-S = Clinical Global Impression-Severity; CI = confidence interval; FAS = Full Analysis Set; HAMD-17 = 17-item Hamilton Rating Scale for Depression; LS = least squares; MMRM = Mixed Model of Repeated Measures; SE = standard error; TRT = treatment.

Data on file. SAGE-217-PPD-301 Topline results memo, Version 1.0. 25 May 2022.

SKYLARK Study: Key Secondary Endpoint Results

Change From Baseline in CGI-S at Day 15 (FAS†)



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

†FAS was defined as all randomized participants who were administered zuranolone 50 mg or placebo with valid baseline and ≥1 post-baseline 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 in order to control for multiplicity: CFB in HAMD-17 at Day 3, Day 28, and Day 45 followed by CFB in CGI-S on Day 15. If an endpoint was not significant at 5% level, the following endpoints in the sequence were interpreted only with nominal p value.

CFB = change from baseline; CGI-S = Clinical Global Impression-Severity; CI = confidence interval; FAS = Full Analysis Set; HAMD-17 = 17-item Hamilton Rating Scale for Depression; LS = least squares; MMRM = Mixed Model of Repeated Measures; SE = standard error; TRT = treatment.

Data on file. SAGE-217-PPD-301 Topline results memo, Version 1.0. 25 May 2022.

SKYLARK Study: Safety/Tolerability

- Over the study period, treatment emergent adverse events (TEAEs) >5% in either treatment group were somnolence, dizziness, sedation, headache, diarrhea, nausea, urinary tract infection, and COVID-19 infection.
- 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.
- The incidence of TEAEs in the zuranolone 50 mg group was 65 (66.3%, 65/98) vs 52 (53.1%, 52/98) in the placebo group.
- Among patients who were dosed, 4 (4.1%) patients in the zuranolone 50 mg and 2 (2.0%) patients in the placebo group discontinued treatment due to AEs.

TEAEs Incidence (>5% in either treatment group) through Day 45

	Placebo N = 98 n (%)	Zuranolone 50 mg N = 98 n (%)
Somnolence	5 (5.1)	26 (26.5)
Dizziness	10 (10.2)	13 (13.3)
Sedation	1 (1.0)	11 (11.2)
Headache	13 (13.3)	9 (9.2)
Diarrhea	2 (2.0)	6 (6.1)
Nausea	6 (6.1)	5 (5.1)
Urinary Tract Infection	4 (4.1)	5 (5.1)
COVID-19	0	5 (5.1)

COVID-19 = coronavirus disease 2019; C-SSRS = Columbia Suicide Severity Rating Scale; PWC-20 = 20-item Physician Withdrawal Checklist; TEAE = treatment-emergent adverse event.
Data on file. SAGE-217-PPD-301 Topline results memo, Version 1.0. 25 May 2022.

Summary and Conclusions

- The SKYLARK Study met its primary endpoint; patients who received zuranolone 50 mg had a statistically significant and clinically meaningful improvement in depressive symptoms at Day 15 as assessed by change from baseline in HAMD-17 total score compared with patients who received placebo.[1]
  - The LS mean (SE) change from baseline in HAMD-17 total score at Day 15 for patients who received zuranolone 50 mg was −15.6 (0.82) compared with −11.6 (0.82) for patients who received placebo (LS mean difference: −4.0; 95% CI [−6.3, −1.7]; p = 0.0007).[1]
- The SKYLARK Study met all key secondary endpoints; patients who received zuranolone 50 mg had a statistically significant improvement in depressive symptoms compared with placebo at Days 3, 28, and 45 as assessed by change from baseline in HAMD-17 total score and a statistically significant change from baseline in CGI-S at Day 15 compared with placebo.[1]
- Zuranolone 50 mg was generally well tolerated and demonstrated a safety profile consistent with the LANDSCAPE and NEST clinical data to date, which include trials evaluating zuranolone across different patient populations (MDD, PPD) and doses (30 mg, 50 mg).[1-4]*
  - The most common (>5%) TEAEs included (% reported zuranolone vs. placebo): somnolence (26.5% vs 5.1%), dizziness (13.3% vs 10.2%), sedation (11.2% vs 1.0%), headache (9.2% vs 13.3%), diarrhea (6.1% vs 2.0%), nausea (5.1% vs 6.1%), urinary tract infection (5.1% vs 4.1%), and COVID-19 (5.1% vs 0).[1]
  - Over the study period, 2 patients (2%) experienced SAEs in the zuranolone group (unrelated to treatment), and no deaths were reported in either treatment group.[1]
  - No evidence of withdrawal symptoms or increased suicidal ideation or behavior were identified as assessed by the PWC-20 and the C-SSRS, respectively.[1]
- In the SKYLARK Study, the efficacy and safety of zuranolone in women with PPD were generally consistent with results observed in the ROBIN Study.[1,3]
  - Due to the duration of both the ROBIN and SKYLARK Studies, long-term efficacy and safety of zuranolone in the PPD population are unknown.[1,3]

*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.

AE = adverse event; CGI-S = Clinical Global Impression-Severity; CI = confidence interval; COVID-19 = coronavirus disease 2019; C-SSRS = Columbia Suicide Severity Rating Scale; HAMD-17 = 17-item Hamilton Rating Scale for Depression; LS = least squares; MDD = major depressive disorder; PPD = postpartum depression; PWC-20 = 20-item Physician Withdrawal Checklist; SAE = serious adverse event; SE = standard error.

1. Data on file. SAGE-217-PPD-301 Topline results memo, Version 1.0. 25 May 2022. 2. CORAL Press Release. Accessed 31 May 2022. https://investor.sagerx.com/press-releases/. 3. Deligiannidis KM, et al. *JAMA Psychiatry*. 2021;78(9):951-959. 4. Cutler AJ, et al. Poster presented at: Society of Biological Psychiatry Annual Meeting; 29 Apr-1 May 2021; virtual congress.

Left untreated, PPD can be devastating to mothers, babies and their families, with detrimental impacts that can last for generations

PPD is an urgent medical condition requiring urgent treatment. It is a crippling mood disorder that leaves mothers to suffer in fear, confusion, and silence[1]

Strong predictors of PPD include ***previous history of depression***, stressful recent life events, and poor social support[2]

Women with PPD may have ***intense feelings of sadness, anxiety,*** irritability, and/or rage[2]

Mothers with PPD can face ***challenges with functioning and bonding with their infants***[1,3-6]

Mothers with PPD are at ***higher risk for substance abuse and suicidality*** posing risk to mothers and babies[7]

Women with PPD may continue to be ***at risk of ongoing depression*** beyond a year postpartum[10]

COVID-19 has led to substantial increases in maternal depression and anxiety[14]

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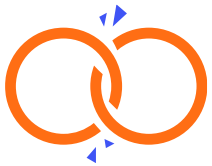
1. Beck CT, et al. Am J Nurs. 2006;106(5):40-50. 2. Yim IS, Tanner Stapleton LR, Guardino CM, Hahn Holbrook J, Dunkel Schetter C. Biological and psychosocial predictors of postpartum depression: systematic review and call for integration. Annu Rev Clin Psychol . 2015;11:99 137. 3. Wouk K, et al. Pediatrics. 2016;137(1). 4. Kerstis B, et al. Arch Womens Ment Health. 2016;19(1):87-94. 5. Lilja G, et al. Scand J Caring Sci. 2012;26(2):245-253. 6. Gaglardi L, et al. Arch Dis Child. 2012;97(4):355-357. 7. Fitelson E, et al. Int J Womens Health. 2010;3:1-14. 8. Gressier F, et al. J Psychiatr Res. 2017;84:284-291. 9. Bodnar-Deren S, et al. J Womens Health. 2016;25(12):1219-1224. 10. Vliegen N et al. 2014 Harv Rev Psychiatry;22(1):1-22. 11. Putnik DL, et al. Pediatrics. 2020;146(5):e20200857. 12. Vliegen N, Casalin S, Luyten P. The course of postpartum depression: a review of longitudinal studies. Harv Rev Psychiatry . 2014;22(1):1 22. 13.Netsi E, et al. JAMA Psychiatry. 2018;75(3):247-253. 14. Davenport MH, et al. Front Glob Womens Health. 2020;1:1.

The burden of PPD extends beyond mothers; PPD has significant impact on child development, family relationships and healthcare costs

Undiagnosed or unresolved PPD can adversely affect the mother-infant relationship and lead to long-term emotional problems for the child[1]

Children of mothers with PPD symptoms are at ***long-term heightened risk for negative behavioral, cognitive, and psychological outcomes*** throughout childhood and into adulthood[1]



PPD has been associated with decreased marital satisfaction and ***higher separation and divorce.***[2,3] Partners face higher levels of stress, anxiety, and *depression*[4]

Households of mothers with PPD experienced ***22% higher medical costs***[5]

—

Significant ***PPD related costs from the impact on child development***[6]

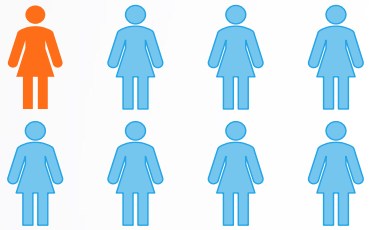
Without new, accessible treatment options for PPD, moms and their families are left at risk

1. Moore Simas TA, Huang M-Y, Patton C et al. The humanistic burden of postpartum depression: a systematic literature review. Curr Med Res Opin. 2019;35(3):383-393. 2. Pearson RM et al. JAMA Psychiatry. 2013;70(12):1312-1319. 3. Lilja G, et al. Scand J Caring Sci. 2012;26(2):245-253 4. Letourneau NL, et al. Issues Ment Health Nurs. 2012;33(7):445-457. 5. Moore Simas TA, et al. Curr Med Res Opin. 2019;35(3):383-393. 6. Epperson CN, et al. Curr Med Res Opin. 2020;36(10):1707-1716.

PPD is one of the most common medical conditions impacting mothers during and after pregnancy

Prevalence of PPD:

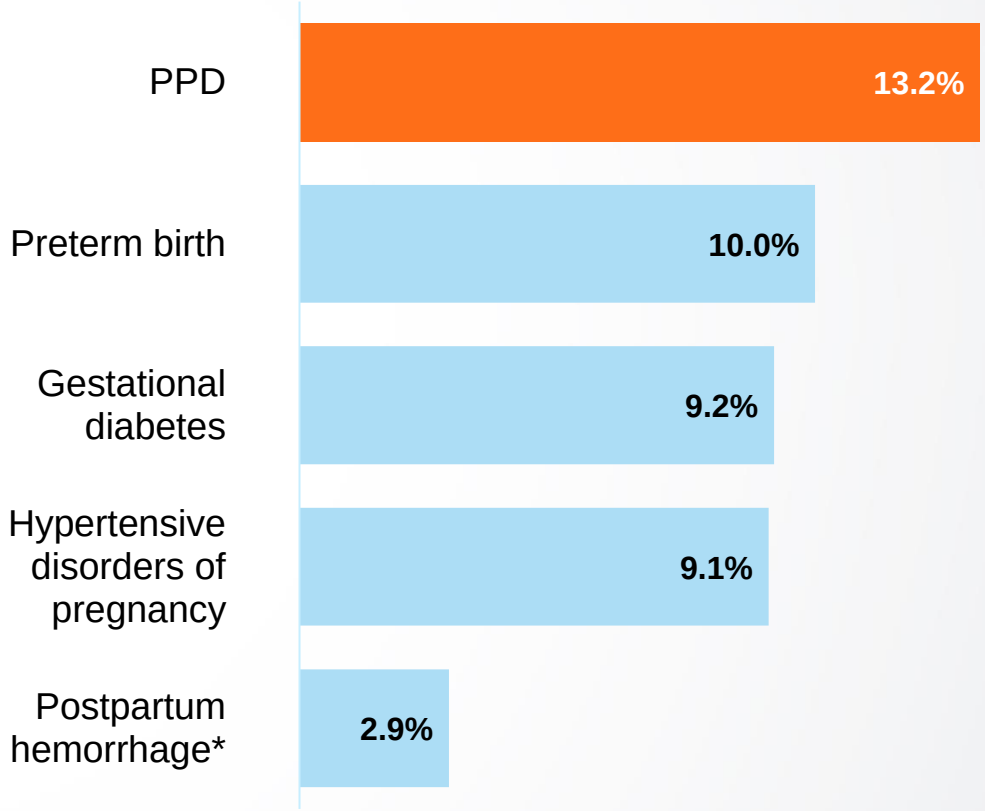
~1 in 8 (13.2%) women experience symptoms of PPD in the US[1,2]



Patients with PPD symptoms: ~500k[3,4]

Patients *diagnosed* with PPD (28%): ~133k[5]

Estimated Rates of Common Complications of Childbirth:[6-12]



**Includes both primary and secondary postpartum hemorrhage.*

1. Bauman BL, et al. MMWR Morb Mortal Wkly Rep. 2020;69(19):575-581 2. Data on file. PPD epidemiology 07-16-2020. 3. Bauman BL, et al. Morb Mortal Wkly Rep. 2020; 69(19):575-581. 4. CDC. National Vital Statistics Report. Volume 70, Number 17; February 7, 2022. https://www.cdc.gov/nchs/data/nvsr/nvsr70/nvsr70-17.pdf. 5. Gjerdingen D, et al. Ann Fam Med. 2009;7:63-70. 6. Bauman BL et al. MMWR Morb Mortal Wkly Rep. 2020;69(19):575-581. 7. Martin JA et al. National Vital Statistics Reports; vol 68 no 13. Hyattsville, MD: National Center for Health Statistics. 2019. 8. DeSisto CL et al. Prev Chronic Dis. 2014;11:E10. 9. Centers for Disease Control and Prevention. Updated June 12, 2018. Accessed March 26, 2020. https://www.cdc.gov/reproductivehealth/maternalinfanthealth/diabetes-during-pregnancy.htm 10. Centers for Disease Control and Prevention. Updated February 28, 2019. Accessed March 24, 2020. https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pregnancy-complications-data.htm 11. Roberts JM et al. American College of Obstetricians and Gynecologists Task Force on Hypertension in Pregnancy. Obstet Gynecol. 2013;122(5):1122-1131. 12. Callaghan WM et al. Am J Obstet Gynecol. 2010;202(4):353.e1-e6.

Zuranolone clinical data supports its potential to fulfill unmet needs for people with PPD, if approved

Rapid & Sustained

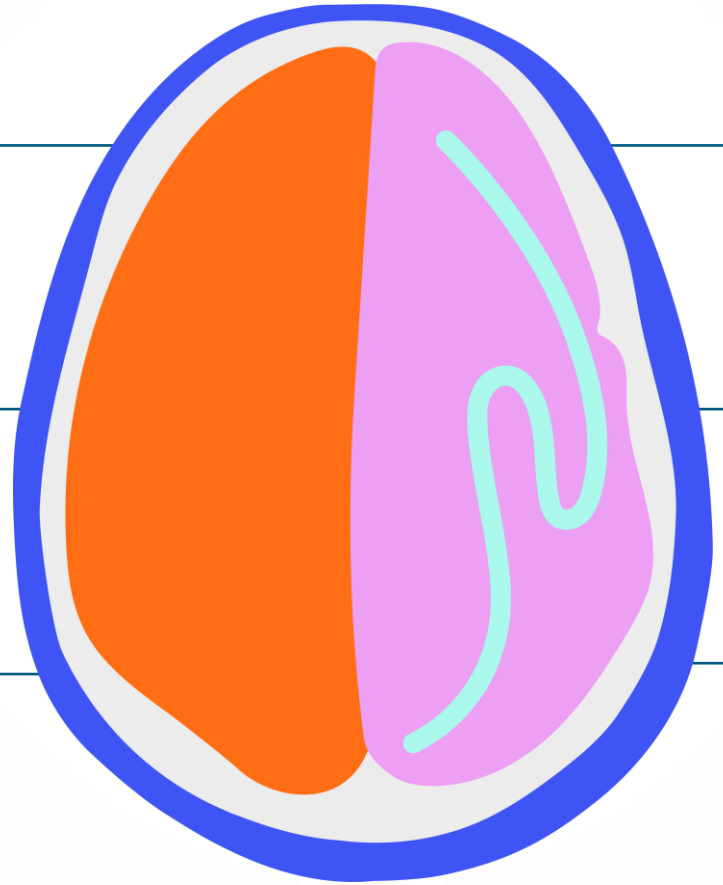
- Rapid response – seen in as few as 3 days
- Benefit that was sustained beyond last dose

Well-Tolerated

- Favorable tolerability profile

Improved Well-Being and Functioning

- Data from the ROBIN Study showed improvements across domains of patient quality of life



Short Course

- Once-daily, oral therapy
- 2-week, at-home treatment course

Novel MOA

- Selectively modulates GABAAR
- May help neuronal networks rebalance[1]

Flexible Approach

- Improvement seen in depressive symptoms in PPD patients when used as mono or adjunctive therapy
- Potential for PPD patients, many of whom experience elevated anxiety

Profile based on data demonstrated in clinical studies with zuranolone to date
Note: Success of zuranolone and the product profile depend on the clinical development program and regulatory approval.
[1]Antonoudiou, P. et al. Allopregnanolone mediates affective switching through modulation of oscillatory states in the basolateral amygdala. *Biological Psychiatry*, 2021.2003.2008.434156, doi:10.1016/j.biopsych.2021.07.017 (2021).

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Q&A