Health Technology Briefing
April 2023

Zuranolone for treating moderate to severe postpartum depression

Company/Developer	Biogen

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 13448	NICE TSID: 11863	UKPS ID: Not available

Licensing and Market Availability Plans

Zuranolone is currently in Phase III clinical trials.

Summary

Zuranolone is a medication currently in clinical development for the treatment of women with postpartum depression. Postpartum depression normally occurs within six weeks of a woman giving birth but can happen up to a year after delivery. The main symptoms are persistently feeling sad and having a low mood, a lack of interest and enjoyment in the wider world, a lack of energy and trouble sleeping at night, amongst others. These symptoms can impact on women's quality of life. Currently, treatment guidelines for severe postpartum depression recommend either undertaking an intensive psychological intervention (such as cognitive behavioural therapy), medicines, or a combination of both. However, these can sometimes take a long time to work, and women will often need to try many different treatment options to find one that works for them.

Zuranolone is a type of medication called a neuroactive steroid, which works by targeting specific brain functions that are responsible for functions such as mood, arousal, behaviour, and cognition. In clinical trials, it has been administered as either an oral solution or an oral capsule. If licensed, zuranolone will provide another treatment option for women with postpartum depression.

Proposed Indication

Treatment of severe postpartum depression in women.[1,2]

Technology

Description

Zuranolone (SAGE-217, BIIB125) is an investigational oral neuroactive steroid (NAS) GABA-A receptor positive allosteric modulator (PAM).[3] The GABA system is the major inhibitory signalling pathway of the brain and central nervous system, contributing to regulating brain function.[3] It has been theorised that postpartum depression could develop due to perinatal changes in circulating levels of allo-pregnanolone, a NAS GABA-A receptor ($GABA_AR$)–PAM.[4] Zuranolone has a novel mechanism of action as a positive allosteric modulator of GABA-A receptors, helping to rebalance dysregulated neuronal networks to improve brain functions such as mood, arousal, behaviour and cognition.[5]

Zuranolone is being evaluated in women with postpartum depression. In two phase III trials (NCT02978326, NCT04442503), zuranolone was administered orally to women with postpartum depression.[1,2] In one of the trials (ROBIN, NCT02978326), zuranolone was administered twice daily as 15mg or 20mg oral solution, or 30mg capsules orally once daily.[1] In a second trial (SKYLARK, NCT04442503), zuranolone was administered once daily as 50mg oral capsules.[2,3]

Key Innovation

Current treatments for postpartum depression can take weeks or months to provide relief from symptoms, with people needing to cycle through treatment options to address their needs.[5] Preclinical studies have previously demonstrated that administering a $GABA_AR$–PAM that targets both synaptic and extrasynaptic receptors in late pregnancy could reduce postpartum depression-like behaviour in mice.[6] The efficacy and safety of zuranolone has been evaluated against placebo in two Phase III clinical trials (ROBIN, NCT02978326 and SKYLARK, NCT04442503).[1,2] In these trials, zuranolone has showed statistically significant improvements from baseline in HAMD-17 score at day 15 and was generally well-tolerated.[3,4] If licensed, the availability of zuranolone may provide an additional treatment option for women with postpartum depression.

Regulatory & Development Status

Zuranolone does not currently have marketing authorisation in the EU/UK for any indication. Zuranolone has the following regulatory designation: a Breakthrough Therapy by the US FDA for postpartum depression in 2022.[3]

Zuranolone is also currently in a phase III trial for major depressive disorder (MDD).[7]

Patient Group

Disease Area and Clinical Need

Postpartum depression is common type of depression that affects women after they have given birth. The causes of postpartum depression are not clear but risk factors include: a history of mental health problems earlier in life; a history of mental health problems during pregnancy; having no close friends or family as

support; having a difficult relationship with a partner; recent stressful life events (e.g. bereavement); and physical or psychological trauma (e.g. domestic abuse).[8] Postpartum depression usually manifests within six weeks of giving birth but can emerge up to a year after the baby is born.[9] Postpartum depression can dissipate in a few months but 3 in 10 people will still have the condition after the first year.[9] The main symptoms of postpartum depression include: feeling sad, low in mood or tearful most of the time; feeling agitated or irritable towards a partner, baby or other children; lack of energy and feeling constantly tired; difficulty sleeping at night; issues concentrating or making decisions; loss or appetite or overeating; negative thoughts; feelings of guilt; feeling anxious that something bad may happen to the baby; and problems bonding with the baby, with no sense of enjoyment being with them.[10]

It is estimated that postpartum depression affects more than 1 in every 10 women within a year of giving birth.[8] In a cohort study conducted in the UK between 2000 and 2013, 23,623 of 206,517 (11%) of women had a record of depressive diagnosis or symptoms in the year after delivery, with more than one in eight women receiving antidepressant treatment.[11] At the time of writing this briefing, more updated data for the population likely to receive zuranolone could not be estimated from available published sources. However, statistics note that there were 694,684 births in the UK in 2021.[12] With the assumption that these were all singleton births, there may have been up to 69,468 cases of postpartum depression in 2021.

Recommended Treatment Options

Currently, the National Institute for Health and Care Excellence (NICE) recommend the following interventions for women with moderate or severe depression in pregnancy or the postnatal period:[13]

- a high-intensity psychological intervention, such as cognitive behavioural therapy (CBT);
- a tricyclic antidepressant, SSRI, or SNRI if the woman understands the risks associated with the medication and has either expressed a preference for medication, has declined psychological intervention or has symptoms that have not responded to psychological intervention; or
- a high-intensity psychological intervention combined with medication if the woman understands the risks associated with the medication and has symptoms that have had a limited response or no response to psychological intervention or medication alone.

If a woman's postnatal depression is very severe and does not respond to treatment, they may be referred to a specialist community perinatal mental health team.[14]

Clinical Trial Information

Trial	**ROBIN,** NCT02978326; A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of SAGE-217 in the Treatment of Adult Female Subjects With Severe Postpartum Depression **Phase III** – Completed **Location(s):** USA **Study completion date:** 11 December 2018
Trial Design	Randomised, parallel assignment, quadruple-blind, placebo-controlled
Population	N = 276 (actual); Has ceased lactating at screening or must agree to temporarily ceasing giving breast milk to their infant(s); had a major depressive episode that began no earlier than the third trimester and no later than the first four weeks

	following delivery as diagnosed by the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM) 5 Axis I Disorders (SCID-I); ≤ six months postpartum; female aged between 18 and 45 years.
Intervention(s)	Part A: SAGE-217 oral solution at 15mg twice daily for the first two days, followed by SAGE-217 at 15mg or 20 mg oral solution twice daily starting on day three for up to 14 days, as tolerated Part B: SAGE-217 30mg capsules orally, once daily for up to 14 days
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome: • Change from baseline in the 17-Item Hamilton Rating Scale for Depression (HAM-D); total score at day 15 [Time frame: Parts A and B: baseline, day 15] See trial record for full list of other outcomes
Results (efficacy)	Zuranolone showed statistically significant day 15 HAMD-17 score improvements from baseline compared with placebo (−17.8 vs −13.6; difference, −4.2; 95% CI −6.9 to −1.5; P = 0.003). Sustained differences in HAMD-17 scores favouring zuranolone were observed from day three (difference, −2.7; 95% CI, −5.1 to −0.3; P = .03) through to day 45 (difference, −4.1; 95% CI, −6.7 to −1.4; P = .003).Sustained differences at day 15 favouring zuranolone were observed in HAMD-17 response (odds ratio, 2.63; 95% CI, 1.34-5.16; P = .005), HAMD-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)[4]
Results (safety)	Zuranolone was generally well tolerated. The most common treatment-emergent AEs in the zuranolone group (≥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 (≥5%) were headache (12% [9 of 73]), somnolence (11% [8 of 73]), nausea (8% [6 of 73]), dizziness (6% [4 of 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.[4]

Trial	**SKYLARK**, NCT04442503, EudraCT- 2020-001424-34; A Randomized, Double-Blind, Placebo-controlled Study Evaluating the Efficacy and Safety of SAGE-217 in the Treatment of Adults With Severe Postpartum Depression **Phase III** – Completed **Location(s)** – One country in the EU, UK and USA **Study completion date**: 12 April 2022
Trial Design	Randomised, parallel assignment, quadruple-blinded, placebo-controlled

Population	N = 200 (actual); has ceased lactating at screening or must agree to temporarily ceasing giving breast milk to their infant(s); had a major depressive episode that began no earlier than the third trimester and no later than the first four weeks following delivery as diagnosed by the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM) 5 Axis I Disorders (SCID-I); ≤ 12 months postpartum at screening and day one; female aged between 18 and 45 years.
Intervention(s)	Zuranolone 50mg oral capsules, once daily for 14 days.[3]
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome: • Change from baseline in the 17-Item Hamilton Rating Scale for Depression (HAM-D); total score at day 15 [Time frame: baseline, day 15] See trial record for full list of other outcomes
Results (efficacy)	Women treated with zuranolone (n=98) demonstrated statistically significant and clinically meaningful improvement in depressive symptoms at day 15 compared to placebo (n=97) as measured by a change from baseline (CFB) in the HAMD-17 total score. The least-squares (LS) mean (SE) CFB in HAMD-17 total score at Day 15 for women who received zuranolone 50 mg was -15.6 (0.82) compared with -11.6 (0.82) for women who received placebo (LS mean difference -4.0 points; p=0.0007). The study met all key secondary endpoints, with rapid and statistically significant improvement in depressive symptoms as early as Day 3 for participants treated with zuranolone 50 mg compared to placebo, which was sustained at all measured timepoints through Day 45 as measured by CFB in HAMD-17 total score.[3]
Results (safety)	Zuranolone was well-tolerated, with the majority of treatment-emergent adverse events (TEAEs) in both arms being mild to moderate in severity. The most common TEAEs in the zuranolone arm were somnolence, dizziness, sedation, headache, diarrhoea, nausea, urinary tract infection and COVID-19.[3]

Estimated Cost

The cost of zuranolone is not yet known.

Relevant Guidance

NICE Guidance

- NICE clinical guideline. Postnatal care (NG194). April 2021.
- NICE clinical guideline. Antenatal and postnatal mental health: clinical management and service guidance (CG192). February 2020.
- NICE quality standard. Postnatal care (QS37). September 2022.
- NICE quality standard. Antenatal and postnatal mental health (QS115). February 2016.

NHS England (Policy/Commissioning) Guidance

- NHS. NHS mental health implementation plan 2019/20 - 2023/24. Publishing Approval Reference: 000830. July 2019.
- NHS England. Implementing the Five Year Forward View for Mental Health. Gateway Reference: 05574. July 2016.

Other Guidance

- World Health Organization. WHO recommendations on Postnatal care of the mother and newborn. 2013.[15]
- Royal College of Obstetricians and Gynaecologists. Management of Women with Mental Health Issues during Pregnancy and the Postnatal Period. 2011.[16]

Additional Information

Biogen did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

References

1 ClinicalTrials.gov. *A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of SAGE-217 in the Treatment of Adult Female Subjects With Severe Postpartum Depression. Trial ID: NCT02978326.* 2016. Status: Completed. Available from: https://clinicaltrials.gov/ct2/show/NCT02978326 [Accessed 13 February 2023].

2 ClinicalTrials.gov. *A Randomized, Double-Blind, Placebo-controlled Study Evaluating the Efficacy and Safety of SAGE-217 in the Treatment of Adults With Severe Postpartum Depression. Trial ID: NCT04442503.* 2020. Status: Completed. Available from: https://clinicaltrials.gov/ct2/show/NCT04442503 [Accessed 13 February 2023].

3 Biogen. *Sage Therapeutics and Biogen Announce that the Phase 3 SKYLARK Study of Zuranolone in Postpartum Depression Met its Primary and All Key Secondary Endpoints*. 2022. Available from: https://investors.biogen.com/news-releases/news-release-details/sage-therapeutics-and-biogen-announce-phase-3-skylark-study [Accessed 13 February 2023].

4 Deligiannidis KM, Meltzer-Brody S, Gunduz-Bruce H, Doherty J, Jonas J, Li S, et al. Effect of Zuranolone vs Placebo in Postpartum Depression: A Randomized Clinical Trial. *JAMA Psychiatry*. 2021;78(9):951-9. Available from: https://doi.org/10.1001/jamapsychiatry.2021.1559.

5 Biogen. *Biogen and Sage Therapeutics Complete Rolling Submission of New Drug Application for Zuranolone in the Treatment of Major Depressive Disorder and Postpartum Depression*. 2022. Available from: https://investors.biogen.com/news-releases/news-release-details/biogen-and-sage-therapeutics-complete-rolling-submission-new [Accessed 13 February 2023].

6 Melón L, Hammond R, Lewis M, Maguire J. A Novel, Synthetic, Neuroactive Steroid Is Effective at Decreasing Depression-Like Behaviors and Improving Maternal Care in Preclinical Models of Postpartum Depression. *Frontiers in Endicoronology*. 2018;9(703). Available from: https://doi.org/10.3389/fendo.2018.00703.

7 ClinicalTrials.gov. *Search for: SAGE-217 | Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | Phase 2, 3*. 2023. Available from: https://clinicaltrials.gov/ct2/results?term=SAGE-217&Search=Apply&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=&rslt=&phase=1&phase=2 [Accessed 23 February 2023].

8 National Health Service. *Overview - Postnatal depression*. 2022. Available from: https://www.nhs.uk/mental-health/conditions/post-natal-depression/overview/ [Accessed 13 February 2023].

9 National Childbirth Trust. *Perinatal depression: the questions you really want to ask*. 2022. Available from: https://www.nct.org.uk/life-parent/how-you-might-be-feeling/perinatal-depression-questions-you-really-want-ask [Accessed 13 February 2023].

10 National Health Service. *Symptoms - Postnatal depression*. 2022. Available from: https://www.nhs.uk/mental-health/conditions/post-natal-depression/symptoms/ [Accessed 13 February 2023].

11 Petersen I, Peltola T, Kaski S, Walters KR, Hardoon S. Depression, depressive symptoms and treatments in women who have recently given birth: UK cohort study *BMJ Open*. 2018;8(10):e022152. Available from: https://doi.org/10.1136/bmjopen-2018-022152.

12 Statista. *Number of live births in the United Kingdom from 1887 to 2021*. 2023. Available from: www.statista.com/statistics/281981/live-births-in-the-united-kingdom-uk/ [Accessed 28 March 2023].

13 National Institute for Health and Care Excellence. *Antenatal and postnatal mental health: clinical management and service guidance (CG192)*. 2020. Available from: https://www.nice.org.uk/guidance/cg192 [Accessed 13 February 2023].

14 National Health Service. *Treatment - Postnatal depression*. 2022. Available from: https://www.nhs.uk/mental-health/conditions/post-natal-depression/treatment/ [Accessed 13 February 2023].

15 World Health Organization. *WHO recommendations on Postnatal care of the mother and newborn*. Available from: https://www.who.int/publications/i/item/9789241506649 [Accessed 28 March 2023].

16 Royal College of Obstetricians and Gynaecologists. *Management of Women with Mental Health Issues during Pregnancy and the Postnatal Period (Good Practice No14)*. Available from: https://www.rcog.org.uk/media/4gikqggv/managementwomenmentalhealthgoodpractice14.pdf [Accessed 28 March 2023].

NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.