Innovation Observatory

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EVIDENCE BRIEFING
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Brexanolone for postpartum depression

NIHRIO ID	10557	**NICE ID**	9223
Developer/Company	Sage Therapeutics Inc.	**UKPS ID**	650593

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Brexanolone as an injection for intravenous infusion is in clinical development for women with moderate and severe postpartum depression (PPD). PPD is a mood disorder that can affect women after childbirth. Women with PPD experience feelings of extreme sadness, anxiety, and exhaustion that may make it difficult for them to complete daily care activities for themselves or for others. After childbirth, the levels of certain hormones in a woman's body quickly drops, leading to chemical changes in areas of the brain that regulates mood. Current treatment of PPD with existing medications such as antidepressants do not address the underlying chemical changes, often resulting in treatment failures.

Brexanolone is an active product of the female reproductive hormone progesterone that regulates a specific neurotransmitter involved in a range of behaviours, including the stress response. Some small studies have shown that brexanolone rapidly and significantly improves the symptoms of PPD and other hormonal mood disorders when compared to other treatments. If licensed brexanolone would be the first PPD treatment that specifically targets the underlying disease process in PPD.

PROPOSED INDICATION

Moderate and severe postpartum depression (PPD).[1,2]

TECHNOLOGY

DESCRIPTION

Brexanolone (SAGE-547; allopregnanolone) is a neuroactive metabolite of progesterone and a barbiturate-like modulator of central gamma-aminobutyric acid (GABA) receptors that modify a range of behaviours, including the stress response. GABA is the primary inhibitory neurotransmitter in the brain. Brexanolone is a steroid created in the body when progesterone, the female sex hormone, is metabolized.[3] It is an allosteric modulator of both synaptic and extrasynaptic GABA type A ($GABA_A$) receptors. Allosteric modulation of neurotransmitter receptor activity results in varying degrees of desired activity rather than complete activation or inhibition of the receptor.[4]

Brexanolone is in clinical development for women with moderate and severe postpartum depression (PPD). In three pivotal trials, patients were randomly assigned to receive a single intravenous injection of either brexanolone 90µg/kg/h, brexanolone 60µg/kg/h, or matching placebo for 60 hours.[1, 5, 6, 2] Brexanolone is a sterile solution of allopregnanolone 5mg/mL in 250 mg/mL sulfobutylether-β cyclodextrin (SBECD) buffered with citrate, which is diluted with sterile water for injection to render it isotonic for intravenous infusion.[7]

INNOVATION AND/OR ADVANTAGES

Considering the pathophysiology of depression in the perinatal period and the negative consequences of untreated PPD, development of efficacious new treatments with more targeted mechanisms of action is warranted.[8]

Selective serotonin reuptake inhibitors (SSRIs) are commonly used as first-line PPD treatment. However, there is limited evidence for their use in the postpartum period specifically, and the proportion of PPD patients treated successfully with SSRIs have a success rate of 43%–88%.[8] Studies have suggested that only 3.2% of women with PPD achieve remission with current treatments.[9]

Preclinical and clinical studies have shown that neuroactive steroids might have an important role in the pathophysiology of PPD.[7] Specifically, the inability of the GABA system to adapt to changes in neuroactive steroid levels during the peripartum period may mediate the onset of PPD symptoms.[10] Neuroactive steroids such as allopregnanolone might function as behavioural switches, suggesting a potentially important role in treatment of reproductive and endocrine-related mood disorders such as PPD. Studies suggest the potential for the development of brexanolone, as a new mechanism for treatment of PPD that is related to the underlying pathophysiology.[7]

According to the Royal College of Psychiatrists, antidepressants may take at least 2 weeks to start working and one might need to take them for around 6 months before they start to feel better. The rapid and marked antidepressant response associated with brexanolone administration contrasts with the time duration needed (and low remission rates) with SSRIs and other antidepressants. The rapid onset of action and duration of effect observed in studies compared to placebo suggest that brexanolone has the potential to address unmet needs in the treatment of patients suffering from PPD.[11]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Brexanolone does not currently have Marketing Authorisation in the UK/EU for any indication.[12]

Brexanolone was granted a PRIME status for PPD by the EMA in November 2016.[13]

Brexanolone was granted a Breakthrough Therapy Designation for PPD by the FDA in September 2016.[14]

PATIENT GROUP

DISEASE BACKGROUND

Postpartum depression (PPD) is a mood disorder that can affect women after childbirth. The condition is common in the perinatal period and remains underdiagnosed and often untreated.[8] Women with PPD experience a range of symptoms, including feelings of extreme sadness, anxiety, and exhaustion that may make it difficult for them to complete daily care activities for themselves or for others.[15]

The exact pathophysiology of PPD is unknown; however, recent evidence supports the hypothesis that PPD may be triggered by an inability of the brain to adapt to fluctuations in allopregnanolone that occur in the peripartum period. This may contribute to the development of changes in network connectivity in the brain associated with depressed brain states in PPD.[16,17]

While the precise factors leading to susceptibility to PPD are not understood, altered profiles of neuroactive steroids and GABA have been observed in women at risk for PPD.[16] In addition, animal models suggest GABA type A ($GABA_A$) receptor expression may contribute to susceptibility for PPD; some types of $GABA_A$ receptors are down-regulated in the brain during pregnancy and recover to pre-pregnancy levels postpartum, in sync with the rise and fall of allopregnanolone.[18] Furthermore, mice deficient in these receptors exhibit depressive-like behaviours only in the postpartum period, suggesting $GABA_A$ receptors may be involved in the ability of brain to respond to fluctuations in neuroactive steroids.[19]

A growing clinical literature suggests that negative mood states during a depressive episode may result from a failure to regulate the activity of multi-region brain networks.[19] Dysregulated network connectivity has been associated broadly with major depressive episodes[20,21,22] and more recently has been observed in PPD,[23] which has also been associated with disruption of resting-state functional network connectivity.[16,17] For example, in a prospective human imaging study in women 9 weeks postpartum, PPD subjects had an attenuation of network connectivity in the anterior cingulate cortex, amygdala, hippocampus, and dorsolateral prefrontal cortex compared to healthy postpartum women.[16]

PPD is a common problem and affects more than 1 in every 10 women within a year of giving birth. It can also affect fathers and partners.[24] Around a third of PPD begins in pregnancy and around a quarter begins before pregnancy.[25] PPD can lead to significant morbidity and mortality for the mother and infant.[5]

Studies suggest that mothers experiencing symptoms of PPD may have long-term impact on child development. Symptoms of PPD among mothers at 2 months post birth were found to significantly increase the risk for behavioural problems in children at age 3.5 years. Children of women with severe PPD symptoms that persisted to 8 months after birth were also found to have higher risk of lower mathematics grades at age 16 years, and depression at age 18 years.[26]

CLINICAL NEED AND BURDEN OF DISEASE

In clinical practice it is estimated that between 10-19% of women will suffer with some form of depression in the first year after the delivery of their baby.[27] At least 7% will have mild major depressive illness and many more could be described as having minor depression; 3-5% will suffer a severe major PPD episode.[28]

Without treatment, most women will recover spontaneously within 3-6 months; however, 1 in 10 will remain depressed at one year.[28] Nearly 9% (8.77%) of mothers were identified as having persistent depressive symptoms (i.e. at 2 and 8 months) in an observational study of 9,848 UK women with varying levels of symptoms of PPD, and the subset of women with persistent depressive symptoms were more likely to display depressive symptoms up to 11 years after childbirth.[26]

A recent examination of the costs of perinatal mental health problems in the UK in 2012 – 2013 reviewed a 5 longitudinal studies examining depression in mothers during pregnancy and after birth which also followed children over time up to age 18. This review suggests that children of mothers with PPD face higher risk of pre-term birth and cognitive impairment, infant death, emotional and conduct problems in childhood and adolescence, special education needs, and leaving school without qualifications. Researchers estimated that the average cost to society of one case of perinatal depression is around £74,000, of which £23,000 relates to the mother and £51,000 relates to impacts on the child.[29]

According to the Office for National Statistics, the number of women who gave birth in 2017 was 679,109.[30] Applying the above percentage to this figure, between 67,910 and 101,866 will have some form of depression in the first year after giving birth. Around 47,538 will have mild depressive illness and between 20,373 and 33,955 will have severe depressive illness. Around 67,910 will remain depressed at one year.

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

According to NICE guidelines regarding antenatal and postnatal mental health, women in postnatal period should be given supportive care along with their partner, family and carers. An integrated plan should be developed which sets out the care and treatment for the mental health problem, the roles of all healthcare professional including who is responsible for coordinating the integrated care plan, the schedule of monitoring and providing the interventions and agreeing the outcomes with the woman.[31]

The three main types of treatment are self-help strategies, therapy and medication which are as follows:[32]

- Self-help involves taking care of oneself, talking to the partner, friends and family, resting well, exercising and eating regularly.
- Therapy/psychological treatments involve guided self-help, cognitive behavioural therapy and interpersonal therapy.
- Medication entails antidepressants for moderate to severe depression and if the patient does not want to try psychological treatment or it has proven unhelpful.

CURRENT TREATMENT OPTIONS

- For a woman with persistent subthreshold depressive symptoms, or mild to moderate depression, in postnatal period, consider facilitated self-help.
- For a woman with a history of severe depression who initially presents with mild depression in pregnancy or the postnatal period, consider a tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) or serotonin and norepinephrine reuptake inhibitors (SNRIs).[31]
- For a woman with moderate or severe depression in pregnancy or the postnatal period, following options should be considered:[31]
    - A high-intensity psychological intervention (for example, cognitive behavioural therapy)
    - TCA, SSRI or SNRI
    - A high-intensity psychological intervention in combination with medication.

PLACE OF TECHNOLOGY

If licensed brexanolone may offer a new treatment option that specifically targets the underlying disease process in women with PPD.

CLINICAL TRIAL INFORMATION

Trial	NCT02942004, **547-PPD-202 B; adult females aged 18–45 years; brexanolone vs placebo, phase III**
Sponsor	Sage Therapeutics Inc.
Status	Completed
Source of Information	Trial registry;[1] Publication;[5] Company
Location	US
Design	Randomised, placebo-controlled, parallel assignment
Participants	n=138; aged 18-45 years; females; severe postpartum depression
Schedule	BRX90 group: Each patient received a single continuous infusion of brexanolone for 60h according to the following schedule: 30µg/kg per h (0–4 h); 60µg/kg per h (4–24 h); 90µg/kg per h (24–52 h); 60µg/kg per h (52–56 h); 30µg/kg per h (56–60 h). BRX60 group: Each patient received brexanolone according to the same dosing schedule, but were administered 60µg/kg per h at 24–52 h.
Follow-up	Active treatment 60 hours, follow-up 30 days
Primary Outcomes	Effect of brexanolone on depressive symptoms in subjects with severe postpartum depression compared to placebo injection as measured by the change from baseline in Hamilton Rating Scale for Depression (HAM-D) total score [Time frame: Hour 60]
Secondary Outcomes	• Secondary efficacy outcome measures were mean HAM-D total score and least-squares (LS) mean change from baseline during the inpatient stay at 0, 2, 4, 8, 12, 24, 36, 48, 60, and 72 h after infusion and follow-up days 7 and 30; HAM-D total scores were further examined for remission (HAM-D total

	score ≤7) and response (reduction in HAM-D total score ≥50%); Clinical Global Impression-Improvement (CGI-I) response, defined as a rating score of 1 (very much improved) or 2 (much improved); change from baseline in score on the Montgomery-Åsberg Depression Rating Scale; change from baseline in HAM-D subscale (including Bech 6, Core, Anxiety, and Maier) score and individual item scores; and change from baseline in scores on the Edinburgh Postnatal Depression Scale, Patient Health Questionnaire, and the Generalized Anxiety Disorder 7-item questionnaire[a] • Safety and tolerability of brexanolone compared with placebo as measured by the change from baseline in the incidence of adverse events, vital signs, clinical laboratory evaluations, and ECG parameters [Time frame: 30 days] • Safety of brexanolone compared to placebo as measured by the change from baseline in suicidal ideation and behaviour assessed by the Columbia Suicide Severity Rating Scale (C-SSRS) score [Time frame: 30 days]
Key Results	HAM-D total scores were significantly reduced in the BRX60 group compared with the placebo group at 24 h and all time points thereafter in the BRX60 group. At 60 h, the primary endpoint, the least-squares (LS) mean reduction in HAM-D total score from baseline was 19.5 points (SE 1.2) in the BRX60 group and 17.7 points (SE 1.2) in the BRX90 group compared with 14.0 points (SE 1.1) in the placebo group (difference –5.5 [95% CI –8.8 to –2.2], p=0.0013 for the BRX60 group; –3.7 [95% CI –6.9 to –0.5], p=0.0252 for the BRX90 group).
Adverse effects (AEs)	19 patients in the BRX60 group and 22 patients in the BRX90 group had adverse events compared with 22 patients in the placebo group. The most common treatment-emergent adverse events in the brexanolone groups were headache (n=7 BRX60 group and n=6 BRX90 group vs n=7 placebo), dizziness (n=6 BRX60 group and n=6 BRX90 group vs n=1 placebo group), and somnolence (n=7 BRX60 group and n=2 BRX90 group vs n=3 placebo group). One patient in the BRX60 group had two serious adverse events (suicidal ideation and intentional overdose attempt during follow-up). This subject had active suicidal ideation at baseline.
Expected reporting date	-

Trial	**NCT02942017, 547-PPD-202 C; adult females aged 18–45 years; brexanolone vs placebo, phase III**
Sponsor	Sage Therapeutics Inc.
Status	Completed
Source of Information	Trial registry;[2] Publication;[5] Company
Location	US
Design	Randomised, placebo-controlled, parallel assignment
Participants	n=108; aged 18-45 years; females; moderate postpartum depression (HAM-D total score 20-25)
Schedule	BRX90 group: Each patient received a single continuous infusion of brexanolone for 60h according to the following schedule: 30µg/kg per h (0–4 h); 60µg/kg per

	h (4–24 h); 90µg/kg per h (24–52 h); 60µg/kg per h (52–56 h); 30µg/kg per h (56–60 h). Placebo group: matching placebo infusion
Follow-up	Active treatment 60 hours, follow-up 30 days
Primary Outcomes	Effect of brexanolone on depressive symptoms in subjects with moderate postpartum depression compared to placebo injection as measured by the change from baseline in Hamilton Rating Scale for Depression (HAM-D) total score [Time frame: 3 days]
Secondary Outcomes	• Secondary efficacy outcome measures were mean HAM-D total score and least-squares (LS) mean change from baseline during the inpatient stay at 0, 2, 4, 8, 12, 24, 36, 48, 60, and 72 h after infusion and follow-up days 7 and 30; HAM-D total scores were further examined for remission (HAM-D total score ≤7) and response (reduction in HAM-D total score ≥50%); Clinical Global Impression-Improvement (CGI-I) response, defined as a rating score of 1 (very much improved) or 2 (much improved); change from baseline in score on the Montgomery-Åsberg Depression Rating Scale; change from baseline in HAM-D subscale (including Bech 6, Core, Anxiety, and Maier) score and individual item scores; and change from baseline in scores on the Edinburgh Postnatal Depression Scale, Patient Health Questionnaire 9, and the Generalized Anxiety Disorder 7-item questionnaire • Safety and tolerability of brexanolone compared with placebo as measured by the change from baseline in the incidence of adverse events, vital signs, clinical laboratory evaluations, and ECG parameters [Time frame: 30 days] • Safety of brexanolone compared to placebo as measured by the change from baseline in suicidal ideation and behaviour assessed by the Columbia Suicide Severity Rating Scale (C-SSRS) score [Time frame: 30 days]
Key Results	HAM-D total scores were significantly reduced in the BRX90 group compared with the placebo group at 48h and until day 7. At 60 h, the LS mean reduction in HAM-D total score from baseline was 14.6 points (SE 0.8) in the BRX90 group compared with 12.1 points (SE 0.8) for the placebo group (difference –2.5 [95% CI –4.5 to –0.5], p=0.0160)
Adverse effects (AEs)	25 patients in the BRX90 group had adverse events compared with 24 patients in the placebo group. The most common treatment-emergent adverse events in the brexanolone groups were headache (n=9 BRX90 group vs n=6 placebo group), dizziness (n=5 BRX90 group vs n=4 placebo group for study 2), and somnolence (n=4 BRX90 group vs n=2 placebo group for study 2). One patient in the BRX90 group had two serious adverse events (altered state of consciousness and syncope), which were considered to be treatment related.
Expected reporting date	-

Trial	**NCT02614547, 547-PPD-202 A; adult females aged 18–45 years; brexanolone vs placebo, phase II**
Sponsor	Sage Therapeutics Inc.
Status	Completed
Source of Information	Trial registry;[6] Publication;[7] Company
Location	US
Design	Randomised, placebo-controlled, parallel assignment
Participants	n=32 (planned); aged 18-45 years; females; severe postpartum depression (HAM-D total score ≥26)

Schedule	Patients received a single continuous intravenous infusion of brexanolone for 60h during inpatient care under the following schedule: 30µg/kg per h (0–4 h); 60µg/kg per h (4–24 h); 90µg/kg per h (24–52 h); 60µg/kg per h (52–56 h); 30µg/kg per h (56–60 h)
Follow-up	Active treatment 60 hours, follow-up 30 days
Primary Outcomes	Effect of brexanolone on depressive symptoms in subjects with severe postpartum depression compared to placebo injection as measured by the change from baseline in Hamilton Rating Scale for Depression (HAM-D) total score [Time frame: 3 days]
Secondary Outcomes	• Secondary analyses included changes in HAM-D score from baseline at 2 h up to 30 days. HAM-D measurements were obtained frequently to monitor for rapid onset of improvement of symptoms and were started within a window of tolerance of 25 min before or after the designated timepoint in the first 24 h. Secondary HAM-D endpoints were the proportion of patients achieving remission (HAM-D total score ≤7), the proportion of patients achieving response (≥50% reduction in HAM-D total score), change from baseline in the Bech-6 subscore, Montgomery-Åsberg Depression Rating Scale (MADRS) total score, Clinical Global Impression-Global Improvement, major depression, and changes in the HAM-D depressed mood item score. Additional prespecified secondary and exploratory endpoints are detailed in the appendix, including the Generalised Anxiety Disorder Questionnaire, Edinburgh Postnatal Depression Scale, Patient Health Questionnaire-9, and Barkin Index of Maternal Function • Safety and tolerability of brexanolone compared with placebo as measured by the change from baseline in the incidence of adverse events, vital signs, clinical laboratory evaluations, and ECG parameters [Time frame: 30 days] • Safety of brexanolone compared to placebo as measured by the change from baseline in suicidal ideation and behaviour assessed by the Columbia Suicide Severity Rating Scale (C-SSRS) score [Time frame: 30 days]
Key Results	At the end of the 60 h infusion, mean reduction in HAM-D total score was 21.0 points (SE 2.9) in the brexanolone group, compared with 8.8 points (2.8) in the placebo group; mean difference between groups –12.2 points (95% CI –20.77 to –3.67; two-tailed t test, (p=0.0075). The effect size for the clinical efficacy at 60 h was 1.2. Prespecified secondary analyses showed a –11.3 point (95% CI –18.86 to –3.65) mean difference between groups at 24 h (two-tailed t test, p=0.0059), with significant improvements seen for the brexanolone group at 36, 48, 60, and 72 h, as well as days 7 and 30. Remission from depression (HAM-D total score ≤7) was seen in seven of ten patients in the brexanolone group and in one of 11 patients in the placebo group at 60h (OR −23.33, 95% CI −1.56 to 1152·71; Z test from log transformation of the OR, p=0·0364). This difference was seen at 24h (six patients in the brexanolone group vs one patient in the placebo group; OR 15·00, 95% CI 1·07–756·72; Z test, p=0·0561) and a difference was maintained until the 30-day follow-up (seven vs two; OR 10·50, 95% CI 1·01–140·57; Z test, p=0·0499). More patients demonstrated a 50% or greater reduction in HAM-D total score in the brexanolone group than in the placebo group across all timepoints. Although this finding was not significant at 60h (70% [seven patients] in the brexanolone group vs 36% [four patients] in the placebo group; p=0·1450), it did achieve significance at both 72h (80% [eight patients] brexanolone vs 27% [three patients] placebo; p=0·0374) and day 7 (80% [eight patients] brexanolone vs 20% [two patients] placebo; p=0·0335).
Adverse effects (AEs)	• There were no deaths, serious adverse events, or discontinuations in either group. Overall, fewer patients who received brexanolone reported adverse

	events compared with patients who received placebo (four of ten patients in the brexanolone group vs eight of 11 in the placebo group). • The most frequently reported adverse events in the brexanolone group were dizziness (two patients in the brexanolone group vs three patients in the placebo group) and somnolence (two vs none). Sedation was reported in one patient in the brexanolone group and in no patients in the placebo group. • Moderate treatment-emergent adverse events in the brexanolone group were sinus tachycardia (one [10%] patient) and somnolence (one [10%] patient). One (9%) patient in the placebo group had a severe treatment-emergent adverse event of insomnia. • Moderate treatment-emergent adverse events in the placebo group were infusion site pain (one [9%] patient) and tension headache (one [9%] patient). All other treatment-emergent adverse events in both groups were mild.
Expected reporting date	-

ESTIMATED COST

The cost of brexanolone is yet not known.

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE clinical guideline. Antenatal and postnatal mental health: clinical management and service guidance (CG192). December 2014. Last updated April 2018.
- NICE quality standard. Antenatal and postnatal mental health (QS115). February 2016.
- NICE clinical guideline. Postnatal care up to 8 weeks after birth (CG37). July 2006. Last updated February 2015.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- No relevant guidance identified.

OTHER GUIDANCE

- Scottish Intercollegiate Guidelines Network (SIGN). Management of perinatal mood disorders. 2012.[33]

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