# Brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials

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## Summary

**Background** Post-partum depression is associated with substantial morbidity, and improved pharmacological treatment options are urgently needed. We assessed brexanolone injection (formerly SAGE-547 injection), a positive allosteric modulator of γ-aminobutyric-acid type A ($GABA_A$) receptors, for the treatment of moderate to severe post-partum depression.

**Methods** We did two double-blind, randomised, placebo-controlled, phase 3 trials, at 30 clinical research centres and specialised psychiatric units in the USA. Eligible women were aged 18–45 years, 6 months post partum or less at screening, with post-partum depression and a qualifying 17-item Hamilton Rating Scale for Depression (HAM-D) score (≥26 for study 1; 20–25 for study 2). Women with renal failure requiring dialysis, anaemia, known allergy to allopregnanolone or to progesterone, or medical history of schizophrenia, bipolar disorder, or schizoaffective disorder were excluded. Patients were randomly assigned (1:1:1) to receive a single intravenous injection of either brexanolone 90 μg/kg per h (BRX90), brexanolone 60 μg/kg per h (BRX60), or matching placebo for 60 h in study 1, or (1:1) BRX90 or matching placebo for 60 h in study 2. Patients, the study team, site staff, and the principal investigator were masked to treatment allocation. The primary efficacy endpoint was the change from baseline in the 17-item HAM-D total score at 60 h, assessed in all patients who started infusion of study drug or placebo, had a valid HAM-D baseline assessment, and had at least one post-baseline HAM-D assessment. The safety population included all randomised patients who started infusion of study drug or placebo. Patients were followed up until day 30. The trials have been completed and are registered with ClinicalTrials.gov, numbers NCT02942004 (study 1) and NCT02942017 (study 2).

**Findings** Participants were enrolled between Aug 1, 2016, and Oct 19, 2017, in study 1, and between July 25, 2016, and Oct 11, 2017, in study 2. We screened 375 women simultaneously across both studies, of whom 138 were randomly assigned to receive either BRX90 (n=45), BRX60 (n=47), or placebo (n=46) in study 1, and 108 were randomly assigned to receive BRX90 (n=54) or placebo (n=54) in study 2. In study 1, at 60 h, 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 (1·2) in the BRX90 group compared with 14·0 points (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). In study 2, 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). In study 1, 19 patients in the BRX60 group and 22 patients in the BRX90 group had adverse events compared with 22 patients in the placebo group. In study 2, 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=7 BRX60 group and n=6 BRX90 group *vs* n=7 placebo group for study 1; n=9 BRX90 group *vs* n=6 placebo group for study 2), dizziness (n=6 BRX60 group and n=6 BRX90 group *vs* n=1 placebo group for study 1; n=5 BRX90 group *vs* n=4 placebo group for study 2), and somnolence (n=7 BRX60 group and n=2 BRX90 group *vs* n=3 placebo group for study 1; n=4 BRX90 group *vs* n=2 placebo group for study 2). In study 1, one patient in the BRX60 group had two serious adverse events (suicidal ideation and intentional overdose attempt during follow-up). In 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.

**Interpretation** Administration of brexanolone injection for post-partum depression resulted in significant and clinically meaningful reductions in HAM-D total score at 60 h compared with placebo, with rapid onset of action and durable treatment response during the study period. Our results suggest that brexanolone injection is a novel therapeutic drug for post-partum depression that has the potential to improve treatment options for women with this disorder.

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## Research in context

### Evidence before this study

The relevance of γ-aminobutyric acid (GABA) signalling in post-partum depression has been established by numerous studies in animals and humans. Plasma concentrations of the neuroactive steroid allopregnanolone, a positive allosteric modulator of GABA type A ($GABA_A$) receptors, increase during pregnancy and decrease substantially after childbirth in both rodents and humans, and fluctuations in allopregnanolone have profound effects on anxiety and depression in animal models. Additionally, GABAergic signalling might be regulated by compensatory post-partum changes in $GABA_A$ receptor levels and composition. Deletion of the $GABA_A$ receptor δ subunit gene in mice results in maternal depression phenotypes restricted to the post-partum period that can be reversed by administration of the $GABA_A$ agonist 4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol. Furthermore, mice deficient in the potassium-chloride cotransporter (KCC2), which is required for functional GABA signalling, also demonstrate these maternal depression phenotypes and lack the ability to suppress stress-induced activation of the hypothalamic-pituitary-adrenal axis, an additional pathway implicated in the development of post-partum depression. Previous phase 1 and 2 clinical studies of brexanolone injection, a proprietary formulation of allopregnanolone, have demonstrated promising treatment effects in measures of mood symptoms in post-partum depression. These data supported further exploration of the association between positive allosteric modulation of $GABA_A$ receptors and post-partum depression.

We searched PubMed from database inception to Feb 13, 2018, without language restrictions, for publications using the search terms "allopregnanolone," "neuroactive steroid," "$GABA_A$ positive allosteric modulator," "postpartum depression," "depression," and "major depressive disorder". With the exception of our two previous studies of brexanolone injection in post-partum depression, our search retrieved no clinical trials investigating the neuroactive steroid or $GABA_A$ positive allosteric modulator mechanism in post-partum depression or major depressive disorder.

### Added value of this study

The two studies presented are the first phase 3 clinical trials to investigate the efficacy of brexanolone injection in post-partum depression and the second and third study of a trio of placebo-controlled post-partum depression studies done according to one umbrella protocol. If the use of brexanolone injection is approved by regulatory authorities, this drug could be the first pharmacological therapy specifically indicated for post-partum depression. In contrast to brexanolone injection, currently available pharmacological treatments for depression, such as selective serotonin-reuptake inhibitors (SSRIs), have limited links to existing hypotheses regarding the cause of post-partum depression. The onset of efficacy for SSRIs ranges from at least 1–2 weeks to months, and remission rates in post-partum depression remain low. The current trials, and previous studies of brexanolone injection, suggest the potential to develop a post-partum depression medication with the possibility of a rapid onset that could alleviate the substantial impact of post-partum depression on the mother, her infant, and family.

### Implications of all the available data

Preclinical studies with allopregnanolone and clinical studies of brexanolone injection, including the current phase 3 studies, suggest that positive allosteric modulation of $GABA_A$ receptors is a viable therapeutic approach that might provide additional treatment options for women with untreated post-partum depression. Additional treatment options for post-partum depression might have important implications across two generations since studies suggest that untreated post-partum depression impacts the mother and her child. Our trials support current and future regulatory applications for brexanolone injection and the continued study of $GABA_A$ receptor positive allosteric modulators for the treatment of post-partum depression.

## Introduction

Post-partum depression is the most common complication of childbirth and can result in considerable suffering for mothers, children, and families.[1,2] Post-partum depression is estimated to affect 10–20% of women who give birth worldwide, and occurs in low-income, middle-income, and high-income countries.[1–4] Approximately 40–80% of cases of post-partum depression are considered moderate to severe.[1,3,5,6] In the USA, the estimated prevalence of post-partum depression in new mothers varies by state from 8–20%, with an overall mean prevalence of 11·5%.[2] The public health impact of post-partum depression is substantial; in the UK, the estimated cost per case is £74000.[7] This economic burden is multifactorial, but contributing factors include maternal death from suicide,[8,9] loss of work days due to depression, maternal morbidity and child morbidity associated with impaired mother–infant attachment, and infant malnutrition during the first year of life.[1,10–12]

The underlying mechanisms of impaired mother–infant attachment are likely due to multiple aspects of disrupted parenting, sometimes termed lack of sensitivity, observed in mothers with post-partum depression, including poor responsiveness, poor recognition of infant cues, disengagement and withdrawal, and intrusiveness.[13,14] The degree of parental sensitivity is associated with a child's emotional regulation during infancy, and studies[15] suggest that infants of mothers with untreated post-partum depression might demonstrate an increased risk of difficulty with emotional regulation in early life and social behaviour as a consequence of disrupted parenting. This increased risk can continue through adolescence and can

be associated with poorer outcomes, including decreased academic performance and increased risk of depression.[16–18] Antidepressant treatment of post-partum depression with a 12 week course of therapy has been associated with improvements in the quality of mother–infant interaction and infant play.[19] Increased understanding of the broad impact of post-partum depression has led to an international consensus on the importance of screening and early treatment of post-partum depression.[15,20–22]

The stigma associated with maternal psychiatric illness often prevents mothers from seeking treatment for post-partum depression, and substantial disparities in education, country, race, and ethnicity might restrict access to effective treatment.[23–25] Many women treated for post-partum depression with currently available therapies, such as selective serotonin-reuptake inhibitors (SSRIs), do not achieve adequate response or full remission of symptoms, and the ability of SSRIs to prevent post-partum depression is also unclear.[26–28] To date, no pharmacological therapies have been developed specifically for post-partum depression. Thus, improved pharmacological treatment options are urgently needed.

The hypothalamic-pituitary-adrenal (HPA) axis, perinatal hormonal fluctuations, and γ-aminobutyric acid (GABA) signalling have been implicated in the pathophysiology of post-partum depression, and previous studies[29–32] have identified associations between these potential mechanisms. In mouse models of GABA dysfunction, mice were found to have post-partum depression-like maternal behaviours and defects in HPA axis regulation, indicating an association between GABA and HPA regulation.[29] Additionally, plasma concentrations of allopregnanolone, a potent positive allosteric modulator of synaptic and extrasynaptic GABA type A ($GABA_A$) receptors, which is an endogenous progesterone metabolite, decrease considerably following childbirth, indicating an association between perinatal hormonal fluctuations and GABA regulation.[33–36]

A soluble, proprietary, β-cyclodextrin-based, intravenous formulation of allopregnanolone—brexanolone injection (formerly SAGE-547 injection)—had rapid and durable antidepressant effects during the study period in our previous double-blind, randomised, phase 2 clinical trial.[37] Here, we report the results of two large phase 3, double-blind, randomised, placebo-controlled trials of brexanolone injection in women with moderate to severe post-partum depression. Additionally, integrated results from all three, placebo-controlled trials of brexanolone injection in post-partum depression are presented.

See Online for appendix

## Methods

### Study design and participants

We did two multicentre, randomised, double-blind, placebo-controlled phase 3 trials at 30 clinical research centres and specialised psychiatric units in the USA under an umbrella protocol that facilitated subsequent integrated data analyses with our previous phase 2 trial,[37] which was completed before the initiation of study 1 and 2.

Patients were recruited to clinical research centres and specialised psychiatric units through self-referrals, physician referrals, and radio-based, television-based, and web-based methods. Pre-screening was done through treatment site patient database searches or phone interviews to confirm patients met high-level entry criteria (ie, ≤6 months post partum, feeling depressed or anxious, aged 18 years or older). The principal investigator at each site was responsible for recruitment and enrolment of patients. The trials were deemed complete when predetermined enrolment targets were achieved.

Both trials enrolled ambulatory female participants aged 18–45 years, who provided a signed informed consent form before any procedures were done, were in good physical health with no clinically significant findings as determined by the principal investigator on physical examination, 12-lead electrocardiogram (ECG), or clinical laboratory tests, had agreed to adhere to study requirements, and had stopped lactating at the time of screening or had temporarily ceased breastfeeding while receiving the study drug until 4 days after the end of infusion. Eligible participants also had to have a negative pregnancy test before initiation of study drug, had a major depressive episode with onset no earlier than the third trimester and no later than 4 weeks after delivery, as determined by the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV Axis I Disorders (SCID-I),[38] had a qualifying HAM-D total score (≥26 for study 1; 20–25 for study 2) before infusion,[39] were 6 months post partum or less at screening, were willing to delay the start of new pharmacotherapeutic drug regimens from study drug infusion until completion of 72 h assessments, and agreed to use an approved form of birth control during the study and for 30 days thereafter. Women with onset of post-partum depression in the peri-partum period were included on the basis of previous literature demonstrating post-partum depression development in this time period.[6,40,41] Participants taking prescribed psychotropic medication at baseline had to be at a stable dose 14 days before screening until completion of the 72 h assessments. Concomitant psychotropic medications are listed in the appendix.

Individuals were excluded if they had renal failure requiring dialysis, fulminant hepatic failure, anaemia (baseline haemoglobin <10 g/dL), known allergy to allopregnanolone or to progesterone, active psychosis (determined by investigator), medical history of schizophrenia, bipolar disorder, or schizoaffective disorder, had attempted suicide during the current episode of post-partum depression, or a history of alcohol or drug abuse in the previous 12 months (by self-report or drug screening). Individuals were also excluded if they had been exposed to another investigational medication up to 30 days before screening, had previously participated in this study or other studies of brexanolone injection,

or had electro-convulsive therapy up to 14 days before screening or had therapy planned within 7 days after infusion.

Relevant institutional review boards or independent ethics committee approved both studies, and all patients provided written informed consent.

### Randomisation and masking

Eligible patients were randomly assigned (1:1:1) to receive brexanolone injection 90 µg/kg per h (BRX90), brexanolone injection 60 µg/kg per h (BRX60), or matching placebo infusion in study 1, or (1:1) BRX90 or matching placebo infusion in study 2, according to a computer-generated randomisation. The first randomisation schedule for each study was generated by Applied Statistics and Consulting (Spruce Pine, NC, USA), and subsequent schedules were generated by Sage Therapeutics, Inc (Cambridge, MA, USA). The second and third randomisation schedules were produced to accommodate regulatory authority requests for increased sample sizes and stratification of randomisation based on antidepressant use, and were implemented using Prancer interactive response technology system (4G Clinical, Wellesley, MA, USA): the second list was unstratified and the third list was stratified by antidepressant use. Overall, less than 25% of the randomly assigned participants in the two studies were randomised manually using the first randomisation list. The remaining participants were randomly assigned using interactive response technology based on the second and third lists. All participants in study 1 were randomly assigned using a block size of 6. In study 2, the first randomisation list used a block size of 2 and subsequent lists had a block size of 4. MedSource (Houston, TX, USA) provided masked randomisation code lists to the site pharmacists for treatment assignment for the first randomisation list in each study. The Prancer interactive response technology system dispensed treatment assignments for subsequent randomisation lists. The site pharmacist who prepared the study drug (brexanolone injection or matching placebo) was not masked to treatment assignment. The site pharmacist provided masked study drug to the study team with only the rate of infusion noted to maintain study blind. Patients, the study team (including medical monitors), site staff (with the exception of the pharmacists), and the principal investigator were masked to treatment allocation, and infusion bags for all treatment groups were identical in appearance. Two placebo infusion rates were used in study 1 and one placebo infusion rate in study 2, which matched the active dose groups, thereby fully maintaining the blind.

The shared study database for studies 1 and 2 was locked when the final visit of the last randomised and infused patient was completed, data entry into the database for all patients was completed, and the database for all patients was deemed clean, without any outstanding queries (Nov 3, 2017). Randomisation lists were held by Applied Statistics and Consulting and 4G Clinical until database lock, to maintain blinding of study personnel throughout the studies. In the event of a medical emergency, the principal investigator was required to contact the medical monitor to initiate the unmasking process; no such unmasking events occurred.

### Procedures

Brexanolone injection is a sterile solution of 5 mg/mL allopregnanolone in 250 mg/mL sulfobutylether-β-cyclodextrin, which is buffered with citrate and diluted with sterile water to render it isotonic for intravenous use.[37] For the BRX90 groups, each patient received a single continuous infusion of study drug for 60 h according to the following schedule: 30 µg/kg per h (0–4 h); 60 µg/kg per h (4–24 h); 90 µg/kg per h (24–52 h); 60 µg/kg per h (52–56 h); 30 µg/kg per h (56–60 h). Patients in the BRX60 group received study drug according to the same dosing schedule, but were administered 60 µg/kg per h at 24–52 h. The dose and infusion rates were based on pharmacokinetic modelling and previous studies.[37,42] Changes to infusion rates were made on the basis of pre-determined protocol rules and tolerability. Patients were treated in a medically-supervised setting for 72 h, consisting of 60 h of study drug infusion and an additional 12 h for completion of assessments. Patients were followed up until day 30, with clinical and safety assessments done at days 7 and 30.

### Outcomes

The primary efficacy outcome measure in both studies 1 and 2 was the change from baseline in mean 17-item Hamilton Rating Scale for Depression (HAM-D)[39] total score at 60 h post-infusion. Blinded on-site raters were trained on the use of the HAM-D scale by MedAvante (Hamilton, NJ, USA) to enable consistent scoring. The on-site investigators made the final decision on the HAM-D scores throughout the study. An additional quality control measure was introduced during the study (for approximately 50% of patients enrolled in studies 1 and 2) to have the HAM-D interviews recorded and scored by an independent, blinded, central reviewer at MedAvante (who was not an employee of the study sponsor) to ensure that each site was following the HAM-D rater guidelines and to provide an opportunity for intervention, such as retraining the site raters, if needed. The on-site rater could decide to accept or reject the central rater score if the two scores were different. Additional information on rating is described in the appendix.

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; Clinical Global Impression-Improvement (CGI-I) response, defined as a rating of 1 (very much improved) or 2 (much improved);[43] change from

baseline in score on the Montgomery-Åsberg Depression Rating Scale;[44] change from baseline in HAM-D subscale (including Bech 6,[45] Core,[46] Anxiety,[47] and Maier[48]) score and individual item scores; and change from baseline in scores on the Edinburgh Postnatal Depression Scale,[49] Patient Health Questionnaire 9,[50] and the Generalized Anxiety Disorder 7-item questionnaire.[51]

Safety and tolerability were investigated by recording adverse events, vital signs, clinical laboratory assessments, ECG parameters, and Columbia Suicide Severity Rating Scale scores.[52]

### Statistical analysis

On the assumption of a two-sided *t* test at an α level of 0·05 for study 1, a sample size of 120 patients (40 patients per group) would provide 90% power to detect a mean treatment difference of 9·0 between the brexanolone and placebo groups, with an assumed SD of 12 points. On the assumption of a two-sided *t* test at an α level of 0·05 for study 2, a sample size of 100 patients (50 patients per group) would provide 90% power to detect a mean treatment difference of 8·0 between the brexanolone and placebo groups, with an assumed SD of 12 points.

The primary efficacy endpoint was analysed in the modified intention-to-treat population, which included all patients who started infusion of study drug or placebo, had a valid HAM-D baseline assessment, and had at least one post-baseline HAM-D assessment. The safety population included all randomised patients who started infusion of study drug or placebo.

For both studies, LS mean HAM-D total score and the change in LS mean HAM-D total score from baseline were analysed using a mixed effects model for repeated measures, as prespecified in the protocol and statistical analysis plan. The linear model included centre (pooled), treatment, baseline antidepressant use, baseline HAM-D total score, assessment timepoint, and timepoint-by-treatment as explanatory variables, which were treated as fixed effects. Least square means, 95% CIs, and p values were calculated using model-based point estimates and reported for each timepoint. A generalised estimating equation method for repeated binary responses was used to analyse categorical variables, such as response and remission.

We did a separate, pre-planned analysis of the integrated datasets from our previous 2017 trial,[37] and studies 1 and 2, using the same statistical methods as previously described, to assess the safety and efficacy of brexanolone in the largest possible placebo-controlled post-partum depression patient population. The integrated analysis was preplanned in conjunction with regulatory authorities for the efficacy and safety analyses. For efficacy analyses, all placebo groups and all BRX90 groups were integrated. Efficacy data for the single BRX60 group was not included in this integrated analysis. Similar to the individual studies, the primary endpoint was analysed using a mixed effects model for repeated measures. The model included study, pooled study site, treatment, baseline antidepressant use, visit timepoint, and treatment-by-visit timepoint interaction terms as fixed effects, and baseline HAM-D total score as a covariate. For safety analyses, a conservative approach was used, including treatment-emergent adverse events observed in any group receiving brexanolone injection.

All statistical analyses were done using SAS (version 9.3). The completed trials are registered with ClinicalTrials.gov, numbers NCT02942004 (study 1) and NCT02942017 (study 2).

### Role of the funding source

The study funder was involved in the study design, data analysis, interpretation, and writing of the report. All authors had full access to all the data, and the corresponding author had final responsibility for the decision to submit for publication.

## Results

Study 1 was done between Aug 1, 2016, and Oct, 19, 2017, and study 2 between July 25, 2016, and Oct 11, 2017. Across both studies, we screened 375 women simultaneously, of whom 138 were randomly assigned to receive either BRX90 (n=45), BRX60 (n=47), or placebo (n=46) in study 1, and 108 were randomly assigned to receive BRX90 (n=54) or placebo (n=54) in study 2 (figure 1). 25 (18%) of 138 patients discontinued study 1, and eight (7%) of 108 patients discontinued study 2. The most common reasons for discontinuation were patients did not receive the infusion, were lost to follow-up, or withdrew consent (appendix). In both studies, the number of patients in the safety and efficacy analysis populations were the same. Three (2%) of 122 patients in study 1, and three (3%) of 104 patients in the study 2 had missing data for the primary efficacy outcome at 60 h. All patients in both studies had at least one safety assessment.

Demographics and baseline characteristics were generally well balanced across treatment groups within each study (table 1). In study 1, the mean age was 27·8 years (SD 6·0) in the BRX90 group, 27·3 years (6·1) in the BRX60 group, and 27·0 years (6·0) in the placebo group. In study 2, the mean age was 28·4 years (SD 6·1) in the BRX90 group and 27·4 years (5·9) in the placebo group. Of 246 patients included in both studies, most patients were white (153 [62%]); 86 (35%) were black or African-American and 43 (17%) were Hispanic or Latino. The onset of post-partum depression was similar across all groups. Across all cohorts in both studies, a higher proportion of patients had onset of post-partum depression within 4 weeks of delivery than the third trimester (range 67–78%). Across both studies, 53 (22%) of 246 patients were taking antidepressants at baseline. The use of psychotropic medication is shown in the appendix.

At the end of the 60 h infusion, in study 1, the LS mean reduction in HAM-D total score was 19·5 points (SE 1·2)

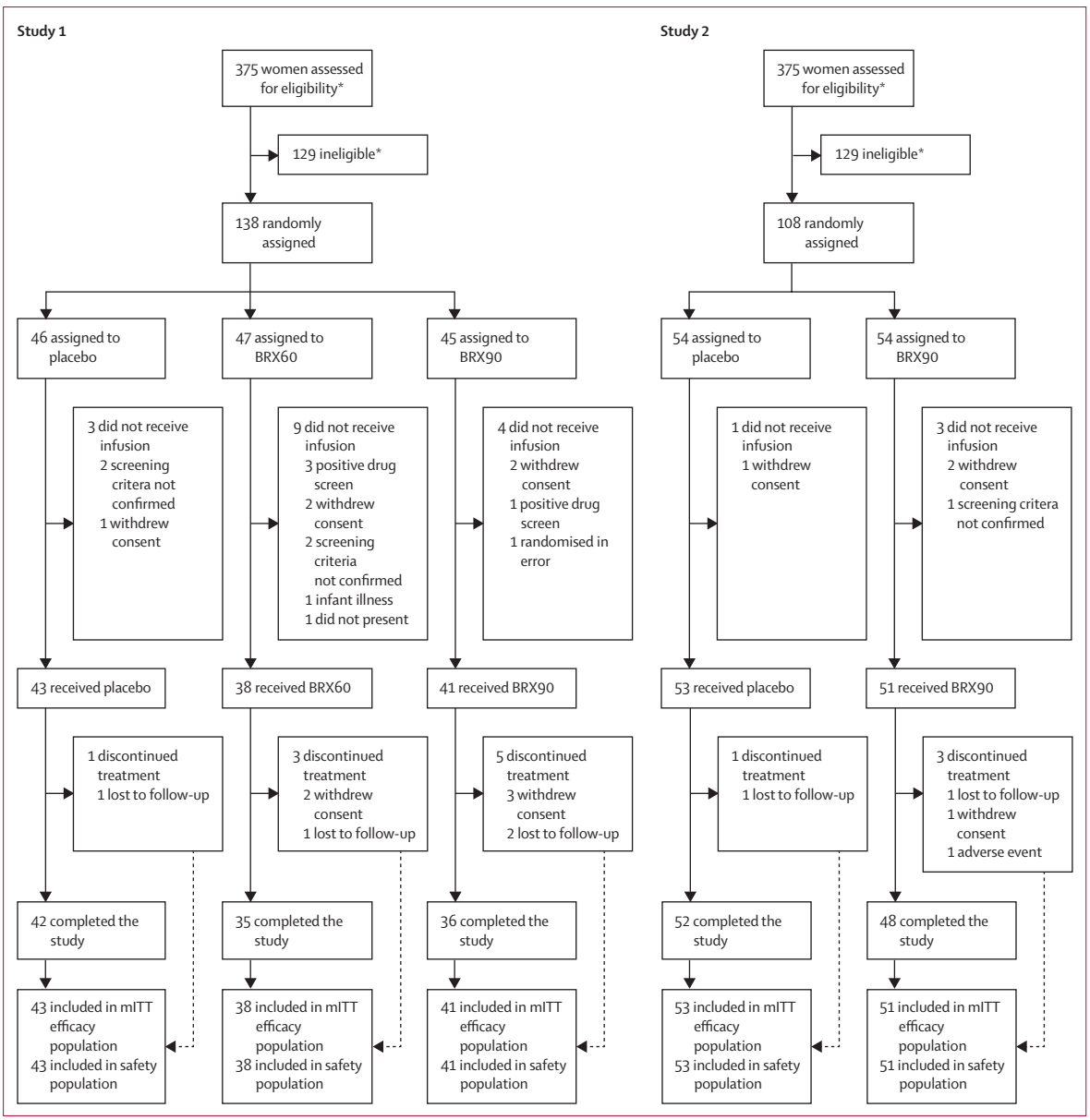


***Figure 1:*** **Trial profiles for studies 1 and 2**
mITT=modified intention-to-treat. BRX60=brexanolone injection 60 μg/kg per h. BRX90=brexanolone injection 90 μg/kg per h. *Screening for studies 1 and 2 was done simultaneously because of protocol similarities, thus the same 375 women were screened for both studies. In study 1, data for the 60 h (primary outcome) were available for 43 patients in the placebo group, 37 patients in the BRX60 group, and 39 patients in the BRX90 group. Data was obtained from 42 patients in the placebo group, 35 patients in the BRX60 group, and 36 patients in the BRX90 group at day 30. In study 2, data for the 60 h (primary outcome) were available for 52 patients in the placebo group and 49 patients in the BRX90 group. Data was obtained from 52 patients in the placebo group and 48 patients in the BRX90 at day 30.

in the BRX60 group and 17·7 points (1·2) in the BRX90 group compared with 14·0 points (1·1) in the placebo group (table 2). The mean difference between the placebo group and both brexanolone injection groups was statistically significant (–5·5 [95% CI –8·8 to –2·2], p=0·0013 for BRX60; –3·7 [–6·9 to –0·5], p=0·0252 for BRX90; table 2). At the end of the 60 h infusion, in study 2, the 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 (0·8) in the placebo group (–2·5 [95% CI –4·5 to –0·5], p=0·0160; table 2).

In study 1, HAM-D total scores were significantly reduced in the BRX60 group compared with the placebo group at 24 h and all timepoints thereafter in the BRX60 group. In study 2, HAM-D total scores were significantly reduced in the BRX90 group compared with the placebo group at 48 h and until day 7 (table 2). HAM-D total score did not return to baseline by day 30 in any of the

| | Study 1 | | | Study 2 | |
|---|---|---|---|---|---|
| | Placebo (n=46) | BRX60 (n=47) | BRX90 (n=45) | Placebo (n=54) | BRX90 (n=54) |
| **Characteristics** | | | | | |
| Age, years | 27·0 (6·0) | 27·3 (6·1) | 27·8 (6·0) | 27·4 (5·9) | 28·4 (6·1) |
| Ethnicity | | | | | |
| Hispanic or Latino | 8 (17%) | 3 (6%) | 7 (16%) | 14 (26%) | 11 (20%) |
| Not Hispanic or Latino | 38 (83%) | 44 (94%) | 38 (84%) | 40 (74%) | 43 (80%) |
| Race | | | | | |
| Black or African-American | 17 (37%) | 15 (32%) | 12 (27%) | 19 (35%) | 23 (43%) |
| White | 28 (61%) | 31 (66%) | 29 (64%) | 34 (63%) | 31 (57%) |
| Other | 1 (2%) | 1 (2%) | 4 (9%) | 1 (2%) | 0 |
| Height, cm | 165·3 (7·9) | 163·9 (6·2) | 164·3 (6·6) | 162·5 (8·3) | 164·3 (6·0) |
| Weight, kg | 82·2 (23·3) | 83·8 (20·7) | 80·7 (20·6) | 86·5 (24·3) | 86·7 (24·3) |
| Body-mass index, kg/m² | 30·1 (8·2) | 31·2 (7·5) | 29·8 (7·0) | 32·6 (8·1) | 32·0 (8·3) |
| **Personal history of psychiatric disorders** | | | | | |
| Depression (non-PPD) | 20 (43%) | 19 (40%) | 21 (47%) | 18 (33%) | 13 (24%) |
| Anxiety | 15 (33%) | 20 (43%) | 21 (47%) | 19 (35%) | 17 (31%) |
| Premenstrual dysphoric disorder | 0 | 1 (2%) | 3 (7%) | 1 (2%) | 2 (4%) |
| Substance abuse | 0 | 0 | 1 (2%) | 0 | 1 (2%) |
| Other | 3 (7%) | 5 (11%) | 2 (4%) | 3 (6%) | 2 (4%) |
| Previous PPD episodes | 16 (35%) | 17 (36%) | 12 (27%) | 21 (39%) | 19 (35%) |
| **Family history of PPD** | | | | | |
| Yes | 9 (20%) | 13 (28%) | 16 (36%) | 13 (24%) | 17 (31%) |
| No | 37 (80%) | 34 (72%) | 29 (64%) | 41 (76%) | 37 (69%) |
| **Onset of PPD** | | | | | |
| Third trimester | 14 (30%) | 11 (23%) | 10 (22%) | 12 (22%) | 12 (22%) |
| Within 4 weeks of delivery | 31 (67%) | 35 (74%) | 35 (78%) | 42 (78%) | 42 (78%) |
| **Antidepressant use** | | | | | |
| Baseline antidepressant use | 12 (26%) | 12 (26%) | 10 (22%) | 10 (19%) | 9 (17%) |
| Previous antidepressant use | 14 (30%) | 15 (32%) | 13 (29%) | 10 (19%) | 12 (22%) |
| Concomitant antidepressant use | 14 (30%) | 14 (30%) | 13 (29%) | 15 (28%) | 12 (22%) |
| **Other measures*** | | | | | |
| HAM-D | 28·6 (2·5) | 29·1 (2·7) | 28·4 (2·5) | 22·7 (1·6) | 22·6 (1·6) |
| EPDS | 21·7 (3·0) | 21·7 (3·4) | 20·0 (3·9) | 18·7 (4·1) | 18·9 (3·9) |

Data are n (%) or mean (SD). Weight, height, and body-mass index data were obtained at screening. Medical histories were coded according to the Medical Dictionary for Regulatory Activity version 19.1 or later. BRX60=brexanolone injection 60 µg/kg per h. BRX90=brexanolone injection 90 µg/kg per h. PPD=post-partum depression. HAM-D=Hamilton Rating Scale for Depression. EPDS=Edinburgh Postnatal Depression Scale. *Assessed before infusion on day 1.

***Table 1:*** **Baseline demographics and characteristics**

brexanolone groups (figure 2). In study 1, the LS mean reduction in HAM-D total score in both BRX60 and BRX90 groups at day 30 was similar to that observed at the end of the 60 h infusion (19·5 points [SE 1·4] at day 30 *vs* 19·5 points [1·2] at 60 h for BRX60; 17·6 points [1·4] at day 30 *vs* 17·7 points [1·2] at 60 h for BRX90), and the reduction in HAM-D total scores from baseline at day 30 was significantly higher in the BRX60 group (p=0·0044) and BRX90 group (p=0·0481) than the placebo group (table 2). In study 2, the LS mean reduction in HAM-D total score observed in the BRX90 group at day 30 (14·7 points [SE 1·0]) was of similar magnitude to that observed at the end of the 60 h infusion (14·6 points [0·8]). In study 2, a marked improvement in the HAM-D total score was found in the placebo group after day 7, with no significant difference identified in HAM-D total scores between the BRX90 and placebo groups at day 30 (table 2). In study 1 and 2, the LS mean change in HAM-D total score from baseline was similar for patients in the brexanolone injection groups with and without concomitant antidepressant treatment, and the proportion of patients who received rescue antidepressant treatment during the follow-up period was low (appendix).

HAM-D total scores were further examined for remission (HAM-D total score ≤7) and response (reduction in HAM-D total score ≥50%; appendix). In study 1, between 24 h and 72 h and at day 30, the proportions of patients achieving HAM-D remission were higher for both the BRX60 and BRX90 groups compared with placebo, with statistical significance achieved for the

BRX60 group at multiple timepoints, including at the end of the 60 h infusion (19 [51%] of 37 patients in the BRX60 group *vs* seven [16%] of 43 patients in the placebo group; odds ratio [OR] 6·0 [95% CI 2·1 to 17·8], p=0·0011). In study 2, the proportion of patients achieving HAM-D remission was higher for the BRX90 group than the placebo at all timepoints between 8 h and day 7 (appendix), reaching statistical significance at multiple timepoints, including at the end of the 60 h infusion (30 [61%] of 49 patients in the BRX90 group *vs* 20 [38%] of 52 patients in the placebo group; OR 3·4 [95% CI 1·5 to 7·9], p=0·0033). The proportion of patients who achieved a HAM-D response was similar for both brexanolone injection groups in study 1 between 24 h and day 30, with statistical significance achieved for both the BRX90 and BRX60 groups across multiple timepoints. The proportion of patients achieving a HAM-D response in study 2 was also higher in the BRX90 group compared with placebo between 24 h and day 7, reaching statistical significance at all timepoints between 48 h and day 7.

HAM-D data were supported by CGI-I response data (appendix). In study 1, the proportion of patients with available response data at 60 h who achieved a CGI-I response was significantly higher in the BRX60 group (31 [84%] of 37 patients; OR 4·0 [95% CI 1·3 to 11·7], p=0·0131) and BRX90 group (32 [82%] of 39 patients, OR 4·0 [1·4 to 11·6], p=0·0095) than the placebo group (24 [56%] of 43 patients). The proportion of patients achieving a CGI-I response was significantly higher in the BRX90 group than the placebo group at 72 h and day 30, and significantly higher in the BRX60 group than the placebo group at 36, 48, 60, and 72 h, and at days 7 and 30. In study 2, the proportion of patients with available response data at 60 h who achieved a CGI-I response was significantly higher in the BRX90 group than the placebo group (39 [79·6%] of 49 patients in the BRX90 group *vs* 29 [55·8%] of 52 patients in the placebo group; OR 5·0 [95% CI 2·0 to 12·5], p=0·0005). These significant increases in CGI-I response occurred as early as 36 h and were sustained at day 7. The HAM-D and CGI-I results are also consistent with additional secondary efficacy outcomes that were directionally supportive (appendix).

Brexanolone injection was generally well tolerated in both studies (table 3; appendix). The most common treatment-emergent adverse events were headache (seven patients in the BRX60 group and six patients in the BRX90 group *vs* seven patients in the placebo group for study 1; nine patients in the BRX90 group *vs* six patients in the placebo group for study 2), dizziness (six patients in the BRX60 and BRX90 groups *vs* one patient in the placebo group for study 1; five patients in the BRX90 group *vs* four patients in the placebo group for study 2), and somnolence (seven patients in the BRX60 group and two patients in the BRX90 group *vs* three patients in the placebo group for study 1; four patients in the BRX90 group *vs* two patients in the

| | Study 1 | | | | | | | Study 2 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Placebo (n=43) | BRX60 (n=38) | | | | BRX90 (n=41) | | | Placebo (n=53) | BRX90 (n=51) | | |
| | LS mean change from baseline (SE) | LS mean change from baseline (SE) | LS means difference* (SE) | 95% CI | p value* | LS mean change from baseline (SE) | LS means difference*(SE) | 95% CI | p value* | LS mean change from baseline (SE) | LS mean change from baseline (SE) | LS means difference* (SE) | 95% CI | p value* |
| 2 h | -5·0 (0·7) | -5·0 (0·7) | 0·1 (1·0) | -1·8 to 1·9 | 0·9591 | -4·9 (0·7) | 0·2 (0·9) | -1·7 to 2·0 | 0·8677 | -4·0 (0·6) | -4·6 (0·6) | -0·6 (0·7) | -2·1 to 0·9 | 0·4216 |
| 4 h | -6·9 (0·8) | -9·0 (0·9) | -2·1 (1·2) | -4·5 to 0·3 | 0·0827 | -7·2 (0·9) | -0·3 (1·2) | -2·6 to 2·0 | 0·7968 | -6·6 (0·7) | -7·3 (0·7) | -0·8 (0·9) | -2·6 to 1·0 | 0·3947 |
| 8 h | -8·1 (0·9) | -10·2 (1·0) | -2·0 (1·3) | -4·7 to 0·6 | 0·1292 | -8·5 (1·0) | -0·4 (1·3) | -2·9 to 2·2 | 0·7801 | -7·4 (0·7) | -8·4 (0·7) | -1·0 (1·0) | -2·9 to 1·0 | 0·3280 |
| 12 h | -9·8 (1·0) | -11·0 (1·1) | -1·3 (1·4) | -4·1 to 1·6 | 0·3840 | -9·1 (1·0) | 0·7 (1·4) | -2·0 to 3·5 | 0·6097 | -8·0 (0·8) | -9·1 (0·8) | -1·1 (1·0) | -3·1 to 0·8 | 0·2522 |
| 24 h | -10·7 (1·1) | -15·0 (1·2) | -4·3 (1·6) | -7·5 to -1·1 | 0·0094 | -13·0 (1·2) | -2·3 (1·6) | -5·5 to 0·8 | 0·1440 | -9·8 (0·8) | -11·4 (0·8) | -1·6 (1·1) | -3·8 to 0·6 | 0·1431 |
| 36 h | -12·6 (1·1) | -17·7 (1·2) | -5·1 (1·6) | -8·3 to -1·9 | 0·0020 | -13·9 (1·2) | -1·4 (1·6) | -4·5 to 1·8 | 0·3906 | -10·5 (0·8) | -12·3 (0·8) | -1·9 (1·1) | -4·1 to 0·4 | 0·0991 |
| 48 h | -13·6 (1·2) | -18·0 (1·3) | -4·5 (1·7) | -7·9 to -1·1 | 0·0110 | -16·9 (1·2) | -3·3 (1·7) | -6·7 to 0·0 | 0·0511 | -10·6 (0·9) | -13·0 (0·9) | -2·4 (1·2) | -4·7 to -0·1 | 0·0389 |
| 60 h | -14·0 (1·1) | -19·5 (1·2) | -5·5 (1·6) | -8·8 to -2·2 | 0·0013 | -17·7 (1·2) | -3·7 (1·6) | -6·9 to -0·5 | 0·0252 | -12·1 (0·8) | -14·6 (0·8) | -2·5 (1·0) | -4·5 to -0·5 | 0·0160 |
| 72 h | -14·7 (1·2) | -19·7 (1·3) | -5·0 (1·7) | -8·5 to -1·6 | 0·0046 | -17·2 (1·2) | -2·5 (1·7) | -5·9 to 0·8 | 0·1389 | -11·8 (0·8) | -15·3 (0·8) | -3·5 (1·1) | -5·7 to -1·3 | 0·0022 |
| 7 days | -13·3 (1·3) | -17·4 (1·4) | -4·1 (1·8) | -7·7 to -0·4 | 0·0288 | -14·9 (1·3) | -1·6 (1·8) | -5·2 to 2·0 | 0·3799 | -10·7 (1·0) | -14·0 (1·1) | -3·2 (1·4) | -6·1 to -0·4 | 0·0255 |
| 30 days | -13·8 (1·3) | -19·5 (1·4) | -5·6 (1·9) | -9·5 to -1·8 | 0·0044 | -17·6 (1·4) | -3·8 (1·9) | -7·6 to 0·0 | 0·0481 | -15·2 (0·9) | -14·7 (1·0) | 0·5 (1·3) | -2·0 to 3·1 | 0·6710 |

The change from baseline in the total LS mean HAM-D score was analysed using a mixed effects model for repeated measures. p values were calculated by two-sided *t* test. HAM-D=Hamilton Rating Scale for Depression. LS=least squares. BRX60=brexanolone injection 60 μg/kg per h. BRX90=brexanolone injection 90 μg/kg per h. *Compared with placebo.

***Table 2:*** **LS mean HAM-D scores**

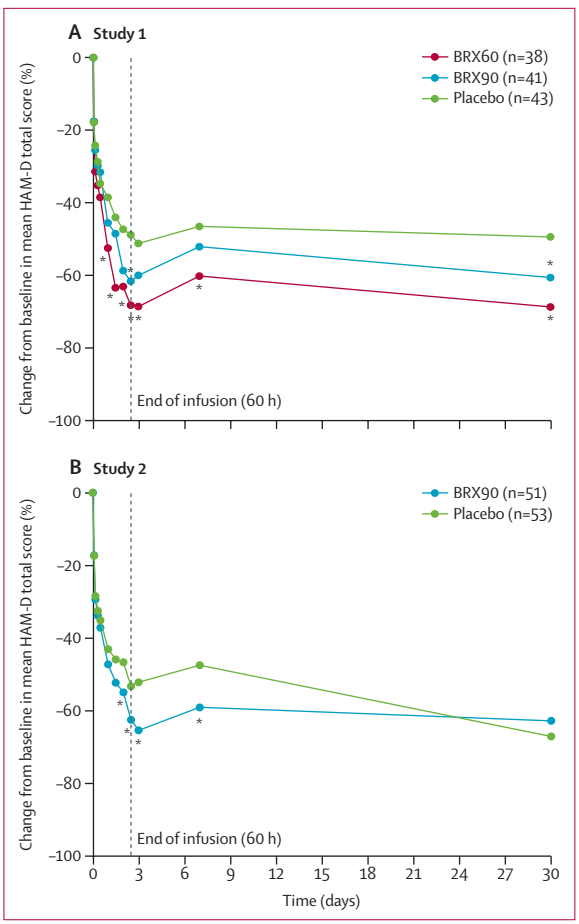


***Figure 2:*** **Percentage change from baseline in mean HAM-D total score in study 1 (A) and 2 (B)**

p values were calculated by two-sided *t* test. BRX60=brexanolone injection 60 μg/kg per h. BRX90=brexanolone injection 90 μg/kg per h. *p<0·05 *vs* placebo.

placebo group for study 2), with dizziness and somnolence occurring more frequently in patients receiving brexanolone injection than placebo. These sedation-related events were generally mild, short-lived, and self-limiting. In study 1, one (3%) of 38 patients in the BRX60 group had two serious adverse events (suicidal ideation and intentional overdose attempt during follow-up). This patient had three previous suicide attempts before the study, and the event was not considered drug related by the principal investigator. One (3%) of 38 patients in the BRX60 group had two severe adverse events (somnolence and loss of consciousness) during treatment, completing treatment following interruption of dosing and rapid resolution of the adverse events. In study 2, one (2%) of 51 patients in the BRX90 group had two serious adverse events (altered state of consciousness and syncope), which were moderate in intensity and considered to be treatment related. Two (4%) of 51 patients in the BRX90 group had severe adverse events (fatigue [n=1] and presyncope [n=1]). Overall, of the 130 patients who received brexanolone across studies 1 and 2, five (4%) patients had excessive sedation considered to be due to brexanolone injection; in all cases, the patients alerted staff and infusion was stopped immediately. All patients who lost consciousness regained consciousness within 15 min of infusion cessation, and all excessive sedation events were completely resolved within 90 min. No respiratory or haemo-dynamic compromise was associated with these cases of excessive sedation. No clinically significant differences in laboratory parameters, vital signs, or ECGs were observed between the brexanolone injection groups and placebo groups.

Our previous 2017 phase 2 trial of the BRX90 dose[37] was done using the same umbrella protocol as studies 1 and 2, facilitating analysis of integrated comparative efficacy of BRX90 versus placebo groups across all three trials (appendix). Patients in the BRX60 group in study 1 were not included in this integrated analysis. Similar to the individual studies, the integrated BRX90 analysis showed a rapid decrease in HAM-D scores (ie, depressive symptoms) in the BRX90 group compared with the placebo groups, which was sustained until day 30 (figure 3). At the end of the 60 h infusion, the LS mean reduction in HAM-D total score from baseline was significantly larger in the BRX90 group than the placebo group (LS mean difference −4·1 [95% CI −6·0 to −2·3], p<0·0001; appendix), which was also observed at 24 h (−3·0 [95% CI −4·8 to −1·2], p=0·0012) and was sustained at day 30 (−2·6 [95% CI −4·7 to −0·4], p=0·0213).

In the integrated analysis, the LS mean difference in HAM-D total score was higher in the BRX90 subgroups (with and without concomitant antidepressant treatment) than the placebo group at 60 h (−4·3 [95% CI −6·5 to −2·2], p<0·0001 for patients without antidepressant treatment; −4·5 [95% CI −8·4 to −0·5], p=0·0282 for patients with antidepressant treatment; appendix). At 60 h, subgroup analyses also showed greater LS mean differences in HAM-D score in the BRX90 group compared with the placebo group from baseline in all subgroups examined for race, age, ethnicity, body-mass index, personal history of post-partum depression, family history of major depressive disorder, duration between delivery and index treatment, time of symptom onset, and HAM-D severity (appendix). The proportion of patients who required rescue medication was low (13 [13%] of 102 patients in the BRX90 cohort *vs* 13 [12%] of 107 patients in the placebo cohorts; appendix).

Of the patients with available data, a higher proportion of patients in the BRX90 cohort achieved remission than did patients in the placebo cohort between 24 h (26 [26%] of 101 patients in the BRX90 cohort *vs* 16 [15%] of 106 patients in the placebo cohort; OR 2·5 [95% CI 1·2 to 5·1], p=0·0142) and day 7 (43 [43%] of 100 patients in the BRX90 cohorts *vs* 30 [28%] of 106 patients in the placebo cohorts; OR 2·4 [95% CI 1·2 to 4·5], p=0·0087), and a higher proportion of patients in the BRX90 group had HAM-D response than patients in the placebo group

between 24 h (51 [50%] of 101 patients in the BRX90 cohort *vs* 43 [41%] of 106 patients in the placebo group; OR 2·1, 95% CI 1·1 to 3·8, p=0·0183) and day 30 (66 [70%] of 94 patients in the BRX90 group *vs* 65 [62%] of 105 patients in the placebo group; OR 1·9, 95% CI 1·0 to 3·6, p=0·0408; appendix). Of the 70 patients in the BRX90 group who had a response at 60 h and had available data at day 30, 66 (94%) did not relapse at day 30 (appendix).

In the integrated study population, the changes from baseline in all calculated HAM-D subscales and individual HAM-D items were consistent with the changes in overall HAM-D total scores observed (appendix). These HAM-D results were further supported by the analysis of CGI-I response in the integrated study population: of the patients who had available data, the proportion of patients who achieved a CGI-I response was significantly higher than placebo at both 24 h (52 [51%] of 101 patients in the BRX90 group *vs* 44 [42%] of 106 patients in the placebo group, OR 2·1 [95% CI 1·1 to 3·7], p=0·0177) and day 30 (73 [78%] of 94 patients *vs* 66 [63%] of 105, OR 2·8 [1·4 to 5·5], p=0·0028; appendix).

To examine safety and tolerability of brexanolone in the largest possible study population available, we used a more conservative approach, including safety assessments from the BRX60 study 1 group (brexanolone-ALL group; n=140). Across all placebo-controlled post-partum depression studies, two (1%) of 140 patients in the brexanolone-ALL group had two serious adverse events each, compared with no patients in the placebo group, and three (2%) of 140 patients in the brexanolone-ALL group had at least one severe adverse event compared with two (2%) of 107 patients in the placebo group. The proportion of patients who had at least one adverse event was similar between groups (54 [50%] of 107 patients in the placebo cohorts; 70 [50%] of 140 patients in the brexanolone-ALL group). The most common adverse events in the brexanolone-ALL group were headache (n=22), dizziness (n=19), and somnolence (n=15; appendix). No deaths or unexpected adverse events were reported.

| | Study 1 | | | Study 2 | |
|---|---|---|---|---|---|
| | Placebo (n=43) | BRX60 (n=38) | BRX90 (n=41) | Placebo (n=53) | BRX90 (n=51) |
| **Overall** | | | | | |
| Any adverse event | 22 (51%) | 19 (50%) | 22 (54%) | 24 (45%) | 25 (49%) |
| Severe adverse event | 0 | 1 (3%) | 0 | 1 (2%) | 2 (4%) |
| Serious adverse event | 0 | 1 (3%) | 0 | 0 | 1 (2%) |
| Adverse event leading to discontinuation of study treatment | 1 (2%) | 1 (3%) | 0 | 0 | 2 (4%) |
| Deaths | 0 | 0 | 0 | 0 | 0 |
| **Adverse events in three or more patients** | | | | | |
| Headache | 7 (16%) | 7 (18%) | 6 (15%) | 6 (11%) | 9 (18%) |
| Dizziness | 1 (2%) | 6 (16%) | 6 (15%) | 4 (8%) | 5 (10%) |
| Somnolence | 3 (7%) | 7 (18%) | 2 (5%) | 2 (4%) | 4 (8%) |
| Infusion site pain | 1 (2%) | 1 (3%) | 4 (10%) | 2 (4%) | 5 (10%) |
| Nausea | 3 (7%) | 1 (3%) | 0 | 2 (4%) | 5 (10%) |
| Dry mouth | 0 | 4 (11%) | 0 | 1 (2%) | 2 (4%) |
| Fatigue | 0 | 1 (3%) | 1 (2%) | 2 (4%) | 3 (6%) |

Data are n (%). Treatment-emergent adverse events were defined as an adverse event with onset after the start of study drug, or any worsening of a pre-existing medical condition or adverse event with onset after the start of study drug. Treatment-emergent adverse events were coded according to the Medical Dictionary for Regulatory Activities version 19.1 or later. BRX60=brexanolone injection 60 μg/kg per h. BRX90=brexanolone injection 90 μg/kg per h.

***Table 3:*** **Treatment-emergent adverse events**

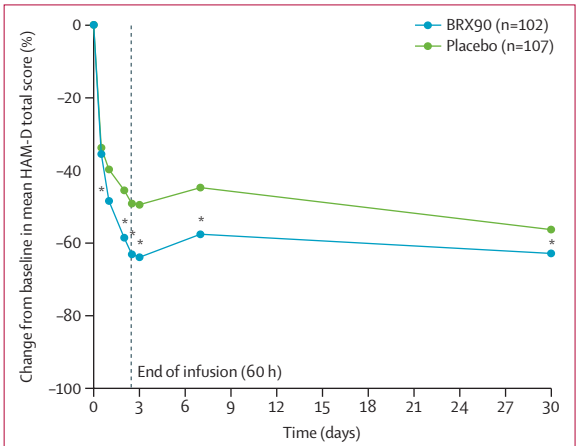


***Figure 3:*** **Percentage change from baseline in mean HAM-D total score in the integrated BRX90 study population**
p values were calculated by two-sided *t* test. BRX90=brexanolone injection 90 μg/kg. *p<0·05 *vs* placebo.

## Discussion

Women with post-partum depression have an increased risk of morbidity and mortality, and thus additional treatment options are urgently needed.[53] The present phase 3, double-blind, randomised, placebo-controlled trials of brexanolone injection in women with moderate to severe post-partum depression HAM-D score ≥20), confirm and extend the findings of our smaller phase 2 study,[37] which showed that brexanolone injection reduced depressive symptoms compared with placebo. The HAM-D is considered the gold standard assessment in clinical trials of major depression,[54] including pharmacotherapy trials in post-partum depression.[55–57] Consequently, as post-partum depression is considered a subtype of major depression in the DSM-5 and the International Classification of Diseases, the HAM-D was considered the most appropriate primary endpoint.[58] Across all three studies, brexanolone injection was associated with rapid onset of action (within 60 h) and durable responses that were sustained for up to 30 days after infusion. Of the patients who had a response at 60 h, 94% did not relapse at day 30.

Although this trial was not designed to investigate the effects of brexanolone on children and families of patients, the potential impact of a treatment with rapid onset of action should not be underestimated. Netsi and

colleagues,[15] examined the adverse effects of post-partum depression on child development in a large observational study of women and their offspring and found that children of women with persistent and severe post-partum depression showed increased risk for behavioural problems by age 3·5 years, and lower mathematics grades and depression during adolescence. Furthermore, women with persistent post-partum depression were more likely to experience depressive symptoms lasting at least 11 years after childbirth, prolonging the impact on both mother and child.[15] Additional studies[59,60] have revealed an association with infanticide and decreased use of preventive paediatric health care.

Thus, we believe the results from these two phase 3 studies have the potential to change the treatment approach for post-partum depression. After the 60 h infusion, patients in the BRX90 groups had significantly larger reductions from baseline in LS mean HAM-D total scores than patients in the placebo groups, regardless of initial HAM-D total score stratification. In study 1, a similar effect was observed for patients in the BRX60 group. Therefore, our data indicate that substantial relief of post-partum depressive symptoms can be provided within less than 3 days of treatment.

The majority of patients in all three studies did not receive antidepressants during the study, indicating that brexanolone injection is a primary, rather than adjunctive, therapy in post-partum depression. When the reduction in depressive symptoms was examined according to antidepressant medication use, no differences were observed. Additionally, consistent with the HAM-D subscale and individual item analyses showing an improvement in core symptoms of depression, brexanolone injection had antidepressant effects. The broad antidepressant response observed in HAM-D individual items also shows that the effect of brexanolone injection was not driven solely by improvements in sleep. The treatment effect persisted for the duration of study (until day 30) in the BRX90 and BRX60 treatment groups, as assessed by HAM-D total scores, HAM-D remission, HAM-D response, and CGI-I response. Although mean differences in HAM-D total score from baseline were not statistically significant at all timepoints after the acute 60 h treatment, overall variability in depression response in patients between completion of dosing and day 30 was negligible. This maintenance of response is consistent with phase 2 data.[37]

Previous studies[61,62] of depression (predominantly in major depressive disorder) have demonstrated highly variable responses to placebo, and large placebo effects might contribute to the inability of some studies to show significant treatment effects.[61,63] Higher levels of supervision and frequent assessment of patients in addition to expectancy of outcome in clinical trial participants are hypothesised to contribute to this variability. These hypotheses can be applied to the current studies, in which we observed a similar variable placebo response across our three placebo-controlled trials of brexanolone injection in post-partum depression; however, despite the robust placebo response in studies 1 and 2, the primary endpoint was met, with clinically meaningful and statistically significant treatment differences observed between the brexanolone injection groups and placebo groups. Furthermore, integrated analyses of efficacy in the placebo-controlled study population revealed that the variability of the estimates was reduced due to increased sample size, and additional timepoints and secondary endpoints showed statistically significant improvements for BRX90 relative to placebo. Brexanolone injection has only been assessed in the context of post-partum depression, thus it is unclear whether positive allosteric modulation of GABA might be generally applicable in major depressive disorder outside of the perinatal period, although studies of a candidate have been announced by the study sponsor.

The tolerability profile in these phase 3 trials is consistent with the GABAergic effect of brexanolone injection. Consistent with the primary pharmacology of brexanolone injection, which is a GABA positive allosteric modulator, somnolence, dizziness, and sedation occurred in approximately 30% of patients. The overall incidence of adverse events in the drug and placebo groups were similar. The most common adverse events in studies 1 and 2 and across all placebo-controlled brexanolone injection studies were headache, dizziness, and somnolence. The incidence of dizziness and somnolence was higher in the brexanolone injection groups than the placebo groups, but these events were typically mild in severity and did not lead to discontinuation of treatment.

One limitation of these data is that the patient population in these trials is representative of moderate to severe post-partum depression patients in the USA,[37] and thus the generalisability of these data to a wider population has yet to be determined. Trial participants had moderate to severe symptoms according to the HAM-D, but few would qualify or require an inpatient care. All patients were administered brexanolone injection in a supervised setting. The majority of patients were treated at research centres, with some treated in other settings, such as psychiatry inpatient units. Additionally, the HAM-D results could have been affected by respondent fatigue due to frequent administration. Although these trials assessed women for a 30-day follow-up period, the effects of brexanolone injection treatment after this time period are unknown, which is an important limitation of these trials. Data on the effectiveness of current antidepressant therapy in post-partum depression are scarce, so the long-term efficacy of brexanolone injection compared with currently available oral antidepressants remains unclear.

These findings confirm the results of our previously reported phase 2 data and provide strong evidence for the efficacy and safety of brexanolone injection in women with moderate to severe post-partum depression. The presumed

mechanism of action of brexanolone injection (ie, positive allosteric modulation of $GABA_A$ receptors) is a novel approach in the development of a therapeutic drug for post-partum depression that has the potential to improve treatment options for women with post-partum depression.

#### Contributors

All authors contributed to the design of the study and writing of the manuscript. SM-B, SK, and HC designed the study. SM-B and SK wrote the first draft. CNE, KMD, RR, and DRR were investigators in the study. HL and AJS did statistical analysis.

#### Declaration of interests

SM-B reports personal fees from MedScape and grants from Sage Therapeutics, Inc, awarded to the University of North Carolina (Chapel Hill, NC, USA) during the conduct of the study, and grants from Janssen outside the submitted work. HC, HL, AJS, CC, AS, are JJ are employees of Sage Therapeutics, Inc, and own stock or stock options in the company. CNE reports personal fees from Asarina Pharma, personal fees for consultancy and grants from Sage Therapeutics, Inc. KMD received a grant from Sage Therapeutics, Inc, awarded to her institution. DRR reports personal fees and has stock options in Sage Therapeutics, Inc. SK is an employee of Sage Therapeutics, Inc, owns stocks in the company, and has a patent pending (SAGE-547 for Neuropsychiatric Conditions). RR declares no competing interests.

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