Insomnia Symptom Response in Patients with Postpartum Depression Treated with the Neuroactive Steroid Brexanolone

**Introduction**

- Postpartum depression (PPD) is one of the most common complications during and after pregnancy.
- Altered sleep states are both a risk factor for and a symptom of PPD.
- Reduced sleep quality may be associated with increased depressive symptomology.
- Brexanolone injection (BRX) is a neuroactive steroid GABA receptor positive allosteric modulator with a pharmacological profile distinct from benzodiazepines, as approved by the FDA for the treatment of PPD in adults.
- The safety, tolerability, and efficacy of BRX in PPD were evaluated in three double-blind, randomized, placebo-controlled trials (RCTs) where patients treated with BRX90 met the primary efficacy endpoint at Hour 60, by achieving significantly greater Hamilton Rating Scale for Depression (HAM-D-17) total score reduction from baseline compared with placebo (p=0.0012).
- In addition, improvements in baseline insomnia symptoms were maintained up to Day 30.
- Some patients also had loss/altered consciousness, and flushing/hot flushes.
- The common TEAEs (≥5% of BRX compared with placebo) included sedation/somnolence, and dry mouth.
- No dose interruption, ranged from 15 to 60 minutes. All patients recovered with dose interruption.

**Methods**

- An integrated dataset of three pivotal studies in PPD was used for these analyses.
- Women (n=209), 18–45 years of age, with PPD (defined as a major depressive episode with onset in the 3rd trimester or 4 weeks postpartum) and a qualifying HAMD-17 total score (Studies A and B) or HAMD-17 total score (Study C; HAMD-17 20-25) were enrolled.

**Results**

**Table: HAMD-17 TOTAL SCORE**

<table>
<thead>
<tr>
<th>Time (Days)</th>
<th>Placebo (N=107)</th>
<th>BRX90 (N=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 3</td>
<td>41.5</td>
<td>35.6</td>
</tr>
<tr>
<td>Day 7</td>
<td>32.1</td>
<td>28.0</td>
</tr>
<tr>
<td>Day 30</td>
<td>26.0</td>
<td>22.9</td>
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</tbody>
</table>

**Table: HAMD-17-INS RESPONSE WITH BRX VS PLACEBO**

<table>
<thead>
<tr>
<th>Time (Days)</th>
<th>Placebo (N=104)</th>
<th>BRX90 (n=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hour 24</td>
<td>74.7</td>
<td>75.7</td>
</tr>
<tr>
<td>Hour 48</td>
<td>75.7</td>
<td>75.7</td>
</tr>
<tr>
<td>Hour 72</td>
<td>75.7</td>
<td>75.7</td>
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<tr>
<td>Hour 144</td>
<td>75.7</td>
<td>75.7</td>
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</tbody>
</table>

**Conclusions**

- BRX treatment in women with PPD has been shown to positively affect HAMD-17 total score and reduction in depressive symptoms (HAMD-17 total score and Bech-6 score) and significantly reduce insomnia symptoms (HAMD-17 total score and Bech-6 score) at all subsequent measured time points up to Day 30 compared with placebo.
- In addition to its effects on core symptoms of depression in this trial, these post-hoc analyses showed that BRX treatment also resulted in a significantly greater improvement in reported symptoms of insomnia from the HAMD-17.4.4, and higher proportions of patients achieving HAMD-17.4.4 response compared with placebo.

**SAFETY**

- BRX common TEAEs (≥5% of BRX and ≥1% of placebo) included sedation and somnolence, dry mouth, loss of consciousness, and flushing.

**Supplementary Information**

- Funding and Author Disclosure: All authors are employed by Sage Therapeutics, which owns the rights to brexanolone injection (BRX90). Development of this treatment is supported by the National Institute of Mental Health. SM-B reports personal fees from MedScape and grants from Sage Therapeutics, Inc., and has stock/stock options.

**Abbreviations**

- HAMD: Hamilton Rating Scale for Depression
- HAM-D-17: Hamilton Depression Scale
- BRX: Brexanolone Injection
- TEAE: Treatment-emergent adverse event
- RCT: Randomized controlled trial
- MANOVA: Multivariate analysis of variance
- BMI: Body mass index
- PPD: Postpartum depression
- DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition
- HAM-D: Hamilton Depression Scale
- HAMD-17: Hamilton Depression Scale-17
- HAMD-17-Ins: Hamilton Depression Scale-17 Insomnia Subscale
- SD: Standard deviation
- %: Percentage
- SE: Standard error
- CI: Confidence interval
- p: Probability
- CFB: Change from baseline
- BMQ: Brexanolone injection Meltzer-Brody, MD, MPH
- E10.1016/PLoS ONE.2013.02.054