# Safety, Tolerability, and Pharmacokinetics of BRII-296, An Extended-Release Injectable Aqueous Suspension Formulation of Brexanolone in Healthy Adult Subjects

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## Background

- Postpartum depression (PPD) is associated with risks to the mother as well as effects on the maternal-infant relationship and subsequent child longer-term development outcomes.
- BRII-296 is an extended-release injectable aqueous suspension formulation of brexanolone (BXN) for the treatment and prevention of PPD.
- BRII-296 provides substantial clinically meaningful advantages over currently available treatment option for PPD via a single intramuscular (IM) administration and directly observed treatment in outpatient clinics.
- BRII-296 can achieve desired exposures associated with efficacy via continuous drug release/absorption, maintained plasma level, and slow tapered elimination while maintaining a favorable safety and tolerability profile including minimal exposure to breastfed infants due to very limited oral bioavailability.

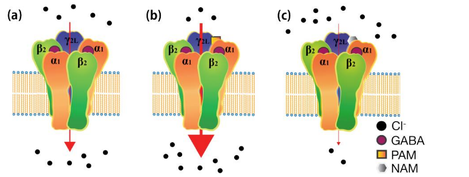
## Study Design

- BRII-296-001 is an ongoing open-label, phase 1, single ascending dose (SAD) study to evaluate the safety, tolerability, and PK.
- Three formulation concentrations were administered via one or more IM injections to healthy adult subjects. The doses and concentrations were BRII-296-A (300 mg/mL), BRII 296-B (100 mg/mL) and BRII-296-C (200 mg/mL) at total dose levels of 30 mg, 75 mg, 100 mg, 200 mg, 300 mg and 600 mg.
- In addition, oral prophylactic treatment, as well as BRII-296 co-injection or admixed with steroids administration by one or more injections were also evaluated to manage local injection site reactions (ISRs).
- The primary endpoints were safety and PK assessments.

- **Staged Treatment Regimen (Cohorts) Information:**
  - **Stage 1: Cohorts: 1-6**
    - Objective: SAD PK and safety
    - Dose: 30-300 mg BRII-296 (formulations A-B)
  - **Stage 2: Cohort: 7-10**
    - Objective: Prophylaxis treatment options
    - Dose: 100-300 mg BRII-296-C + oral or IM prophylaxis
  - **Stage 3: Cohort: 11-15**
    - Objective: Dose regimen optimization
    - Dose: 300-600 mg BRII-296 admixed up to 40 mg IM steroid prophylaxis

## Therapeutic Rationale

### Mechanism of Action of Allopregnanolone in PPD




Effects of positive allosteric modulator (PAM) and negative allosteric modulator (NAM) on GABA-induced $Cl^-$ flow through $GABA_A$ receptors. (a) Binding of GABA to the receptor causes channel opening and $Cl^-$ influx. (b) PAM binds to the allosteric site to increase $Cl^-$ influx. (c) NAM reduces $Cl^-$ influx.

*Reference: Current Drug Targets. 2015;16(7):735-46*

- **Allopregnanolone** (also known as brexanolone) is a naturally occurring neuroactive steroid that acts as a positive allosteric modulator (PAM) of GABA's action at $GABA_A$ receptors.
- Toward late gestation, levels of allopregnanolone in a woman's blood rise gradually to approximately 50 ng/mL. Shortly after giving birth, allopregnanolone levels drop precipitously.
- PAMs operate by increasing the frequency with which the chlorine channel opens when GABA binds to its own site on the GABA receptor. This action results in an increase in the Cl- ion concentration in the postsynaptic neuron and causes immediate hyperpolarization of this neuron, making it less excitable and thus inhibiting the possibility of an action potential and preventing the release of excitatory neurotransmitters.

## Results

### BRII-296-001 Safety Data

Of the 108 subjects enrolled across the 15 cohorts, 3 subjects did not complete the study (1 subject each from Cohort 2 and 5 due to withdrawal by subject; 1 subject from Cohort 3 due to non-compliance with protocol).

**Table 1. Demographics and Baseline Characteristics (All Subjects Enrolled)**

| | Cohort 1-15 Total (N=108) |
|---|---|
| **Age (years)** | |
| Mean (SD) | 36 (8.3) |
| Median (Min, Max) | 36 (19, 51) |
| **Sex, n (%)** | |
| Male | 56 (51.9) |
| Female | 52 (48.1) |
| **Ethnicity, n (%)** | |
| Hispanic or Latino | 9 (8.3) |
| Not Hispanic or Latino | 99 (91.7) |
| **Race, n (%)** | |
| Black or African American | 71 (65.7) |
| White | 33 (30.6) |
| Asian | 2 (1.9) |
| **BMI ($kg/m^2$)** | |
| Mean (SD) | 27.2 (3.71) |
| Median (Min, Max) | 27.6 (19.5, 34.3) |

NOTE: Baseline is defined as the last measurement prior to the first dose of study drug..

**Table 2. Treatment-Emergent Adverse Events Overall Summary (Safety Population)**

| | Cohort 1-15 Total (N=108) n (%) |
|---|---|
| **Any TEAE** | 89 (82.4) |
| Mild (Grade 1) | 46 (42.6) |
| Moderate (Grade 2) | 29 (26.9) |
| Severe (Grade 3) | 14 (13) |
| Life Threatening (Grade 4) | 0 |
| **Drug-related TEAE** | 87 (80.6) |
| Mild (Grade 1) | 44 (40.7) |
| Moderate (Grade 2) | 29 (26.9) |
| Severe (Grade 3) | 14 (13) |
| Life Threatening (Grade 4) | 0 |
| **Treatment-emergent injection-site reactions** | 84 (77.8) |
| Mild (Grade 1) | 43 (39.8) |
| Moderate (Grade 2) | 27 (25) |
| Severe (Grade 3) | 14 (13) |
| Life Threatening (Grade 4) | 0 |

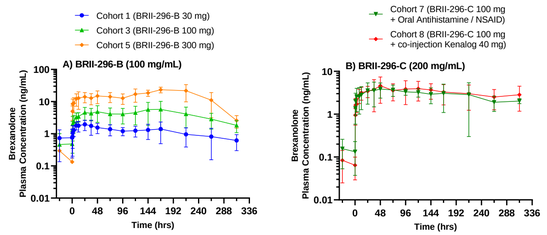
NOTE: Injection site reaction adverse events were graded by DAIDs Version 2.1 to four possible categories: Grade 1, 2, 3, or 4; all other adverse events were graded according to protocol section 10.3.3 to three possible categories: Mild, Moderate, and Severe.

- A total of 89 subjects reported TEAEs from the 15 cohorts. There were no life threatening TEAEs, TEAEs leading to premature discontinuation of study, SAEs, or deaths. TEAEs reported during the study were predominately mild (42.6%) and moderate (26.9%) in severity. TEAEs of severe severity accounted for 14 out of 108 subjects (13%).
- Majority of the reported TEAEs were considered drug-related, and the majority were attributed to treatment-emergent injection-site reactions. Across cohorts, the most common TEAEs (> 5%) by preferred term included injection site pain (77.8%), injection site induration (20.4%), injection site erythema (7.4%), injection site reaction (6.5%), and headache (10.2%).
- Co-administration of BRII-296 with Depo-Medrol (up to 40 mg per injection) effectively reduce severity of ISRs without additional safety issues.

## Results

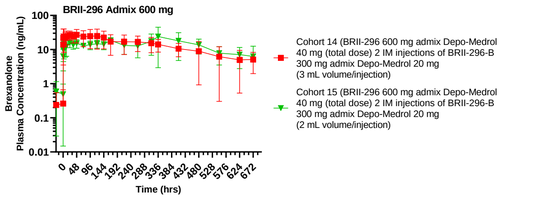
### BRII-296-001 Pharmacokinetic (PK) Data

**Figure 1. BXN Plasma Concentration – Time Profile in Healthy Adult Subjects after Single IM Administration of BRII-296 Aqueous Suspension Formulations A) BRII-296 Formulation B, B) BRII-296 Formulation C**




- BRII-296 formulation B exhibited desired IM administration PK profiles with dose linearity, early drug absorption phase, and modified release profiles (7-14 days).
- Oral and IM prophylaxis treatment with steroids via co-injection method did not alter the drug release and absorption process.

**Figure 2. BXN Plasma Concentration – Time Profile in Healthy Adult Subjects after Single IM Administration of 600 mg BRII-296 with Aqueous Suspension Formulations Admixed with Steroid (Depo-Medrol)**




- BRII-296 formulation concentration and injection volume had played a role in the overall drug release and absorption processes.
- Optimal dose and exposure for Phase 2 study has been achieved and selected for further drug development (600 mg BRII-296 admixed with 80 mg steroid).

## Conclusions

- The safety and PK profiles of BRII-296 IM administration was consistent with the long-acting aqueous suspension formulation.
- The selected dose regimen will achieve target coverage with good ISR profiles for efficacy evaluation of BRII-296 admixed with IM Depo-Medrol in a single treatment Phase 2 study for PPD patients.
- IM Depo-Medrol is also chosen for its reported low distribution of methylprednisolone to breastmilk to minimize infant exposure.
- Brii believes that BRII-296 will offer a much-needed alternative treatment option for adults with PPD.