# Brexanolone Injection, for Intravenous Use

## Sponsor Briefing Document – Addendum

## Joint Meeting of the Psychopharmacologic Drug Advisory Committee and Drug Safety and Risk Management Advisory Committee

## Meeting Date: November 2, 2018

## Advisory Committee Briefing Materials: Available for Public Release

# INTRODUCTION

This addendum highlights several areas where the Sponsor agrees with FDA's evaluation of brexanolone and proposal for strategies to minimize risk during the infusion. Some of these agreements have been made since the completion and publishing of the Sponsor's briefing document. In addition, this addendum provides clarifications on select points.

# DOSE RECOMMENDATION

Efficacy of brexanolone was demonstrated in three placebo-controlled trials evaluating the 90 dose regimen (across all three studies) and the 60 dose regimen (Study 202B). While the 90 dose regimen did not confer incremental efficacy compared to the 60 dose regimen, there also did not appear to be an added risk of adverse events based on the clinical trial data. The Sponsor's briefing document therefore focused on the 90 dose regimen. However, it is common in the labeling of many medications to recommend a lower dose, based on an overall approach to benefit-risk. For brexanolone, the data to support the 60 dose regimen is evidenced, not only by the demonstration of improvements in depressive symptoms compared to placebo in study 202B, but also by the trend for the 90 dose regimen toward separation from placebo at Hour 24 when patients had not yet received the 90 dose. This separation was statistically significant at Hour 24 in Study 202A and for the pooled data from the three studies. Importantly, our thinking has evolved regarding the potential risks which could be observed in the post-approval setting. In particular, the simpler design of the 60 dose regimen may reduce the risk of medication errors, eliminating two dose adjustments, and the risk of higher plasma concentrations which could lead to excessive sedation. We believe this information is important to the discussion of dose selection and support inclusion of information regarding both doses in the label.

# HEALTHCARE PROFESSIONAL OVERSIGHT AND MONITORING

The Sponsor and the Agency are in agreement that a healthcare professional (HCP) must be available onsite to provide oversight of treatment for the duration of the infusion and to monitor patients for excessive sedation. Patients will be instructed to alert the HCP if they feel effects such as dizziness or somnolence to allow for closer supervision and assessment for possible progression. In the case of excessive sedation, such that patients experience functional impairment, the HCP can respond with dose adjustment or interruption. In the case of loss of consciousness, dosing should be immediately stopped and can be restarted when the patient has fully recovered.

The Sponsor and the Agency further agree that pulse oximetry will be employed for the duration of the infusion to provide further assurance of patient safety, including in the event of deep sedation overnight.

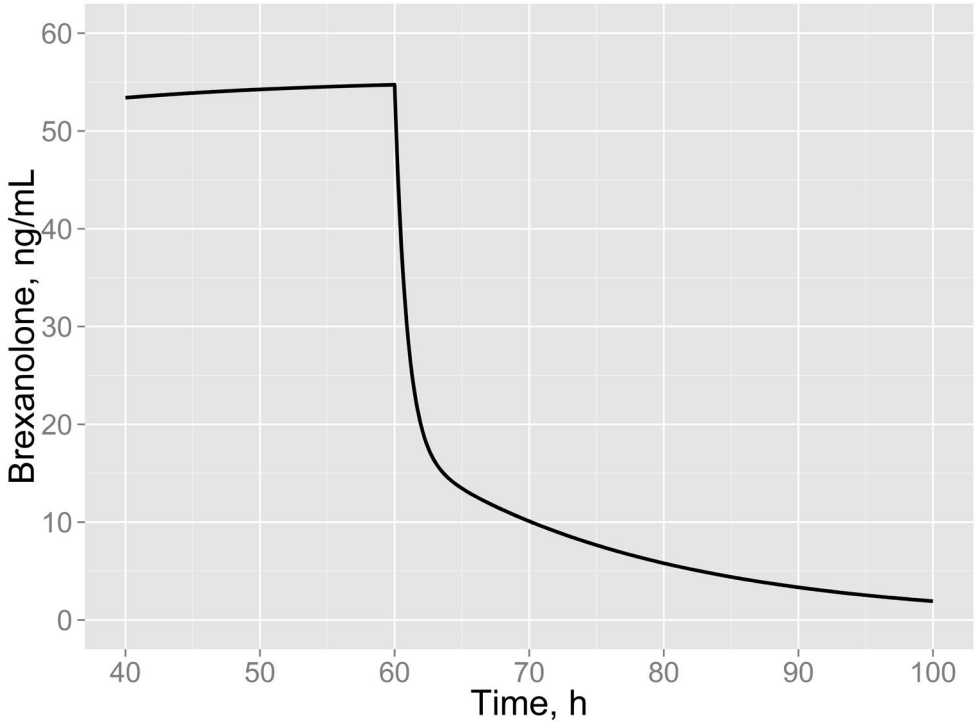
The Sponsor would like to clarify that pulse oximetry was continuously monitored in Study PPD-202A as well as in Studies PPD-202B and PPD-202C until protocol amendment 3 (dated 31 January 2017). Please note that there was an error (confusing version 3 with amendment 3 of the protocol) in the Sponsor's Briefing Document and we would like to clarify that this included 95 patients rather than 23 patients. Any indication of oxygen desaturation was to be recorded as an adverse event at the discretion of the Investigator. No such adverse events were reported. Respiratory rate was recorded as part of vital sign measurements. No evidence of respiratory depression was observed. Pulse oximetry data are available at the time of the event for two patients who experienced excessive sedation (Patients C and D). There was no evidence of oxygen desaturation ($O_2$ saturation = 98% and 100%, respectively). In addition, pulse oximetry data were recorded in clinical pharmacology studies. In the thorough QT study (CLP-106), a 55 year old male administered a supratherapeutic dose of 180 µg/kg/h experienced severe somnolence, confusion, and (<1 minute) apnea (oxygen saturation 98%). The infusion was stopped and this subject did not lose consciousness. The subject recovered from the events without sequelae and completed the study.

## BREXANOLONE PHARMACOKINETICS

The time-course of brexanolone elimination is important to understanding the management of sedation-related events. While the half-life of brexanolone is approximately 9 hours, brexanolone metabolism is biphasic and the large majority of the drug is rapidly cleared from the plasma. Following cessation of an infusion, plasma concentrations are described by a two-compartment PK model declining biexponentially with a precipitous initial drop followed by slower elimination.

The population PK model has been used to simulate an abrupt termination of a 60 µg/kg/h steady-state infusion (Figure 1). Based on this model, the median distribution half-life is approximately 40 minutes leading to a precipitous initial decline when the pump is shut off. While the terminal half-life is the relevant parameter used to describe accumulation or wash out, the distribution half-life describes the decline in plasma concentrations that is most relevant to interrupting or stopping the pump. This short half-life is consistent with the rapid resolution of sedation-related events following dose adjustment or interruption and is an appropriate metric for consideration of resuming normal function, either following a sedation-related event or at the end of treatment.

**Figure 1: Simulated Stop of the Infusion Pump During a 60 µg/kg/h SteadyState Infusion**




## LOSS OF CONSCIOUSNESS EVENT

The Sponsor would like to provide additional details around the loss of consciousness (LOC) case from PPD-202C referenced in the Agency's Addendum, Section 2.2. The details of the patient's course further describe adverse event onset and timing, prior to LOC.

This patient is a 25-year-old woman with a BMI of 29.6 kg/m$^2$ and relevant medical history that included anxiety, depression and tobacco use. On Day 1 approximately 8.5 hours after the start of the infusion and 4.5 hours after the start of 60 µg/kg/h, the subject developed dizziness, vision change, lightheadedness, and nausea on ambulating to the nurse's station. The subject reported that she had not eaten much except for several pieces of candy. Her blood glucose was 84 (units of measure and reference ranges were not provided), which was not considered to be a hypoglycemic level; however, due to her symptoms, she was given orange juice and Jello, which she tolerated well but reported no improvement in symptoms. At that time, she had no chest pain, headache, abdominal pain, focal weakness or paresthesias, but reported feeling altered. Her vital signs were within normal limits and oxygen saturation was 98% on room air. Approximately 10 minutes after the onset of the dizziness, while sitting in the bed, the subject dropped her spoon, closed her eyes, and became unresponsive. Approximately 3 minutes after the onset of the event, study drug was discontinued and within 10 minutes of the onset of the

event, the patient started opening her eyes to verbal and noxious stimuli, however, she was not noted to respond with any vocalization or other responses. Emergency services were called and the patient was taken to the Emergency department (ED) of a local hospital for further evaluation. Within approximately 45 minutes from the onset of the event the patient was reported to be back to her baseline and was awake and oriented. Please refer to Appendix C of the Sponsor's briefing book for the complete narrative of this case.

## REMS AND PATIENT REGISTRY

The Sponsor and the Agency agree that distribution of brexanolone will be restricted to certified healthcare settings under a REMS with Elements to Ensure Safe Use. A registry will be established to gather information such as medical history and concomitant medications in all subjects and additional details (vital signs, oxygen saturation, etc) for those subjects that develop excessive sedation to better characterize the risk of loss of consciousness. The Sponsor is developing the details of the REMS and the data which will be collected as part of the registry.

## APPROACH TO TREATMENT IN HOME SETTINGS

Currently, approximately 97% of women with PPD are not admitted for inpatient treatment, as most do not meet hospital admission criteria. In addition, there is significant stigma around the diagnosis and treatment of PPD which presents further obstacles to treatment. While the Sponsor agrees to restrict distribution to certified healthcare settings, we are also concerned that this will significantly impede patient access to treatment. Known serious risks of untreated PPD include suicidal ideation and behavior, maternal morbidity, and lost work days due to depression, as examples.

It is anticipated that data from the REMS and patient registry can inform and characterize the risk of excessive sedation in the post-approval setting. We appreciate the Agency's invitation to discuss the approach to extending the same principles of safe administration to treatment in the home, including healthcare professional oversight and monitoring for the duration of the infusion, careful patient selection and application of the REMS and registry. We welcome the opportunity to further explore what information may be helpful to ensure safe use in this treatment setting.