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RESPONSE TO PREA NON-COMPLIANCE LETTER
DEFERRAL EXTENSION REQUESTED

June 13, 2024

Rigoberto Roca, MD, Acting Director
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
Office of Drug Evaluation II
Food and Drug Administration
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266
USA

Re: NDA 212295
Sequence No.: 0198
BYFAVO® (remimazolam) for injection (CB-07-01; CNS 7056)
Indication: the induction and maintenance of procedural sedation in adults undergoing procedures lasting 30 minutes or less.
Sponsor: Acacia Pharma Ltd, an indirect wholly owned subsidiary of Eagle Pharmaceuticals, Inc.

Dear Dr. Roca,

Reference is made to our new drug application (NDA) for Byfavo (remimazolam) for injection, which was approved on July 2, 2020. Further reference is made to the Agency's "Notification of Non-Compliance with PREA" letter dated May 1, 2024, pertaining thereto. A copy of the May 1st communication is provided herein for reference.

We acknowledge the Agency's determination that we have not met the post marketing requirements (PMRs) of the Pediatric Research Equity Act (PREA) for this application due to not submitting our pediatric assessment for the following PMRs:

> **3889-3:** A juvenile animal toxicology study in a rodent model to characterize the effects of remimazolam on the developing central nervous system to support clinical studies in pediatric patients under three years of age. (Deferred until December 31, 2022)
>
> **3889-5:** A juvenile animal toxicology study in a rodent model to characterize the effects of remimazolam on the developing central nervous system to support a clinical indication for use in pediatric patients greater than or equal to three years of age and below 18 years of age. (Deferred until December 31, 2022).

Sponsor Response

Background

We refer the Agency to our December 15, 2023, IND 102486 Amendment (Serial No.: 0162) which provided an update for PMRs 3889-3 and 3889-5 as well as the remaining PMRs for this NDA as described in the NDA approval letter dated July 2, 2020.

At the time of NDA approval, the original timetables listed in the approval letter seemed realistic and activities were initiated with the intent to fulfill the post marketing requirements of PREA in accordance with original timelines. As work progressed, over time it became increasingly apparent that extensive exploratory/pilot studies and associated work would be required to ensure proper study designs for the two primary studies referenced above. The additional exploratory/ pilot work proved challenging and required more time than initially anticipated. This is further explained below.

PMR 3889-3

Acacia/Eagle is partnering with co-development partner, Paion UK Ltd (Paion), in the conduct of this pediatric assessment. As described above and in our December 15, 2023 IND amendment, multiple pilot/exploratory studies were required before the primary study could be initiated as follows:

- Study 35340 – Re-validation of Analytical Method for the Determination and Quantification of Remimazolam (CNS7056) in Aqueous Solution (b) (4) with HPLC-UV Detection (see (b) (4) Report No. 35340). The objective of the study was the re-validation of an analytical HPLC-UV method for the quantification of Remimazolam besylate (CNS7056B)) \in aqueous solution samples. **Status: Completed.**
- Study 38415 – Explorative Study of Remimazolam Besylate to Investigate Juvenile Neurotoxicity in Rats on Post-Natal Days 7 and 10 (see (b) (4), Study Report 38415). The purpose of this study was to determine suitable conditions to investigate the neurotoxicity of remimazolam during the phase of brain growth spurt in the rodent model. **Status: Completed.**
- Study 172-351-5266 – 28-Day Repeated Dose Intravenous Toxicity Study of Dextran 40 in Wistar Rats, followed by a 14-Day Recovery Period, including Toxicokinetics (see (b) (4), Study Report 172-351-5266). The purpose of this study was to obtain information on the toxicity of Dextran 40 following daily intravenous administration to Wistar rats for 20 consecutive days. In addition, the reversibility of any changes assessed during a 14-day post-dosing (recovery) period. **Status: Completed**
- Study 2022-058 – Remimazolam Besylate: Explorative Juvenile Toxicity Study in the Rat with Administration on Post-Natal Day 7 (see (b) (4) Document No. 2022-0058-R), was conducted to ascertain suitable dosing of **remimazolam and controls (ketamine and midazolam)** for the induction of sedation of comparable depth and duration to guide dosing to be used in the main juvenile toxicity study in rats on PND7 (Study 2022-059). **Status: Completed.**
- Study 2023-0122 – Ketamine: Explorative Juvenile Toxicity Study in the Rat to Verify Neurodegenerative Effects after Multiple Intraperitoneal Administration on Post-Natal Day 7 (see (b) (4) Document No. 2023-0122-R). This study was conducted to establish the histopathological and immunohistochemical methods to be applied in the main study (Study 2022-059) for the assessment of neurodegeneration following exposures, confirm that the ketamine dose schedule induces neurodegeneration which is measurable using these methods and to determine the optimal time point for the preparation of brains following exposure regarding increase in apoptotic cells. **Status: Completed**.

- Study 2022-059 – Remimazolam Besylate: Juvenile Toxicity Study in the Rat with Administration on Post-Natal Day. The purpose of this study is to determine the potential neurotoxicity of remimazolam besylate in comparison to well-known neurotoxic drugs as midazolam and ketamine when administered to male and female pups on Postnatal Day (PND) 7 using a repeat dose scheme over six hours to be able to maintain animals in a comparable status of sedation. **Status: Ongoing**. Please refer to Deferral Extension Request below.

Please refer to our December 15, 2023 IND update for any applicable reports related to the above reference studies. We note Study 2023-0122-R, which was necessary to support the conclusions of 2022-058-R, and by extension is necessary to conduct PMR 3889-3, was concluded in May of 2023. The final draft report became available to Acacia/Eagle in early December 2023.

Assessment of the data from the five (5) pilot/exploratory studies was needed to prepare the new protocol for PMR 3889-3 (Study 2022-0059-P: Remimazolam Besylate – Juvenile Toxicity Study in the Rat with Administration on Post-Natal Day 7) which was submitted to the IND for review on December 15, 2023.

To address the recommendations related to the above referenced protocol in the Agency's February 12, 2024 Advice/Information Request letter, Acacia/Eagle and Paion needed to identify appropriate resources to ensure the Agency's recommendations (specifically item 2) would be included in the submission of the juvenile studies.

Acacia/Eagle and Paion plan to initiate the primary study for PMR 3889-3 in June 2024 with a September 2025 target for submission of the pediatric assessment for PMR 3889-3. Please also refer to our Deferral Extension Request below.

PMR 3889-5

The pilot studies referenced above played a vital role in providing the necessary foundation for the primary study of PMR 3889-5. These preliminary investigations were essential in identifying key parameters and ensuring the feasibility of the main study. (b) (4) This ongoing work is critical for accurately characterizing dose exposure, with a particular focus on the area under the curve (AUC).

Current bioavailability data is insufficient to establish an appropriate dosage for the primary study, highlighting the need for further investigation. Moreover, the pilot studies aim to address the significant challenge of animal mortality, which has posed a considerable obstacle. By refining dosage accuracy and improving overall study conditions, these efforts are expected to yield more reliable and comprehensive data, ultimately supporting the success of the primary study.

(b) (4)

Acacia/Eagle has initiated work for both pilot studies with plans to initiate the first and second pilots in mid-2024. The protocol for the primary study has been drafted and will be finalized for submission to the Agency when the pilot data is available. We anticipate finalizing the draft protocol for PMR 3889-5 and submitting it to the IND in Q4 2024. Please also refer to our Deferral Extension Request below.

DEFERRAL EXTENSION REQUESTED

Based on the above responses for PMRs 3889-3 and 3889-5, Acacia, as a wholly owned indirect subsidiary of Eagle Pharmaceuticals, Inc. requests a deferral extension for the below PMRs as follows:

PMR 3889-3

A juvenile animal toxicology study in a rodent model to characterize the effects of remimazolam on the developing central nervous system to support clinical studies in pediatric patients under 3 years of age.	Final Protocol: 12/15/2023
	Study Initiation: 06/2024
	Study Completion: 03/2025
	Final Report Submission: 09/2025

PMR 3889-5

A juvenile animal toxicology study in a rodent model to characterize the effects of remimazolam on the developing central nervous system to support a clinical indication for use in pediatric patients greater than or equal to three years of age and below 18 years of age.	Draft Protocol Submission: 12/2024
	Final Protocol Submission: 03/2025
	Study Initiation: 07/2025
	Study Completion: 03/2026
	Final Report Submission: 09/2026

Pursuant to PREA requirements, Acacia/Eagle certifies that the grounds for deferral of required pediatric assessments continue to be met, and that Acacia/Eagle will continue to work toward completing its PREA PMRs with due diligence at the earliest possible time.

We trust the above adequately responds to the Agency's PREA non-compliance communication of May 1, 2024, and supports our deferral extension request for PMRs 3889-3 and 3889-5. If any further information is required or if there are additional questions, please do not hesitate to contact me directly.

This submission has been provided in eCTD format in accordance with the eCTD specifications described in current guidance. An Electronic Submission Specifications form from our publishing vendor ((b) (4) is provided as an attachment to this cover letter. A letter of non-repudiation authorizing (b) (4) to provide electronic signatures on behalf of Eagle was submitted to FDA on December 29, 2016.

Sincerely,

Marc Stern (on behalf of Janis Picurro)

Digitally signed by Marc Stern (on behalf of Janis Picurro)
Date: 2024.06.12 12:42:46 -04'00'

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Electronic Submission Specifications

This submission is compliant with FDA's Guidelines for Industry and current eCTD specifications.

All files were checked and verified to be free of viruses prior to transmission through the electronic submission gateway.

Anti-Virus Program	Microsoft Defender Antivirus
Program Version	4.18.24050.7
Virus Definition Date	06/12/2024
Submission Size	Approx. 5.2 MB