



Our STN: BL 125772/0

**LATE-CYCLE  
MEETING MEMORANDUM**  
October 28, 2022

CSL Behring LLC  
Attention: Poorva Chiddarwar  
1020 First Avenue  
P.O. Box 61501  
King of Prussia, PA 19406-0901

Dear Ms. Chiddarwar:

Attached is a copy of the memorandum summarizing your September 30, 2022, Late-Cycle Meeting teleconference with CBER. This memorandum constitutes the official record of the meeting. If your understanding of the meeting outcomes differ from those expressed in this summary, it is your responsibility to communicate with CBER in writing as soon as possible.

Please include a reference to the appropriate Submission Tracking Number (STN) in future submissions related to the subject product.

If you have any questions, please contact the Regulatory Project Manager, Shalini Seetharaman at (240) 672-8158 or by email at [Shalini.Seetharaman@fda.hhs.gov](mailto:Shalini.Seetharaman@fda.hhs.gov).

Sincerely,

Steven S. Oh, PhD  
Acting Director  
Division of Cellular and Gene Therapies  
Office of Tissues and Advanced Therapies  
Center for Biologics Evaluation and Research

### Late-Cycle Meeting Summary

**Meeting Date and Time:** September 30, 2022; 10:00 AM to 11:00 AM  
**Meeting Location:** Teleconference (via Zoom)  
**Application Number:** BL 125772/0  
**Product Name:** etranacogene dezaparvovec  
**Proposed Indication:** Treatment of adults with hemophilia B (congenital Factor IX deficiency) (b) (4)

**Applicant Name:** CSL Behring LLC  
**Meeting Chair:** Anurag Sharma, PhD  
**Meeting Recorder:** Shalini Seetharaman, MS

### FDA ATTENDEES

Emmanuel Adu-Gyamfi, PhD, CBER/OTAT/DCGT  
Rachael Anatol, PhD, CBER/OTAT  
Bethany Baer, PhD, CBER/OBPV/DPV/PB  
Kimberly Benton, PhD, CBER/OTAT  
Margaret Benny Klimek, PhD, CBER/OTAT/DCEPT  
Lilia Bi, PhD, CBER/OTAT/DCGT  
Stacey Borenstein, PhD, CDRH/OPEQ/OHTVII  
Wilson W. Bryan, MD, CBER/OTAT  
Andrew Byrnes, PhD, CBER/OTAT/DCGT  
Colleen Caldwell, MS, MPH, CBER/OTAT/DRPM  
Gregory Conway, PhD, MA, CBER/OTAT/DCEPT  
James Crim, PhD, CBER/OCBQ/DMPQ  
Donald Ertel, PhD, CBER/OTAT/DMPQ  
Varsha Garnepudi, PhD, CBER/OCBQ/DBSQC  
Denise Gavin, PhD, CBER/OTAT/DCGT  
Alifiya Ghadiali, PhD, CBER/OTAT/DMPQ  
Jie He, CBER/OCBQ/DMPQ  
Lin Huo, PhD, CBER/OBPV/DB  
Adnan Jaigirdar, MD, FACS, CBER/OTAT/DCEPT  
Courtney Johnson, MD, CBER/OTAT/DCEPT  
Megha Kaushal, MD, CBER/OTAT/DCEPT  
Carolyn Laurencot, PhD, CBER/OTAT/DCGT  
Wei Liang, PhD, CBER/OTAT  
Yuqun Abigail Luo, PhD, CBER/OBPV/DB  
Rommel Maglalang, CBER/OTAT/DRPM  
Ronit Mazor, PhD, CBER/OTAT/DCGT  
Adamma Mba-Jonas, MD, MPH CBER/OBPV/DPV/PB  
Leyish Minie, MSN, RN, CBER/OTAT/DRPM  
Massoud Motamed, PhD, CBER/OTAT/DCGT  
Steven Oh, PhD, CBER/OTAT/DCGT

Mikhail Ovanesov, PhD, CBER/OTAT/DPPT  
Tejashri Purohit-Sheth, MD, CBER/OTAT/DCEPT  
Rong, Rong, MD, CDRH/OPEQ/OHTVII/DIHD/HB  
Wendy Rubinstein, MD, CDRH/OPEQ/OHTVII  
Kimberly Schultz, PhD, CBER/OTAT/DCGT  
John Scott, PhD, MA, CBER/OBPV/DB  
Shalini Seetharaman, MS, CBER/OTAT/DRPM  
Anurag Sharma, PhD, CBER/OTAT/DCGT  
Abigail Shearin, VMD, PhD, CBER/OTAT/DCEPT  
Ramani Sista, PhD, CBER/OTAT/DRPM  
Pan Tao, PhD, CBER/OCBQ/DBSQC/LAC  
Million Tegenge, PhD, CBER/OTAT/DCEPT  
McKenna Tennant, PhD, CDRH/OPEQ/OHTVII  
Edward Thompson, CBER/OTAT/DRPM  
Natasha Thorne, PhD, CDRH/OPEQ/OHTVII/DIHD/HB  
Triet Tran, PhD, CBER/OCBQ/DIS/BMB  
Lori Tull, CBER/OTAT/DRPM  
Ramjay Vatsan, PhD, CBER/OTAT/DCGT  
Xiaofei Wang, PhD, CBER/OTAT/DCEPT  
Min Wu, PhD, CDRH/OPEQ/OHTVII/ DIHD/HB  
Lihan Yan, PhD, CBER/OBPV/DB

#### **APPLICANT ATTENDEES**


Emmanuelle Lecomte Brisset, Global Regulatory Affairs Head  
Angela Mikroulis, North America Therapeutic Area Lead, Global Regulatory Affairs  
Poorva Chiddarwar, North America Regulatory Lead, Global Regulatory Affairs  
Scott Hambaugh, Head of Global Product Strategy, Global Regulatory Affairs  
Patrick Swann, Head of CMC, Global Regulatory Affairs  
Larissa Milke, Global CMC Lead, Global Regulatory Affairs  
Pedro Campino, Global Regulatory Lead, Global Regulatory Affairs  
John Blewitt, Global Regulatory Lead – Devices, Global Regulatory Affairs  
Paul Monahan, Senior Director, Clinical Development  
Yanyan Li, Director, Biostatistics  
Jacqueline Tarrant Global Biomarkers Lead, Clinical Development  
Silpa Nuthalapati, Director, Clinical Pharmacology  
Michael Fries, Executive Director, Biostatistics  
Roberto Guillen-Gonzalez Senior Director, Clinical Safety  
Jason Newman, Executive Director, CMC  
Kye Ehart, Senior Director, CMC

#### **BACKGROUND**

BLA 125772/0 was submitted on March 24, 2022, for etranacogene dezaparvovec.

Proposed indication: Treatment of adults with hemophilia B (congenital Factor IX deficiency) (b) (4)

(b) (4)

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PDUFA goal date: November 22, 2022

In preparation for this meeting, FDA issued the Late-Cycle Meeting Materials on September 20, 2022.

## DISCUSSION

### 1. Discussion of Substantive Review Issues

#### A. Chemistry, Manufacturing and Controls

The applicant committed to submit the following information to the BLA by September 22, 2022 (the information has not been received at the time this letter was drafted):

1. The genomic titer (b) (4) assay protocol must add a positive control for (b) (4) activity. Absence of this control may permit falsely high genomic titer results that could lead to errors in batch strength and consequent errors in relative reporting of impurities and under-dosing of patients. We requested this assay control in an Information Request (IR) dated June 17, 2022, and in the mid-cycle communication to the applicant. CSLB has agreed (response dated August 4, 2022) to include the (b) (4) activity control to the genomic copies titer (b) (4) assay and submit the revised protocol.

**Meeting Discussion:** The applicant confirmed that the information regarding inclusion of the (b) (4) activity control to the genomic copies titer (b) (4) assay was submitted on 20 September 2022. FDA acknowledged the receipt of the submission and stated that the submission is being reviewed.

FDA asked the applicant to submit the revised (b) (4) SOP and the verification protocol by mid-October. The applicant agreed.

2. During the mid-cycle meeting and in the response (dated August 4, 2022) to IR (dated July 14, 2022), the applicant proposed to validate assays for (b) (4) based on assay priority (i.e., impact on safety and quality), starting with higher priority (Tier 1) first and submit the results to the BLA. Validation of (b) (4) for some of the lower priority assays (Tier 2) will be submitted as a prior approval supplement (see agenda item #7 post-marketing commitment), if the BLA is approved. The (b) (4) validation data for the Tier 1 assays including (b) (4) are yet to be submitted.

**Meeting Discussion:** The applicant requested FDA confirmation that the submission of the Tier 2 assays (non-safety related limit assays) method validation package for assay (b) (4) can be submitted as a Change Being Effected (CBE30) supplement and not as a Prior Approval Supplement (PAS). FDA agreed.

3. Please also refer to the LCM agenda item #7 Postmarketing Requirements/ Postmarketing Commitments.

## Clinical

### Efficacy

1. Preexisting neutralizing antibodies threshold/Companion Diagnostic:  
In this BLA submission, the applicant proposed a target threshold of neutralizing antibodies of (b) (4) but after discussion with CDRH, the new target threshold proposed is (b) (4). This threshold will need to be reviewed as there is no clear correlation with efficacy and unknown safety correlation. Further discussion with CDRH is planned.

### Safety:

2. The preexisting neutralizing antibodies threshold remains under review. There does not currently appear to be any significant correlations for safety.

**Meeting Discussion:** The Applicant noted that the proposed clinically meaningful target NAb threshold remains at 1:700 based on the safety and efficacy results of the therapy in the CT-AMT-061-02 study, and asked if FDA reviewed the 120-day safety data that were submitted by the Applicant in July. FDA commented that the target threshold is being evaluated and review of the safety study data has not been completed.

## B. Clinical Pharmacology

1. In study #CT-MT-061- 01, the three subjects had anti-AAV5 neutralizing antibodies (NAbs) before dosing. However, the NAbs titer level was below 50 and all the three subjects achieved FIX activity >30%. In study #CT-MT-061-02, 38.9 % (21/54 subjects) had anti-AAV5 NAbs before dosing with a median titer of 1:57 (range: 1:9 to 1:3,212).
2. Following infusion of  $2 \times 10^{13}$  gc/kg of HEMGENIX the mean FIX activity at Month 12 was  $42 \pm 22$  % in subjects with NAbs titer  $\leq 1:100$  (n=46) and FIX activity was  $26 \pm 20$  % in subjects with NAbs titer  $>1:100$  (n=8). The mean FIX activity at Month 12 was  $41 \pm 22$  % in subjects with NAbs titer  $\leq 1:350$  (n=49) and  $22 \pm 17\%$  in subjects with NAbs titer  $>1:350$  (n=5). Please discuss the limited sample size, and a significant decrease in FIX activity with higher cutoff values such as 1:100 and 1:350 for NAbs.

### Meeting Discussion:

The applicant indicated that some subjects were using replacement FIX products with potential impact on FIX activity levels. As such, the Applicant employed literature derived half-life to calculate uncontaminated FIX activity. FDA raised concerns regarding the determination of threshold for NAbs based on a limited number of subjects and the use of literature derived half-life values for accounting for potential contamination of FIX activity. FDA

noted that the FIX activity calculation for higher NABs titer should also include the subject with the titer of 1:3212. FDA indicated that the best approach for determination of uncontaminated FIX activity is the use of individual subject PK parameters for FIX replacement therapy.

The applicant enquired if historical individual subject PK data would be helpful in the uncontaminated FIX activity determination. FDA responded that historical PK data on individual subjects are more accurate than literature data in understanding the Factor IX activity. FDA pointed out that FIX activity is a more informative quantitative measure, but the ABR data could be noisy for the determination of a NABs threshold. FDA also recommended employing the missing data imputation method to account for potentially contaminated FIX activity at specific time points. FDA reiterated that both FIX activity and ABR endpoints should be considered to inform the Nab threshold. FDA pointed out that the FIX activity level of interest is the one in the absence of help from replacement products and it is highly likely a plausible imputation exists even when no uncontaminated measurements were available at a given timepoint. For example, if a subject continued prophylaxis and therefore FIX activity were “contaminated”, it is reasonable to assume that the subject’s FIX activity at that timepoint would have been very low, e.g., 1-2%, if no replacement product were used, and the “missing” value should be imputed as such.

## 2. Additional Applicant Data

Applicant indicated that they do not expect to submit additional data for review.

## 3. Information Requests

- a. Clinical Information Request sent on September 14, 2022; Response due September 21, 2022
- b. Clinical Information Request sent on September 16, 2022; Response due September 22, 2022

**Meeting Discussion:** FDA noted the responses to the above Information Request was received by the Agency. Applicant was informed that response to DMPQ IR was pending, and a response was expected by October 7, 2022.

## 4. Postmarketing Requirements/Postmarketing Commitments

### **Chemistry, Manufacturing, and Controls:**

- a. Currently, lot release testing for (b) (4) is performed by calculating the ratio of (b) (4) which is an indirect method for the assessment of capsid content. The applicant committed to introduce

- (b) (4) as a more direct method for lot release testing as a prior approval supplement (PAS), if the BLA is approved.
- b. The applicant is developing and validating (b) (4) as a release test for (b) (4) on the Drug Product. The applicant committed to introduce (b) (4) for lot release testing as a PAS, if the BLA is approved.
  - c. The applicant committed to submit a completed long-term leachables study in the intended Drug Product (b) (4) container closures (at the intended storage condition) by end of March 2024, if the BLA is approved [response (dated July 28, 2022) to IR (dated July 14, 2022)].
  - d. The applicant committed to submit validation for (b) (4) of the Tier 2 analytical assays by December 2022, if the BLA is approved [response (dated Aug 4, 2022) to IR (dated July 14, 2022)].
  - e. The applicant committed to implement a (b) (4) potency assay (b) (4) as part of lot release testing by end of June 2023, if the BLA is approved [response (dated Aug 4, 2022) to IR (dated July 14, 2022)].
  - f. The applicant committed to revisit/revise the acceptance criteria (to further narrow) for lot release tests after manufacturing (b) (4) commercial lots, if the BLA is approved [response (dated Aug 26, 2022) to IR (dated Aug 16, 2022)].
  - g. The applicant committed to implement release testing of the sucrose batches for (b) (4) concentration and set an appropriate acceptance criterion [response (dated Sept 01, 2022) to IR (dated June 17, 2022)].

**Meeting Discussion:** The applicant confirmed to implement the release testing of sucrose batches for (b) (4) concentration and set an appropriate acceptance criterion. The applicant asked FDA if the implementation of (b) (4) testing can be reviewed in terms of GMP inspections. FDA agreed and asked the applicant to submit the incoming material testing information of the sucrose batches to the BLA. The applicant agreed.

**Meeting discussion regarding the stability data amendment received on September 13, 2022:** The applicant stated that they have addressed cumulative stability issue and have proposed a (b) (4) drug substance shelf life, followed by 24 months DP shelf-life based on cumulative stability data. The applicant asked for FDA's initial feedback on the acceptability of this approach. FDA stated that although the approach appears to be acceptable, the final determination will be made after the review of the data submitted. The applicant also proposed to submit an alternative approach for shelf-life based on cumulative stability for FDA review. FDA agreed to review the applicant's alternative proposal.



## 5. Major Labeling Issues

No major labeling issues have been identified at this time. The labeling review is ongoing

**Meeting Discussion:** No further discussion.

## 6. Review Plans

Label will be sent to Applicant for negotiations by October 21, 2022.

**Meeting Discussion:**

FDA reiterated that the initial draft PI and PMC's will be sent to the applicant by October 21, 2022

## 7. Applicant Questions

**Meeting Discussion:** There was no discussion from the applicant.

FDA reiterated the concern regarding the deficiencies in the companion diagnostic assay that was also communicated to the applicant during the mid-cycle communication. FDA stated that it is generally expected that the therapeutic product and its corresponding IVD companion diagnostic device get approved contemporaneously, and if the companion diagnostic is not approved, BLA for the product will not get approved. However, there may be exceptions to this requirement and FDA may decide to approve a therapeutic product even if an IVD companion diagnostic device is not yet approved or cleared when the therapeutic product is intended to treat a serious or life-threatening condition for which no satisfactory alternative treatment exists and the benefits from the use of the therapeutic product are so pronounced as to outweigh the risks from the lack of an approved or cleared IVD companion diagnostic device. FDA stated that there are established replacement FIX therapies available that may be considered "satisfactory alternate treatment". In that case the therapeutic product does not meet the criterion for a non-contemporaneous approval. FDA stated that final determination regarding the approval of the BLA is yet to be made but given the therapeutic product possibly not meeting the criteria for non-contemporaneous approval and considering the unresolved deficiencies in the neutralizing antibody titer assay, it is likely that FDA will issue a complete response letter for this BLA because of the absence of an FDA approved companion diagnostic device. The applicant acknowledged and stated that an alternate proposal is being explored that will be discussed separately in subsequent informal joint telecon meeting with CBER and CDRH.

## 8. Wrap-up and Action Items

### **Meeting Discussion:**

FDA stated applicant will receive the Late Cycle Meeting Summary within 30 days, and applicant provided their understanding of the meeting discussion.

This application has not yet been fully reviewed by the signatory authorities, Division Directors and Review Committee Chair and therefore, this meeting did not address the final regulatory decision for the application.