



Our STN: BL125772/0

LATE-CYCLE MEETING MATERIALS

September 20, 2022

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

Dear Ms. Chiddarwar:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for HEMGENIX (etranacogene dezaparvovec) Injection for intravenous infusion with dosage of 1E13 gc/mL.

Attached are our meeting materials, including our agenda, for the Late-Cycle Meeting (LCM) scheduled for September 30, 2022 from 10:00AM to 11:00AM

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.

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

ENCLOSURE:
Late-Cycle Meeting Materials

Late-Cycle Meeting Materials

Meeting Date and Time: September 30, 2022; 10:00 AM to 11:00 AM
Meeting Location: Teleconference (via Zoom)
Application Number: BLA125772/0
Product Name: etranacogene dezaparvovec
Indication: Treatment of adults with hemophilia B (congenital Factor IX deficiency) (b) (4) [REDACTED] to reduce the frequency of bleeding episodes (b) (4) [REDACTED]
Applicant Name: CSL Behring LLC

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authorities, division directors, and application Chair. Therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting. During the meeting, we may discuss additional information that could be submitted to address any identified issues. We may also discuss whether the submission of such information would be expected to trigger an extension of the PDUFA goal date if the Review Committee should decide, upon receipt of the information, to review it during the current review cycle.

Please note: If you submit any new information in response to the issues identified in this background package prior to this LCM, we may not be prepared to discuss that information at this meeting.

1. Substantive Review Issues to be discussed during the LCM**SUBSTANTIVE REVIEW ISSUES HAVE BEEN IDENTIFIED**

The following substantive review issues have been identified to date:

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.

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 genomic copies titer (b) (4) are yet to be submitted.
3. Please also refer to the LCM agenda item #7 Postmarketing Requirements/Postmarketing Commitments.

B. 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.

C. 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 2×10^{13} gc/kg of HEMGENIX the mean FIX activity at Month 12 was 42 ± 22 % in subjects with NABs titer $\leq 1:100$ (n=46) and FIX

activity was 26 ± 20 % in subjects with NAb's titer $>1:100$ ($n=8$). The mean FIX activity at Month 12 was 41 ± 22 % in subjects with NAb's titer $\leq 1:350$ ($n=49$) and 22 ± 17 % in subjects with NAb's 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 NAb's.

For inspections: Bioresearch Monitoring (BIMO) inspections are ongoing. A final recommendation is pending at this time. However, if we learn of any issues from the outstanding facility inspections, the agenda will be modified accordingly.

Amendment: We acknowledge your amendment #38(received September 13, 2022) regarding additional real-time stability data for the ongoing long-term stability studies for drug substance (DS) and drug product (DP) Process Validation (PV)/Process Performance Qualification (PPQ) batches. A review of this amendment is ongoing and a final decision on this issue is pending.

2. Advisory Committee Meeting

An Advisory Committee meeting is not planned.

3. Risk Management Actions (e.g., REMS)

A. RISK MANAGEMENT/REMS ACTIONS HAVE NOT BEEN IDENTIFIED

We have not identified any issues related to risk management. We do not believe that a risk management action (e.g., REMS) is needed at this time.

LCM AGENDA

1. Introductory Comments – 3 minutes (RPM)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 25 minutes

Each issue will be introduced by FDA and followed by a discussion.

- CMC
- Clinical
- Clinical Pharmacology

3. Additional Applicant Data – 10 minutes (Applicant)

4. Information Requests – 1 minute

- 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

5. Postmarketing Requirements/Postmarketing Commitments – 10 minutes

Chemistry, Manufacturing, and Controls:

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

6. Major labeling issues – 1 minute

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

7. Review Plans – 1 minute

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

8. Applicant Questions –5 minutes
9. Wrap-up and Action Items – 4 minutes