



Our STN: BL 125722

**LATE-CYCLE
MEETING MEMORANDUM**

PTC Therapeutics, Inc.
Attention: Agnes Cobbum, MS
100 Corporate Court
South Plainfield, NJ 07080

Dear Agnes Cobbum:

Attached is a copy of the memorandum summarizing your August 29, 2024 Late-Cycle Meeting with CBER. This memorandum constitutes the official record of the meeting. If your understanding of the meeting outcomes differs 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 Tolani Ishola at (240) 858-2819 or by e-mail at tolani.ishola@fda.hhs.gov.

Sincerely,

Beatrice Kallungal, MS
Director
Division of Review Management and Regulatory Review 1
Office of Review Management and Regulatory Review
Office of Therapeutic Products
Center for Biologics Evaluation and Research

Late-Cycle Meeting Summary

Meeting Date and Time: August 29, 2024 at 12:00 PM
Meeting Location: WO, Building 75 1535/1540

Application Number: BLA 125722
Product Name: Eladocagene exuparvovec
Proposed Indications: Treatment of patients with aromatic L-amino acid decarboxylase (AADC) deficiency
Applicant Name: PTC Therapeutics

Meeting Chair: Bo Liang, PhD
Meeting Recorder: Tolani Ishola, PharmD

FDA ATTENDEES

Afsah Amin, MD, MPH, CBER/OTP/OCE
Jacob Bitterman, PhD, CBER/OTP/OGT
Andrew Byrnes, PhD, CBER/OTP/OGT
Susan Butler, PhD, CBER/OTP/OGT
Cecilia Crowley, CBER/OTP/ORMRR
Benjamin Cyge, CBER/OCBQ/DCM/APLB
Aigbokhai Dirisu, MS, PMP, PSM 1, CMDA, CBER/OTP/ORMRR
CDR Donald Ertel, MS, MT(ASCP), CBER/OCBQ/DMPQ
Lola Fashoyin-Aje, MD, MPH, CBER/OTP/OCE
Denise Gavin, PhD, CBER/OTP/OGT
Avanti Golikeri, MD, CBER/OTP/OCE
Andrew Harmon, PhD, CBER/OTP/OGT
Elizabeth Hart, MD, CBER/OTP/OCE
Lin Huo, PhD, CBER/OBPV/DB
Tolani Ishola, PharmD, CBER/OTP/ORMRR
Beatrice Kallungal, MS, CBER/OTP/ORMRR
George Kastanis, MS, CBER/OCBQ/DBSQC
Alyssa Kitchel, PhD, CBER/OTP/OCTHT
Carolyn Laurencot, PhD, CBER/OTP/OCTHT
Bo Liang, PhD, CBER/OTP/OGT
Wei Liang, PhD, CBER/OTP
Heather Lombardi, PhD, CBER/OTP/OCTHT
Tiffany Lucas, PhD, CBER/OTP/OGT
Mondona McCann, PhD, CBER/OTP/OPT
Tyree Newman, MDiv, CBER/OTP/ORMRR
Steven Oh, PhD, CBER/OTP/OCTHT
Kanaeko Ravenell, MS, SBB (ASCP), CBER/OCBQ/DIS/BMB
Laura Ricles, PhD, CBER/OTP/OCTHT
Anurag Sharma, PhD, CBER/OTP/OGT
Patroula Smpokou, MD, CBER/OTP/OCE

Lisa Stockbridge, PhD, CBER/OCBQ/DCM/APLB
Brian Stultz, MS, CBER/OTP/OGT
Nancy Waites, MS, CBER/OCBQ/DMPQ
Shaokui Wei, MD, MPH, CBER/OBPV/DPV
Kerry Welsh, CBER/OBPV/DPV
Sojeong Yi, PhD, CBER/OTP/OCE
Jingyi Zhai, PhD, CBER/OBPV/DB

APPLICANT ATTENDEES

Matthew Klein, MD, MS, FACs
Murad Husain, MS
Lee Golden, MD
Amol Mungikar, PhD
Jennifer Stone, MBA
Samantha Gao-Sheridan, PhD
Terri Richmond, PhD
Rez Rahman, BS, PMP
Agnes Cobbum, MS
Cecilia Della Valle, PhD
Vinay Penematsa, MD
(b) (6)

BACKGROUND

BLA 125722/0 was submitted on March 15, 2024, for Eladocagene exuparvovec

Proposed indication: Treatment of patients with aromatic L-amino acid decarboxylase (AADC) deficiency

PDUFA goal date: November 13, 2024

In preparation for this meeting, FDA issued the Late-Cycle Meeting Materials on August 19, 2024.

DISCUSSION

1. Discussion of Substantive Review Issues

The following substantive review issues have been identified to date:

Chemistry, Manufacturing and Controls

(b) (4) specifications: In the pivotal clinical trial, all subjects were dosed with drug product (DP) at a concentration of 5.6×10^{11} vg/mL, which is the labeled nominal titer for DP. However, your current DP manufacturing process targets a concentration of (b) (4), which is (b) (4) than the nominal titer in the product labeling. You have proposed an acceptance range of (b) (4) to (b) (4) for (b) (4). We are concerned that patients who are administered a lot with a concentration that is at the (b) (4) end of this acceptance range will be exposed to a much (b) (4) dose than was used in clinical studies with Process C DP. Please set an upper limit for (b) (4) to allow for assay and process variability without unduly exceeding the intended dose.

Meeting Discussion

FDA indicated that this concern has been addressed in Applicant's recent agreement to revise the DP lot release acceptance criterion for (b) (4). There was no additional discussion.

(b) (4) Assay Range: The (b) (4) assay has been validated over a range of (b) (4). The reportable value is based on the (b) (4) and must not exceed (b) (4), but it is not clear whether individual assay run results over (b) (4) (and thus outside of the range) will be rejected. We are also concerned that the combination of assay variability and narrow assay range have the potential to result in a high percentage of test sample results that are out of range.

Meeting Discussion

FDA acknowledged the clarifications in the recent IR response, and emphasized the concerns with accepting individual assay run results outside of the validated range because it is unknown whether the assay has adequate accuracy or precision when measuring (b) (4). FDA recommended that the Applicant perform an additional validation study to determine whether the assay has adequate performance at higher levels of (b) (4). FDA also recommended that the Applicant use a separate material from the reference standard for the assay control, and expressed concern that the acceptance range for the assay control exceeds the validated range of the assay. The acceptance range could be addressed by the additional validation study, or a narrowing of the acceptance range. PTC stated that they would work on assessing our recommendations for feasibility. They asked if these studies could be performed as a PMC, and FDA agreed that a PMC would be appropriate.

Clinical

Your application seeks approval based on cerebrospinal fluid (CSF) homovanillic acid (HVA) as a biomarker reasonably likely to predict clinical benefit to support accelerated approval. Uncertainty remains regarding the relationship between CSF HVA and clinical outcomes. Instead, the Agency is currently considering the additional motor data submitted to the BLA as the basis for an accelerated approval decision

Meeting Discussion

The Applicant expressed willingness to provide any additional information needed by FDA to make the regulatory decision. FDA will communicate any additional information needed through information requests.

2. Discussion of Minor Review Issues

Device

We reiterate that the therapeutic product (i.e., eladocogene exuparvovec) and its corresponding cross-labeled administration device (i.e., the SmartFlow cannula) need to be approved contemporaneously by the FDA for the use indicated in the therapeutic product labeling. Hence, we strongly urge you to continue to work closely with your administration device partner to align their De Novo submission with your submission timelines to allow for concurrent regulatory decisions for the BLA and the De Novo.

Meeting Discussion

No discussion of this topic

3. Information Requests

There are no pending Information Requests for this BLA.

Meeting Discussion

No discussion of this topic

4. Risk Management Actions (e.g., REMS, the ability of adverse event reporting and CBER's Sentinel Program to provide sufficient information about product risk)

Currently, a REMS is not anticipated.

Meeting Discussion

No discussion of this topic

5. Postmarketing Requirements/Postmarketing Commitments

There is no anticipation of Postmarketing Requirements/Postmarketing Commitments (PMRs/PMCs) at this time.

Meeting Discussion:

No discussion of this topic.

Post-Meeting Comment: Information about PMRs/PMCs will be communicated to the Applicant by October 2, 2024.

6. Major Labeling Issues

Labeling review is ongoing. There are no major labeling issues to discuss at this time.

Meeting Discussion:

No discussion of this topic

7. Review Plans

Review of this BLA is ongoing. We will continue sending Information Requests as necessary to get clarification on any submitted information.

PDUFA Action Due Date is November 13, 2024

8. Applicant Questions

No discussion

9. Wrap-up and Action Items

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.