



Our STN: BLA 125722

**MID-CYCLE COMMUNICATION  
SUMMARY**  
August 6, 2024

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

Dear Agnes Cobbum:

Attached is a copy of the summary of your July 8, 2024 Mid-Cycle Communication Teleconference with CBER. This memorandum constitutes the official record of the Teleconference. If your understanding of the Teleconference outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER as soon as possible.

Please include a reference to BLA 125722 in your 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](mailto: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

## Mid-Cycle Communication Teleconference Summary

**Application Type and Number:** BLA 125722

**Product Name:** eladocogene exuparvovec

**Proposed Indication for Use:** Treatment of patients with aromatic L-amino acid decarboxylase (AADC) deficiency

**Applicant:** PTC Therapeutics, Inc.

**Meeting Date & Time:** July 8, 2024 12:00 PM -1:00 PM EST

**Committee Chair:** Bo Liang, PhD

**RPM:** Tolani Ishola, PharmD

### Attendees:

#### FDA Attendees:

Meghna Alimchandani, MD, CBER/OBPV/DPV

Rachael Anatol, PhD, CBER/OTP

Jacob Bitterman, PhD, CBER/OTP/OGT

Susan Butler, PhD, CBER/OTP/OGT

Andrew Byrnes, PhD, CBER/OTP/OGT

Shelby Elenburg, MD, CBER/OTP/OCE

CDR Donald Ertel, MS, MT(ASCP), CBER/OCBQ/DMPQ

Feorillo Galivo, MD, PhD, CBER/OTP/OPT

Denise Gavin, PhD, CBER/OTP/OGT

Avanti Golikeri, MD, CBER/OTP/OCE

Andrew Harmon, PhD, CBER/OTP/OGT

Elizabeth Hart, MD, CBER/OTP/OCE

Beatrice Kallungal, MS, CBER/OTP/ORMRR

James Kenney, DSc, CBER/OCBQ/DBSQC

Alyssa Kitchel, PhD, CBER/OTP/OCTHT

Johnny Lam, PhD, CBER/OTP/OCTHT

Bo Liang, PhD, CBER/OTP/OGT

Wei Liang, PhD, CBER/OTP

Heather Lombardi, PhD, CBER/OTP/OCTHT

Mondona McCann, PhD, CBER/OTP/OPT

Tyree Newman, MDiv, CBER/OTP/ORMRR

Bao-Ngoc Nguyen, PhD, CBER/OTP/OCTHT

Steven Oh, PhD, CBER/OTP/OCTHT

Lori Peters, CBER/OCBQ/DMPQ

Anurag Sharma, PhD, CBER/OTP/OGT

Lisa Stockbridge, PhD, CBER/OCBQ/DCM/APLB

Hsiaoling Wang, CBER/OCBQ/DBSQC

Kerry Welsh, CBER/OBPV/DPV

Nadia Whitt, MS, CBER/OTP/ORMRR

Lihan Yan, PhD, CBER/OBPV/DB

Sojeong Yi, CBER/OTP/OCE

Jingyi Zhai, PhD, CBER/OBPV/DB

**Applicant Attendees:**

Matthew Klein, MD, MS, FACS

Murad Husain, RPh, MS

Amol Mungikar, PhD

Samantha Gao Sheridan, PhD

(b) (6)

Jennifer Stone

Agnes Cobbum

Rezwanur Rehman

**Discussion Summary:**

1. Any significant issues/major deficiencies identified by the Review Committee to date.

**Chemistry, Manufacturing and Controls (CMC)**

- a) You set the nominal titer (labeled concentration) for drug product as  $5.6 \times 10^{11}$  vg/mL; however, in your DP manufacturing process, (b) (4)

We are concerned that your manufacturing process is designed to target a titer (b) (4) than the nominal titer in your product labeling. In response to our June 12, 2024 information request (IR) #7 regarding this discrepancy, you stated that you target a (b) (4) product concentration to account for the variability of the (b) (4) assay and the manufacturing process. We are currently assessing your justification for this approach and will discuss how to resolve this issue with you in a future communication. Because of the (b) (4) in your DP and the asymmetrical DP release acceptance criterion of (b) (4) of the labeled nominal titer, we are concerned that patients who receive this product may be exposed to (b) (4) doses of DP than in clinical studies with Process C DP.

- b) You did not agree with our request to include a control for the activity of the (b) (4) assay in our June 6, 2024 IR #6 and June 25, 2024 IR #10. Absence of this control may permit falsely (b) (4) results that could lead to errors in batch dose and under-dosing of patients. Your proposed approach of documenting the step of (b) (4) assay is inadequate to ensure that the (b) (4) You must include a control for (b) (4) as part of the assay suitability criteria.
- c) In your response to our June 12, 2024 IR #7 regarding your plan to generate, qualify, and implement a (b) (4) you indicate that you plan to

manufacture future commercial product using the (b) (4). You committed to submit data on the (b) (4) by August 2024. These data are necessary for us to determine the acceptability of your plans to manufacture future commercial product using a (b) (4), and we ask that you submit the data as soon as they are available. We will be unable to approve your plans for the (b) (4) unless we are able to review all of the relevant data and resolve any remaining concerns with your plans.

**Meeting Discussion:**

- a) The Applicant clarified that they obtained the (b) (4) during manufacturing by doing (b) (4) of the assay. FDA expressed concern that the coefficient of variation is around (b) (4), which is not very precise for a (b) (4) assay for a commercial AAV product. The Applicant agreed to provide the reassessment of precision that they have so far. The Applicant confirmed that they have seen consistent (b) (4) data from stability studies. FDA expressed concern over the upper limit of DP acceptance criteria for the (b) (4) that is (b) (4) than the labeled nominal titer. The Applicant replied that the limits were set based on clinical exposure and manufacturing results. The Applicant confirmed that they will reassess the (b) (4) limit. FDA requested information on the source of variability of the manufacturing process. The Applicant replied that there is nothing on the process side that contributed to the variability, but they improved (b) (4) of the process by (b) (4) assays. The Applicant confirmed that the (b) (4). The Applicant will provide this additional information as an amendment to the BLA. FDA confirmed that they will continue the discussion on this topic throughout the review of the BLA.
- b) The Applicant confirmed agreement on including a control for (b) (4) as part of the assay suitability criteria. The Applicant confirmed that they are working on a plan and will make the change in the SOP and the method as soon as possible.
- c) The Applicant is working on a plan to implement a (b) (4) and will submit the information by late August or earlier if available.

**Clinical**

Your application seeks accelerated approval based on change from baseline in CSF HVA at Week 8 in Study AADC-002. Our review is ongoing, and we have requested additional information in Information Request #12 (Clinical/Clinical Pharmacology Request #2) to assess:

- i. effects of your product versus other factors (e.g., assay variability) on the observed changes in CSF HVA levels, taking into consideration the findings of supportive studies (AADC-010 and AADC-011) included in the BLA.
- ii. correlation between CSF HVA with clinical outcomes, taking into account data from the supportive studies (AADC-010 and AADC-011).

- iii. effects of your product in children with the less severe form of AADC deficiency.
- iv. generalizability of the clinical data to the United States population with AADC deficiency.

**Meeting Discussion:**

The Applicant stated that they will address these issues in their response to IR#12. The Applicant also discussed that their IR response will include information to support the generalizability of the clinical data to all patients with AADC deficiency, independent of both disease severity and ethnicity.

**2. Information regarding major safety concerns.**

We note that there have been five children who died due to cardiorespiratory failure after treatment. Our assessment of these deaths is ongoing.

**Meeting Discussion:**

The Applicant stated that they will address this concern in their response to IR#12. The Applicant discussed that their IR response will also include their evaluation of how their product changes the natural history of the disease and how this may impact disease-related risks such as aspiration.

**3. Preliminary Review Committee thinking regarding a.) risk management, b) the potential need for any post-marketing requirements (PMRs), and/or safety-related PMCs, and c.) the ability of adverse event reporting and CBER's Sentinel Program to provide sufficient information about product risk.**

Risk Evaluation and Mitigation Strategy (REMS) is not anticipated at this time. PMRs or PMCs remain undetermined at this time.

**Proprietary Name Review**

The proposed name, UPSTAZA, may lead to medication errors due to the potential phonetic and orthographic confusion with highly similar product names. Additionally, the proposed name may overstate the efficacy of eladocagene exuparvovec.

**Meeting Discussion:**

The Applicant requested further clarification on why the proposed name, UPSTAZA is unacceptable. FDA responded that the term standing up is misleading and that there are highly similar products that are in the pipeline with potential approval prior to the Applicant's product that could lead to medical errors. The Applicant confirmed that they will submit an amendment with a different name for proprietary name review.

**4. Any information requests sent, and responses not received.**

- IR #10 (CMC IR #4) sent on June 25, 2024 is pending a response by July 9, 2024.
- IR #13 (CMC IR #5) sent on July 2, 2024 is pending a response by July 12, 2024.
- IR#11 (Pharmacovigilance IR #1) sent June 25, 2024 is pending response by July 10, 2024
- IR #12 (Clinical/Clinical Pharmacology IR #2) sent on July 1, 2024 is pending a response by July 10, 2024.

**Meeting Discussion:**

There was no discussion of this agenda topic during the meeting.

5. Any new information requests to be communicated.

As review continues, new information requests will be conveyed as warranted.

**Meeting Discussion:**

There was no discussion of this agenda topic during the meeting.

6. Proposed date for the Late-Cycle Meeting and the Late-Cycle Meeting Materials:

- The Late Cycle Meeting between PTC Therapeutics and FDA is currently scheduled for Thursday August 29, 2024 at 12:00 PM EST.
- The Late Cycle Meeting Materials will be sent by August 19, 2024.

**Meeting Discussion:**

There was no discussion of this agenda topic during the meeting.

7. Updates regarding plans for the AC meeting.

There are no plans for an AC meeting for this BLA at this time.

**Meeting Discussion:**

There was no discussion of this agenda topic during the meeting.

8. Other projected milestone dates for the remainder of the review cycle, including changes to previously communicated dates.

Tentative PMR Target Date: October 2, 2024

Tentative Labeling Target Date: October 14, 2024

Tentative PMC Target Date: October 14, 2024

**Meeting Discussion:**

There was no discussion of this agenda topic during the meeting.

9. Discuss status of inspections (GMP) including issues identified that could prevent approval. Ensure notification of intent to inspect manufacturing facilities has been issued.

Inspection for (b) (4) DP facility (b) (4) located in (b) (4) ,  
(b) (4) is scheduled for (b) (4)

**Meeting Discussion:**

There was no discussion of this agenda topic during the meeting.