

CBER DMPQ CMC/Facility BLA Review Memorandum

BLA STN 125722/0

Eladocagene exuparvovec

Prajakta Varadkar, Ph. D., Biological Reviewer, OCBQ/DMPQ/MRB3

1. **BLA#:** STN 125722/0

2. **APPLICANT NAME AND LICENSE NUMBER**

PTC Therapeutics, Inc., License #: 2168

3. **PRODUCT NAME/PRODUCT TYPE**

USAN: Eladocagene exuparvovec

Proprietary name: TBD

Other names: N/A

4. **GENERAL DESCRIPTION OF THE FINAL PRODUCT**

- a. Pharmacological category: Eladocagene exuparvovec is a recombinant non-replicating adeno-associated virus serotype 2 (AAV2) vector comprising a human dopa decarboxylase (DDC, also referred to as AADC) cDNA transcript.
- b. Dosage form: suspension
- c. Strength/potency: 5.6×10^{11} vg/mL
- d. Route of administration: Intraputaminial Infusion
- e. Indications: Treatment of patients with aromatic L-amino acid decarboxylase (AADC) deficiency.

5. **MAJOR MILESTONES**

Filing Meeting:	April 30, 2024
Mid-Cycle Meeting:	June 24, 2024
Pre-License Inspections (PLIs):	(b) (4)
Late-Cycle Meeting:	August 29, 2024
Action Due Date:	November 13, 2024

Note: STN 125722/0 received Priority Review designation

6. **DMPQ CMC/FACILITY REVIEW TEAM**

Reviewer/Affiliation	Section/Subject Matter
Prajakta Varadkar, Biological Reviewer, OCBQ/DMPQ/MRB3	Drug Substance, Drug Product, Facilities and CMC Reviewer, Lead Inspector (b) (4)
Kinjal Patel, Biological Reviewer, OCBQ/DMPQ/MRB3	Inspector (b) (4)

7. **SUBMISSION(S) REVIEWED**

BLA 125722/0 DMPQ Review Memo (Eladocogene exuparvovec)

Date Received	Submission(s)	Comments/Status
March 15, 2024	Amendment STN 125722/0	Original Submission
April 24, 2024	Amendment STN 125722/0.2 Response to DMPQ IR #1	IR response to provide inspectional information in preparation for PLI and information on the contract testing and primary packaging and labeling facilities.
May 20, 2024	Amendment STN 125722/0.5	Change of address.
May 31, 2024	Amendment STN 125722/0.7 Response to CMC IR	IR response to provide an information on the location of storage of (b) (4)
June 10, 2024	Amendment STN 125722/0.8 Response to DMPQ IR #2	IR response to provide an information on (b) (4) and cross contamination control.
June 17, 2024	Amendment STN 125722/0.10 Response to DMPQ IR #3	IR response to provide inspectional information in preparation for PLI.
September 23, 2024	Amendment STN 125722/0.40	(b) (4) facility's responses to the FDA 483 observations found during PLI
September 23, 2024	Amendment STN 125722/0.41	IR response to (b) (4) Bioburden specification.
September 26, 2024	Amendment STN 125722/0.44 Response to DMPQ IR #4	IR response to provide information on the contract testing facilities.
October 18, 2024	Amendment STN 125722/0.56 Response to DMPQ IR #5	IR response to provide the information on an addition of (b) (4) studies.
October 28, 2024	Amendment STN 125722/0.59 Response to DMPQ IR #6	IR response to provide the information on Sterile filter validation studies.

8. REFERENCED REGULATORY SUBMISSIONS (e.g., IND BLA, 510K, Master File, etc.)

Submission Type	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
BB-MF (b) (4)	ClearPoint Neuro, Inc.	SmartFlow Cannula	Yes	No review is required, Cross-Labeled Delivery Device (ClearPoint SmartFlow Cannula) under CDRH purview.
BB-DMF (b) (4)	(b) (4)	(b) (4) Type (b) (4) borosilicate vials	Yes	No review is required, information pertinent to container closure is provided in the BLA
BB-DMF (b) (4)	(b) (4)	Elastomeric Formulations, Coatings, Films and Vial stopper	Yes	No review is required, information pertinent to container closure is provided in the BLA
BB-DMF (b) (4)	(b) (4)	(b) (4) RU Vials	Yes	No review is required, information pertinent to container closure is provided in the BLA
MF (b) (4)	(b) (4)	(b) (4)	Yes	No DMPQ review required

9. REVIEWER SUMMARY AND RECOMMENDATION


A. EXECUTIVE SUMMARY

PTC Therapeutics Inc, (PTC) is requesting the approval for Eladocagene exuparvovec, a recombinant non-replicating adeno-associated virus serotype 2(AAV2) vector comprising a human dopa decarboxylase (*DDC*, also referred to as *AADC*) cDNA transcript, which encodes human AADC, under the control of the cytomegalovirus immediate-early promoter (b) (4)

Eladocagene exuparvovec drug product (DP) is a sterile, clear to slightly opaque, colorless to faint white solution, packaged in a single-dose, 2-mL Type (b) (4) borosilicate glass vial; stoppered with a siliconized, 13-mm chlorobutyl stopper with (b) (4); and sealed with a 13-mm aluminum/plastic (b) (4) cap. Each vial of drug

product contains an extractable volume of 0.5 mL with a total of 2.8×10^{11} vector genome copies (vg), ensuring delivery of a single dose of 1.8×10^{11} vg in a total dose volume of 0.320 mL. The DP is comprised of (b) (4) excipients including potassium chloride, potassium dihydrogen phosphate, sodium chloride, disodium hydrogen phosphate, and poloxamer 188 in Water for Injection, (b) (4) Eladocagene exuparvovec is indicated for the treatment of patients with AADC deficiency. Eladocagene exuparvovec is administered by bilateral intraputamenal infusion in one surgical session at two sites per putamen.


(b) (4)



The manufacturing of Eladocagene exuparvovec (b) (4) DP is performed at (b) (4). LI of the (b) (4) was performed on (b) (4). At the conclusion of the (b) (4) PLI, a Form FDA 483 was issued on (b) (4), with six inspectional observations, which the firm responded to on August 27, 2024. A review of (b) (4) responses is documented in a separate 483 response review memo, with all inspectional 483 observations being adequately resolved resulting in a Voluntary Action Indicated (VAI) inspection classification. The CMC and facility information provided in the submission appears acceptable.

The following nine facilities are contract testing laboratories performing release and/or stability testing, labeling, and packaging of Eladocagene exuparvovec (b) (4) DP:

(b) (4)



All nine facilities have either an acceptable FDA-inspection history and/or an acceptable recent inspection performed by a foreign regulatory authority with whom the Agency has a cooperative arrangement covered under the Mutual Recognition Agreement (MRA). For these reasons, the decision was made to waive PLIs for all above nine testing, labeling, and packaging facilities. Refer to a separate inspection waiver memo for details.

B. RECOMMENDATION

I. APPROVAL

Based on the information provided, approval is recommended.

II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Prajakta Varadkar, Biological Reviewer, OCBQ/DMPQ/MRB3	Concur	
CDR Donald Ertel, Branch Chief OCBQ/DMPQ/MRB3	Concur	
Carolyn Renshaw, Division Director OCBQ/DMPQ	Concur	

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Module 3

3.2.S DRUG SUBSTANCE (b) (4)

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

(b) (4)

[REDACTED]

(b) (4)

6 pages have been determined to be not releasable: (b)(4)

(b) (4)

3.2.P DRUG PRODUCT (b) (4)

3.2.P.1 Description and Composition of the Drug Product

Eladocogene exuparvec DP is a sterile, clear to slightly opaque, colorless to faint-white solution, packaged in a single-dose, 2-mL Type (b) (4) borosilicate glass vial; stoppered with a siliconized, 13-mm chlorobutyl stopper with (b) (4); and sealed with a 13-mm aluminum/plastic (b) (4) cap.

Each vial of DP contains an extractable volume of 0.5 mL with a total of 2.8×10^{11} vector genome copies (vg), ensuring delivery of a single dose of 1.8×10^{11} vg in a total dose volume of 0.320 mL. The DP is comprised of (b) (4) excipients including potassium chloride, potassium dihydrogen phosphate, sodium chloride, disodium hydrogen phosphate, and poloxamer 188 in Water for Injection, (b) (4). Each vial of DP is for a single dose to be administered per treatment, to be used for a single treatment only.

3.2.P.2.4 Container Closure System

The container closure system (CCS) for Eladocogene exuparvec DP is a clear, colorless, 2 mL, Type (b) (4) borosilicate glass vial with a (b) (4) 13-mm, grey chlorobutyl stopper with (b) (4) and a 13-mm aluminum/plastic (b) (4) cap. All CCS components are supplied ready to use having been sterilized using validated (b) (4) sterilization process. The sterilization of the primary container closure system (CCS) components (vials and stoppers) is performed by (b) (4)

The sterilization of the CCS components is conducted and validated in accordance with (b) (4). The firm provided (b) (4) sterilization and depyrogenation validation report for container closure components. The sterilization of the vials is performed using a validated (b) (4) sterilization (b) (4). All results met the acceptance criteria of the validation using the (b) (4) routine operating conditions.

Table below give the acceptance criteria for vial sterilization (b) (4) .

(b) (4)

(b) (4)

(b) (4)

(b) (4)

The tables below provide final acceptance criteria for vials, stoppers, and caps:

Vial Specification

Test	Acceptance Criteria
Glass containers (b) (4)	Conforms to Type (b) (4) requirements
Identity (visual)	Part number/supplier match
Visual inspection (visual)	No visible or visual defects
Sterility (b) (4)	No growth
(b) (4)	

Abbreviations: (b) (4)

Stopper Specification

Test	Acceptance Criteria
Rubber closures (b) (4)	Conforms to Type (b) (4) requirements
(b) (4)	(b) (4)

Identity (visual)	Part number/supplier match
Conformance to fit (physical)	Fits on vial
(b) (4)	
Visual inspection (visual)	No visible or visual defects
(b) (4)	
Sterility (b) (4)	No growth
(b) (4)	

Abbreviations: (b) (4)

Cap Specification

Test	Method	Acceptance Criteria
Identity	Visual	Part number/supplier match
Conformance to fit	Physical	Fits on vial
Visual inspection	Visual	No visible or visual defects
Sterility	(b) (4)	No growth

The container closure integrity (CCIT) is tested using the (b) (4) test and is performed at (b) (4) facility. The (b) (4) method uses a (b) (4)

All vials met the acceptance criteria.

Reviewer's Assessment

The validation of the CCIT (b) (4) test was provided. (b) (4)

(b) (4) were evaluated as part of the validation. The information provided appears acceptable.

3.2.P.2.5 Microbiological Attributes

Eladocogene exuparvec DP is manufactured under aseptic conditions and stored in pre-sterilized container closure system components as DP cannot be terminally sterilized. The control of microbiological attributes for Eladocogene exuparvec DP occurs at different stages of manufacture and release. These include controls during the manufacturing process, at the manufacturing facility, routine release and stability testing, and the container closure system.

During manufacturing of Eladocogene exuparvec DP, (b) (4)

Routine sterility, endotoxin, and container closure integrity testing are in place for Eladocogene exuparvec DP to ensure microbiological safety. Sterility and endotoxin testing is performed at release for each lot of DP. All lots of DP were tested for endotoxin and sterility at release.

The container closure system for Eladocogene exuparvec DP is a clear, colorless, 2-mL, Type (b) (4) borosilicate glass vial with a siliconized (b) (4), 13-mm, grey chlorobutyl stopper with (b) (4) and a 13-mm aluminum/plastic (b) (4) cap. The container closure components used to fill the DP are supplied ready-to-use by the qualified vendor. They are supplied pre-sterilized using validated (b) (4) sterilization processes. Additionally, the container closure components are tested for sterility and endotoxin at the sterilization site. Container closure integrity is further assured by (b) (4) testing of (b) (4) as part of the stability program.

Reviewer's Assessment

The information provided appears acceptable.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

The Eladocogene exuparvovec DP manufacturers are summarized in the table below

Manufacturers of Eladocogene Exuparvovec Drug Product

Manufacturer	FEI and DUNS	Responsibilities
(b) (4)	(4)	Manufacturing of drug product
		Release testing, stability testing and storage of drug product
		Release testing of drug product
		Stability testing of drug product
		Secondary packaging, labeling and storage of drug product
		Storage of drug product

Abbreviations: DUNS, data universal numbering system; FEI, FDA establishment identifier


3.2.P.3.3 Description of Manufacturing Process

The Eladocogene exuparvovec DP manufacturing process consists of (b) (4) sterile filtration, and aseptic fill into vials. Eladocogene exuparvovec DP is manufactured at (b) (4) facility in the same suite as (b) (4) manufacturing for (b) (4) through sterile filtration. (b) (4) vial fill of the DP.

Eladocogene exuparvovec DP manufacturing steps are listed below.

(b) (4)

(b) (4)




^{(b) (4)} Visual Inspection

DP appearance is evaluated by visual inspection (VI) (b) (4)



P vials meeting the acceptance criteria are reported as: translucent cell suspension, practically free of visible foreign particles. VI operators are qualified by (b) (4)



^{(b) (4)} Freeze

The vials are sampled for testing and frozen at ≤ -65 °C. (b) (4)



Overall Reviewer's Assessment of Section 3.2.P.3.3:


- ❑ The manufacturing steps along with any CPP and IPC were provided. The information provided appears acceptable.

3.2.P.3.4 Controls of Critical Steps and Intermediates




Please refer to the section below, and steps that are not under DMPQ purview are deferred to OTP.

3.2.P.3.5 Process Validation and/or Evaluation

(b) (4)



(b) (4)



9 pages have been determined to be not releasable: (b)(4)

(b) (4)



3.2.P.5 Control of Drug Product

3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)

Sterility and endotoxin testing are part of the product safety specifications. Bacterial endotoxin (EU/mL) and sterility are measured as part of the final DP release specifications. Bacterial endotoxin is measured using the (b) (4) Sterility testing is performed with (b) (4) methods according to (b) (4) The sterility acceptance criterion is specified as “no growth”.

Reviewer’s Assessment

These are (b) (4) tests. We defer review of the sterility, and endotoxin test methods to DBSQC.

3.2.P.5.4 Batch Analyses

To date, there have been no sterility or endotoxin release testing failures for any of the PPQ batches manufactured at (b) (4) facility.

Overall Reviewer’s Assessment of Sections 3.2.P.5.4

- ☐ The information provided appears acceptable.

3.2.P.7 Container Closure System

Please refer to section 3.2.P.2.4 of this review memo.

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data

The drug product (DP) lots were placed on stability at the various storage conditions to demonstrate the physicochemical and biological stability to support the long-term

storage condition and commercial shelf-life. The conditions studied includes long-term ($\leq -65^{\circ}\text{C}$), (b) (4). Additionally, (b) (4) stability studies were conducted.

Stability results were provided for DP on (b) (4) DP lots manufactured at (b) (4) facility (including (b) (4) supportive (b) (4) PPQ (b) (4)). Long-term stability studies were performed on all the lots whereas (b) (4) stability studies were on performed (b) (4) supporting (b) (4) PPQ (b) (4) and is ongoing. CCIT (b) (4) was performed in lieu of sterility. The data suggested that the all lots passed CCIT test under long-term ($\leq -65^{\circ}\text{C}$) for following timepoint intervals (0, 12, 24, 36, 48, (b) (4) months).

Overall Reviewer's Assessment of Section 3.2.P.8.1:

- The CCIT data in lieu of sterility testing appears acceptable from prevention of microbial contamination perspectives. The review of all the other stability test results is deferred to OTP.

3.2.A APPENDICES

The facilities table listing all facilities involved in the manufacture, packaging, testing, and storage is provided in the facilities table below:

Facilities Involved in Eladocogene exuparvovec Manufacture.

Manufacturing/ Testing activities	Inspection? Waiver? or Not Required?	Compliance Check Required for Approval?	RMS-BLA Entry Required?	Comments
(b) (4) FEI: (b) (4) -Manufacturing of drug substance -Storage of (b) (4) -Manufacturing of drug product	Inspection	Yes	Yes	No prior FDA inspection history PLI: (b) (4)

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Manufacturing/ Testing activities	Inspection? Waiver? or Not Required?	Compliance Check Required for Approval?	RMS-BLA Entry Required?	Comments
<p>(b) (4)</p> <p>FEI: (b) (4)</p> <ul style="list-style-type: none"> - Release and stability testing of (b) (4) - Storage of (b) (4) - Release and stability testing of drug product - Storage of drug product - Non-product contact parts (b) (4) 	Waiver	Yes	Yes	Team Biologics (ORA) inspection (b) (4) : VAI
<p>(b) (4)</p> <p>FEI: (b) (4)</p> <ul style="list-style-type: none"> - Release testing of (b) (4) 	Not required	No	Yes	
<p>(b) (4)</p> <p>FEI: (b) (4)</p> <ul style="list-style-type: none"> - Release testing of (b) (4) 	Not required	No	Yes	

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Manufacturing/ Testing activities	Inspection? Waiver? or Not Required?	Compliance Check Required for Approval?	RMS-BLA Entry Required?	Comments
<p>(b) (4)</p> <p>FEI: (b) (4)</p> <p>- Release testing of (b) (4)</p>	Not required	No	Yes	
<p>(b) (4)</p> <p>FEI: (b) (4)</p> <p>- Release testing of (b) (4)</p>	Not required	No	Yes	
<p>(b) (4)</p> <p>FEI: (b) (4)</p> <p>- Release testing of drug product (b) (4), Endotoxin and Sterility)</p>	Waiver	Yes	Yes	<p>Certificate of Compliance (b) (3) (A)</p> <p>ORA inspection (b) (3) (A): VAI (b) (3) (A)</p>
<p>(b) (4)</p> <p>FEI: (b) (4)</p> <p>-Stability testing of drug product</p>	Not required	No	No	

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Manufacturing/ Testing activities	Inspection? Waiver? or Not Required?	Compliance Check Required for Approval?	RMS-BLA Entry Required?	Comments
<p>(b) (4)</p> <p>FEI: (b) (4)</p> <p>- Drug primary labeling of DP vials</p> <p>-Drug secondary packaging and labeling</p> <p>- Storage of drug product</p>	Waiver	Yes	Yes	<p>ORA inspection</p> <p>(b) (4) : NAI</p> <p>(b) (4)</p>
<p>(b) (4)</p> <p>FEI: (b) (4)</p> <p>-Storage of drug product</p>	Not required	No	Yes	


Note: All manufacturing and testing facilities are contracted by PTC Therapeutics, Inc.

(b) (4)


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16 pages have been determined to be not releasable: (b)(4)

(b) (4)



(b) (4)



3.2.R Regional Information (USA)

❑ **Executed Batch Records**

The review of executed batch records is deferred to OTP.

❑ **Combination Products**

Eladocagene exuparvovec is a combination product which will be delivered using delivery device (ClearPoint SmartFlow Cannula). The SmartFlow Cannula will not be copackaged with eladocagene exuparvovec but will be cross labeled with Eladocagene exuparvovec DP. It was agreed upon CDRH will be reviewing the de novo 510(k) submission for the SmartFlow Cannula from ClearPoint.

❑ **Comparability Protocols**

No comparability protocols under DMPQ purview were submitted under STN 125722/0.