

Device-Product Review Memorandum

Center for Biologics Evaluation and Research
Office of Therapeutic Products
Office of Cellular Therapies and Human Tissue CMC



U.S. FOOD & DRUG
ADMINISTRATION

BLA 125722.0

Original Submission

Title: Eladocagene Exuparvovec for the Treatment of Aromatic L-amino Acid Decarboxylase (AADC) Deficiency

Product Description: Eladocagene exuparvovec; AAV-based gene therapy
Dosage Form: Single dose vial; 5.6×10^{11} vg/mL

Proposed Use: To treat patients with aromatic L-amino acid decarboxylase (AADC) deficiency

Route of Administration and Delivery Device: intraputaminal with the ClearPoint Neuro Smartflow MR Compatible Ventricle Cannula

Expedited Program(s) Status: FDA Orphan Designation (16-5269), Rare Pediatric Disease Designation (RPD-2016-63),

CBER receipt date:	March 15, 2024
Filing Date:	May 14, 2024
Mid-Cycle Review Meeting:	June 24, 2024
Complete Discipline Reviews	August 9, 2024
External Late Cycle Meeting:	August 29, 2024
Complete Review:	October 14, 2024
Action Due Date:	November 13, 2024

Signature Block

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Johnny Lam, PhD Primary Device Reviewer OTP/OCTHT/DCT1/CTTB	Concurred	
Alyssa Kitchel, PhD Branch Chief OTP/OCTHT/DCT2/TEB2	Concurred	
Laura Ricles, PhD Director OTP/OCTHT/DCT2	Concurred	

Contact/sponsor/applicant information

	Applicant: PTC Therapeutics, Inc.	Device Applicant ClearPoint Neuro, Inc.
Address:	100 Corporate Court South Plainfield, NJ	120 S. Sierra Ave. Suite 100 Solana Beach, CA 92075

Contact information:	Phone: 908-222-7000 Fax: N/A	Phone: 508-446-1830 Fax: N/A
	Email: acobbum@ptcbio.com	Email: mmcnamara@clearpointneuro.com

Review Team:

RPM	Tolani Ishola	
CMC	Bo Liang	
Pharm/Tox	Abigail Shearin	
Clinical reviewer	Avanti Golikeri	
BIMO	Haecin Chun	
Clinical Pharmacology	Xiaofei Wang	
Statistical	Yuqun (Abigail) Luo	
CONSULT REVIEWERS – DEVICE		
CDRH Device Review Intraparenchymal Cannula	Gregg Kittlesen Adam Pierce	<u>ICCR#00984291</u>
CDRH Device Review General Hospital and Infusion Devices	Kyrán Gibson Jake Lindstrom	<u>ICCR#00983305</u>

Relevant Cross-Referenced File(s) – Delivery Device:

ID	Type	Product	Sponsor	Status	Primary Reviewer	LOA
(b) (4)	Type C	Eladocagene exuparvovec	PTC Therapeutics Inc. (Agilis)	Written Responses	CBER	N/A
IND19653	IND	Eladocagene exuparvovec	PTC Therapeutics Inc.	Active	CBER	N/A
(b) (4)	Q-Sub	SmartFlow Cannula	ClearPoint Neuro	Pre-Submission	CDRH	N/A
(b) (4)	Master File (CDRH)	SmartFlow Cannula	ClearPoint Neuro	Active	CDRH	Yes
DEN240023	De novo classification request	SmartFlow Cannula	ClearPoint Neuro	Active; Under Concurrent Review	CDRH	Yes

Table of Contents

Table of Contents.....	3
I. Executive Summary.....	4
II. Regulatory History – Pre-BLA Type B Meeting.....	5
III. Product Background.....	9
Indication for Use Statement	9
Route of administration (ROA)	9
Relevant Product Release Specifications.....	9
IV. Clinical Data Summary – Relevant Information	11
V. Device Constituents of Combination Product.....	15
1. SmartFlow Cannula (ClearPoint Neuro) – Cross-labeled Device Constituent of Combination Product.....	16
Regulatory Status	16
Device Description	18
Administration Procedure	21
Manufacturer	22
Route of Administration – Device	22
Design Control Summary – Mechanical, Chemical, and Biological Properties.....	23
2. Non-Cross-labeled Device Components – General Use Labeling	25
Device Description – Ancillary Devices.....	25
Design Control Summary and Quality Systems – Ancillary Devices	34
CDRH/OHT3 ICCR# 00983305 – Review of General Use Infusion Devices and General Use Labeling Approach	35
3. Use-Related Risk Assessment.....	36
4. Relevant Preclinical Information – Delivery Device.....	40
5. Device Compatibility Testing with Eladocogene Exuparvovec	40
VI. Draft Labeling – DP Prescribing Information.....	49
VII. Appendix – Information Requests.....	52
1. Response to IR # 18 (Device, SN0027) – August 2, 2024	52
2. Response to IR # 15 (CMC/Device, SN0022/SN0023) – July 23, 2024.....	55
3. Response to IR # 10 (CMC/Device, SN0013) – June 25, 2024.....	58
4. Response to Filing Letter Items (CMC/Device, SN0007) – May 13, 2024	59

I. Executive Summary

Eladocogene exuparvovec is an adeno-associated virus (AAV) based gene therapy intended for treating patients with genetically confirmed aromatic L-amino acid decarboxylase (AADC) deficiency which is an ultra-rare autosomal recessive condition due to dopa decarboxylase (DDC) gene defects that is fatal. Specifically, the drug product (DP) is a recombinant wild type AAV serotype 2 capsid containing the human AADC expression cassette. The DP is packaged in a single-dose, 2 mL vial containing 2.8×10^{11} vg in an extractable volume of 0.5 mL each.

Eladocogene exuparvovec is to be administered via four separate infusions of equal volume to the right anterior putamen, right posterior putamen, left anterior putamen, and left posterior putamen, respectively. The DP is administered into the bilateral putamen of the brain via a stereotactic neurosurgical procedure at a dose of 0.45×10^{11} vector genomes (vg) and a volume of 80 μ L per site to 4 sites (2 per putamen), for a total dose of 1.8×10^{11} vg and a total volume of 320 μ L per patient.

Eladocogene exuparvovec is intended for intraparenchymal administration using the cross-labeled SmartFlow cannula (ClearPoint Neuro) device and ancillary delivery device components that include the stereotactic system, a syringe pump, a syringe, and syringe accessories (filter needle, syringe cap).

The BLA applicant maintains overall responsibility of the cross-labeled gene therapy combination product, which comprises the eladocogene exuparvovec gene therapy product (biologic) and the cross-labeled SmartFlow cannula (device biologic). To support a cross-labeling approach with the SmartFlow cannula and a general use labeling approach for all other ancillary device components required for intraparenchymal administration, the applicant provided data from 5 DP-device compatibility studies. Data from these DP-device compatibility studies permitted the establishment of minimum required technical specifications for delivery device components for inclusion in the DP prescribing information to ensure safe and effective drug delivery.

Additionally, the BLA applicant maintains a quality system that includes procedures to ensure quality compliance of delivery device components. To support the cross-labeling of the SmartFlow cannula (via updated labeling of the device for intraparenchymal administration of the DP), the device manufacturer submitted DEN240023 to CDRH for concurrent review.

<p>Recommendation – From a CBER Device perspective, APPROVAL is recommended. Defer to CDRH for final regulatory decision on DEN240023</p>
--

II. Regulatory History – Pre-BLA Type B Meeting

PTC Therapeutics, the sponsor of IND19653 and the applicant of this BLA, previously engaged with FDA in a Type B Pre-BLA meeting under IND19653.46 (December 2023) to discuss plans of a BLA submission for accelerated approval of eladocagene exuparvovec gene therapy product. Prior to the pre-BLA meeting, a brief summary of the IND19653 sponsor's relevant regulatory history with FDA included:

- Interactions under (b) (4) and IND 19653
- IND 19653 opened in 2019 to initiate Study 002 (to assess safety of the SmartFlow MR Compatible ventricular cannula); amended in May 2023 to assess CSF HVA (at 8 weeks post-administration) as a biomarker of clinical efficacy
- October 6, 2022 – discussion of comparability between clinical drug product (DP) lots and viability of CSF HVA as a biomarker surrogate endpoint of clinical efficacy; amendments submitted to IND
- September 15, 2023 – discussion of comparability between clinical DP lots and CSF HVA biomarker to support accelerated approval; post-meeting feedback shared with sponsor via email (October 2, 2023)

During the pre-BLA meeting, the Agency advised PTC Therapeutics that their device manufacturer (ClearPoint Neuro) should engage in regulatory discussions directly with CDRH and involve CBER regarding the commercial labeling strategy for the SmartFlow Cannula delivery device. Per discussions under Q-Submission (b) (4), it was agreed between FDA and the sponsors that a de novo classification request for the SmartFlow Cannula would be submitted to CDRH to allow concurrent review with the BLA submission.

Key summary points of previous FDA feedback regarding regulatory strategy for the sponsor's intraputaminial delivery device constituents include the following:

Table 1. Regulatory History

Submission ID	Date	Summary
(b) (4) (Agilis)	August 2, 2017 CBER	<ul style="list-style-type: none">• Previous sponsor originally proposed delivery of DP with (b) (4) Sponsor was asked to clarify whether these components will be provided with the product (i.e. co-packaged) for delivery and/or specifically recommended or required for use in the labeling (i.e. cross-labeled) and to provide the regulatory status for these components (e.g., 510(k) number).<ul style="list-style-type: none">○ No further discussions on this topic
(b) (4) (Agilis)	November 28, 2017 CBER	<ul style="list-style-type: none">• Previous sponsor indicated that DP label will not specify a delivery device to be used (referenced TPP in EOP2); compatibility data with the Smartflow device is provided as an example device that could be used to deliver DP<ul style="list-style-type: none">○ FDA advised sponsor that the DP labeling will likely need to contain constraints on delivery devices that can be used with product; compatibility testing would need to include a range of commercially available cleared/approved devices using this approach

		<ul style="list-style-type: none"> ○ Previous sponsor clarified that the (b) (4) catheter used in completed clinical studies is not available commercially in USA; SmartFlow catheter is available in US markets; FDA provided advice regarding compatibility testing
(b) (4) <u>(Agilis)</u>	November 8, 2018 CBER	<ul style="list-style-type: none"> • CMC/Device compatibility testing comments were provided to previous sponsor; no further discussions on device topic
(b) (4) <u>(Agilis)</u>	June 12, 2019 CBER	FDA feedback provided to sponsor regarding facilities information; no discussion on device topic
(b) (4) <u>(Agilis)</u>	December 4, 2019 CBER	<ul style="list-style-type: none"> • Sponsor was advised by FDA about concerns that the details/data/information are not adequate to support the non-specific labeling strategy and interchangeable use of devices; sponsor was advised to provide a detailed risk assessment to determine which device needs to be specifically cross-labeled (e.g., SmartFlow catheter) to meet pre-specified design and performance requirements to achieve intended dose level(s); sponsor was requested to provide specifications/parameters for all device components that are not cross-labeled <ul style="list-style-type: none"> ○ FDA communicated concerns with the sponsor's proposal for general use labeling approach for device components due to: <ul style="list-style-type: none"> ▪ low volume and flow rate to be used for delivery of the product, as the dose accuracy and consistency for these parameters may be significantly impacted based on the delivery device components ▪ the catheter used in the clinical study and the SmartFlow catheter have specialized designs that may necessitate labeling specifically for the catheter(s) that were tested in the compatibility and/or clinical studies ▪ recommend that sponsor define design and performance specifications for the delivery device that will be used to deliver the product in a commercial setting and conduct a risk assessment to determine the appropriate labeling strategy for the delivery device components. This risk assessment should consider each component used to deliver the product, including the syringe, needle, syringe pump, catheter, and stereotactic system, and include comparisons to the delivery device components used in the clinical studies and comparability studies
(b) (4) <u>(Agilis)</u>	December 18, 2019 CBER	<ul style="list-style-type: none"> • During meeting discussion with sponsor about medical device that will be used in the delivery of the commercial product, FDA stated that the drug and delivery device would be regulated as a cross-labeled combination product <ul style="list-style-type: none"> ○ FDA advised that sponsor would need to work with the device manufacturer in cross-labeling the delivery device for the sponsor's product

		<ul style="list-style-type: none"> ○ “As indicated in the meeting discussion, your product, AGIL-AADC, and associated delivery device(s), e.g. Smart Flow “infusion catheter”, may be a combination product based on cross labeling of the separate biological and device products” ○ “You will need to work with the Smart Flow® Ventricular Catheter manufacturer in order for the device to be properly cross-labeled for use with your biological product; Smart Flow® Ventricular Catheter labeling will need be updated to specify your product, AGIL-AADC, can be delivered with this device when used as instructed. We strongly recommend that you resolve these issues with the catheter manufacturer prior to submission of a BLA”
<u>IND 19653</u>	March 2020 CBER, CDRH	<ul style="list-style-type: none"> • Sponsor did not describe their commercialization approach for the device constituents; CBER and CDRH planned to internally meet for discussion
<u>IND 19653</u>	April 2020 CBER, CDRH	<ul style="list-style-type: none"> • Non-hold advisory comment communicated to sponsor to advise that the product may be a combination product: <ul style="list-style-type: none"> ○ Sponsor was advised to enumerate their labeling/delivery device strategy and to provide a list of devices for inclusion in the surgical manual ○ Sponsor was advised that sufficient clinical/nonclinical data and detailed specifications would be needed to support a general labeling approach ○ Sponsor was advised that if a specific device is needed for drug delivery, then the specific component will need to be specified in drug product labeling ○ Sponsor was advised to work with the device manufacturer to update the device labeling to specify delivery with the sponsor’s drug product ○ (b) (5) • CDRH indicated during ICCR that the data collected under this IND to assess the performance of the delivery system for the delivery of the therapeutic should be able to support a future submission that includes a labeling change for the SmartFlow
<u>IND 19653</u> <u>Pre-BLA Type B</u>	December 12, 2023 CBER, CDRH	<ul style="list-style-type: none"> • Sponsor was provided comprehensive preliminary comments, which indicated that the partner device manufacturer should submit a Q-Sub to CDRH to discuss appropriate regulatory pathway for the cross-labelled SmartFlow cannula; comprehensive advice was also provided regarding the sponsor’s proposed general labeling approach for ancillary delivery device components
(b) (4)	February 27, 2024 April 10, 2024	<ul style="list-style-type: none"> • Submitted by ClearPoint Neuro (SmartFlow cannula device manufacturer) to CDRH (with CBER consultation) to discuss appropriate regulatory pathway for the cross-labelled device • Preliminary meeting to discuss regulatory pathway question, where it was agreed that the cross-labelled SmartFlow cannula

		<p>would be most appropriately regulated under a de novo classification request</p> <ul style="list-style-type: none"> • Both ClearPoint Neuro and PTC Therapeutics (in attendance) indicated that they will ensure aligned review timelines for the device submission and BLA submission • Additional feedback was provided to ClearPoint Neuro regarding performance testing of the SmartFlow cannula, including compatibility with eladocagene exuparvovec
--	--	---

Review Comments:

Regulatory history is captured in this section of the review for reference.

Per the regulatory feedback history of (b) (4) IND 19653, the applicant has been advised the following regarding their device constituents:

- The catheter components ((b) (4) ; Smartflow ventricular cannula for US study) have specialized designs for achieving the sponsor's intended dose accuracy/consistency via low volume + flow rate parameters – this may require labeling for the specific components tested, as it is unclear if other non-tested devices can achieve the same dose accuracy
- The drug and delivery device would be regulated as a cross-labeled combination product due to the risks involved with the eladocagene exuparvovec gene therapy product and the intended route of administration
- Based on discussions held under (b) (4) , IND 19653 was initiated to generate clinical data to support use of the Smartflow cannula (K102101) device for delivering eladocagene exuparvovec DP to the brain putamen. The applicant elected to pursue a cross-labeling (i.e., two way labeling) combination product strategy for the Smartflow cannula/catheter (K102101) and the DP.
- Advisory comments given to the applicant during IND review did not commit to any particular commercial labeling strategy for the possible combination product despite firmer advice provided under (b) (4) .

As noted in the applicants's summary of interactions, it was agreed between the PTC Therapeutics (including the SmartFlow cannula device manufacturer) and FDA (CBER and CDRH) that the cross-labeled combination product comprises PTC Therapeutic's (BLA applicant) eladocagene exuparvovec gene therapy product (biologic constituent) and ClearPoint Neuro's SmartFlow cannula (device constituent). To support this approach, it was agreed that the most appropriate regulatory pathway is to regulate the eladocagene exuparvovec gene therapy product under a BLA and the cross-labeled SmartFlow cannula delivery device under a de novo classification request – both the BLA and de novo request submissions will be reviewed concurrently, and final regulatory decision will need to be rendered contemporaneously to avoid any outstanding device/biologics issues. ClearPoint Neuro submitted DEN240023, received by CDRH, on May 22, 2024 to support cross-labeling of the SmartFlow cannula for brain intraparenchymal administration of eludocagene exuparvovec. Since DEN240023 falls under the jurisdictional purview of CDRH, CDRH/OHT5 will conduct the review and

coordinate with CBER during review of the BLA to ensure that the regulatory timelines for both the biologics and device submissions align.

III. Product Background

Eladocogene exuparvovec is an adeno-associated virus (AAV) based gene therapy for treating patients with aromatic L-amino acid decarboxylase (AADC) deficiency which is an ultra-rare autosomal recessive condition due to dopa decarboxylase (DDC) gene defects that is fatal. Specifically, the drug product (DP) is a recombinant wild type AAV serotype 2 capsid containing the human AADC expression cassette. The DP is packaged in a single-dose, 2 mL vial containing 2.8×10^{11} vg in an extractable volume of 0.5 mL each.

Indication for Use Statement

Eladocogene exuparvovec is indicated for treatment of patients with aromatic L-amino acid decarboxylase (AADC) deficiency

Route of administration (ROA)

Eladocogene exuparvovec drug product (DP) provides a functional copy of the DDC gene to permit de novo production of the AADC enzyme for dopamine/serotonin production from L-3,4-dihydroxyphenylalanine (L-DOPA) in the brain.

Eladocogene exuparvovec is to be administered via four separate infusions of equal volume to the right anterior putamen, right posterior putamen, left anterior putamen, and left posterior putamen, respectively. The DP is administered into the bilateral putamen of the brain via a stereotatic neurosurgical procedure at a dose of 0.45×10^{11} vector genomes (vg) and a volume of 80 μ L per site to 4 sites (2 per putamen), for a total dose of **1.8×10^{11} vg** and a total volume of 320 μ L per patient.

The intraparenchymal ROA is selected to allow for the DP to be administered directly to into the targeted brain tissue and bypassing the blood-brain barrier – the intraparenchymal ROA also generally permits the infusion of larger volumes “while limiting neurotoxicity and systemic toxicity,” thereby enabling smaller doses of the DP to be used. The applicant indicates that there is limited immunogenic response to the DP through the intraparenchymal ROA due to the minimal DP volumes used.

Relevant Product Release Specifications

The proposed release specifications for the eladocogene exuparvovec DP is as follows:

Table 2. Release Specifications for Eladocagene Exuparvovec Drug Product

Attribute Category	Test: Method	Acceptance Criteria	
		Release	Shelf-life
Quality	Appearance (post-thaw): Visual inspection	Clear to slightly opaque, colourless to faint white solution, free of visible particulates	Clear to slightly opaque, colourless to faint white solution, free of visible particulates
			(b) (4)
			N/A
			(b) (4)
Identity	(b) (4)	(4)	(b) (4)
Potency			
Purity, identity	(b) (4)	(4)	(b) (4)
Safety			
	Endotoxin (EU/mL): (b) (4)		N/A
	(b) (4)		
	Sterility: (b) (4)	No growth	N/A
	(b) (4)		
	Container closure integrity:	N/A	Pass
	(b) (4)		
Abbreviations: (b) (4) endotoxin			
(b) (4)			

Following drug delivery, the increased levels of homovanillic acid (HVA) in the cerebral spinal fluid is a potentially qualified surrogate endpoint biomarker for predicting clinical efficacy of the eladocagene exuparvovec DP.

Reviewer Comments:

The eladocagene exuparvovec DP is intended to be administered bilaterally, directly into the putamen via an established stereotactic neurosurgical procedure at a nominal dose of 0.45×10^{11} vg and a volume of 80 μ L per site to 4 sites (2 per putamen), for a total dose of 1.8×10^{11} vg and total volume of 320 μ L per patient.

Upon administration, the eladocagene exuparvovec DP is expected to work via several mechanisms involving the (b) (4) within the targeted brain parenchyma to achieve episomal expression of the missing gene encoding AADC enzyme.

The eladocagene exuparvovec DP received Orphan Drug Designation (June 8, 2016), and the applicant received Rare Pediatric Disease Designation for the target indication (November 7, 2016).

Final DP specifications (methods and acceptance criteria) for eladocagene exuparvovec is reproduced for reference – **defer to CMC for final review** of the proposed DP specifications and critical quality attributes.

IV. Clinical Data Summary – Relevant Information

Per the applicant, the eladocagene exuparvovec has been administered to 57 subjects with AADC deficiency as of December 16, 2023 – 43 subjects in the applicant's clinical studies, 5 subjects in the French Compassionate Use study, 1 subject in an individual healing attempt in Germany, 8 patients in a commercial setting (European Commission approval in July 2022).

The applicant's clinical program comprises 5 studies:

- **Two ongoing studies**
 - PTC-AADC-GT-02 [Study 002] pivotal study – to assess pharmacodynamics (PD) of DP by measuring HVA levels as the primary endpoint; to assess safety of the ClearPoint SmartFlow magnetic resonance (MR)-compatible ventricular cannula for DP delivery to brain putamen of pediatric subjects; Process C DP; N=13
 - AADC-1602 long-term follow-up study of AADC-CU/1601, AADC-010, AADC-011; N=26
- **Three completed studies (N=30)**
 - AADC-CU/1601 – National Taiwan University Hospital; retrospective study of compassionate use program, N=8; Process A DP
 - AADC-010 – National Taiwan University Hospital; Phase 1/2 5-yr study, N=10; Process B DP
 - AADC-011 – National Taiwan University Hospital; Phase 2b 13-month study, N=12; Process B DP

The applicant reports experience in delivering eladocagene exuparvovec using the SmartFlow cannula with 5 patients in France and 1 patient in Germany

The applicant also reports commercial experience with eladocagene exuparvovec - 8 patients have received eladocagene exuparvovec using SmartFlow cannula in post marketing experience in France (3), Germany (3), Italy (1), and United Kingdom (1)

Regulatory history of the applicant includes the following milestones:

- European Commission Marketing Authorization in July 2022
- UK MHRA Approval in November 2022
- Israel Ministry of Health – Under Review
- Taiwan FDA – Under Review
- Brazil Health Regulatory Agency ANVISA – Under Review

- US FDA – Orphan Drug designation; Rare pediatric disease designation
 - Type C Meeting under (b) (4) – Nov. 14, 2019
 - Comparability discussion – Oct. 4, 2022
 - Biomarker surrogate endpoint discussion – Nov. 11, 2022
 - Comparability and biomarker surrogate endpoint discussion – Sep. 15, 2023

Per the applicant's clinical program overview in Module 2.5 and summary of clinical safety data (Module 2.7.4), in Study PTC-AADC-GT-002, no treatment-emergent adverse events were considered related to the SmartFlow cannula:

- No TEAEs were considered related to the surgical device (PTC-AADC-GT-002, Table 14.3.1.4).
- 1 subject experienced a TEAE considered related to 18F-DOPA (pyrexia) (PTCAADC-GT-002, Table 14.3.1.6).
- 8 subjects experienced TEAEs considered related to the surgical procedure (discussed in Section 3.1.6.1.2).
 - Pyrexia was the most frequently reported TEAE that was considered related to the surgery procedure
 - No SAEs were considered related to the surgery
- 10 subjects experienced a TEAE considered related to gene therapy, the most frequent of which was dyskinesia in 10 subjects (PTC-AADC-GT-002, Table 14.3.1.3).

While CSF leaks were reported for the integrated supportive clinical studies, no CSF leaks were observed in Study PTC-AADC-GT-002.

Summary of brain imaging information – from PTC-AADC-GT-002:

- No intracerebral hemorrhage or CSF leak observed for any subject during surgery via intersurgical MRI; no findings of neuroinflammation or acute infarction
- CT scan immediately post-surgery showed largely normal results with abnormalities in 3 subjects that include:
 - Paranasal sinus opacification in one subject – related to long-term sinusitis that was present in subject prior to gene therapy
 - Evidence of surgical burr holes and minimal expected pneumocephalus in one subject
 - Changes after injection in one subject – determined not to be clinically significant on subsequent MRI
- Follow-up information
 - One subject had minimal extra-axial fluid and blood products on week 3 that improved by week 8
 - One subject had mild brain atrophy that was also present during screening – due to underlying disease; another subject had brain atrophy finding at 90 weeks post treatment – this finding was noted on a pre-study MRI

Listing 16.2.5.2 Intracerebral MRI - Safety Population

Subject ID	Date (Day)	Intracerebral hemorrhage present	CSF Leak during Procedure?
(b) (6)		No	No
		No	No
		No	No
		No	No
		No	No
		No	No
		No	No
		No	No
		No	No
		No	No

Listing 16.2.5.3 Brain CT - Safety Population

Subject ID	Visit	Date (Day)	Time	Post-Dose CT Results	If Abnormal, Specify
(b) (6)	Day 1	(b) (6)		Normal	
	Day 1			Normal	
	Day 1			Normal	
	Unscheduled			Normal	
	Day 1			Normal	
	Day 1			Normal	
	Day 1			Normal	
	Day 1			Normal	
	Unscheduled			Normal	
	Day 1			Abnormal - NCS	THERE IS EVIDENCE OF THE SURGICAL BURR HOLES BILATERALLY AND MINIMAL EXPECTED PNEUMOCEPHALUS
	Day 1			Abnormal - NCS	EXTENSIVE PARANASAL SINUS OPACIFICATION.
	Day 1			Normal	
	Day 1			Normal	
	Day 1			Abnormal - NCS	CHANGES AFTER INJECTION FOLLOWED BY NCS MRI FINDING..
	Unscheduled			Abnormal - NCS	NORMAL CT
	Day 1			Normal	

The applicant reported 6 deaths from the integrated supportive clinical studies (AADC-CU/1601, AADC-010, AADC-011, and AADC-1602). The applicant indicated that all deaths were determined by investigators to be related to the underlying AADC deficiency.

Reviewer Comments:

It is noted that the applicant's comprehensive safety profile of the eladocagene exuparvovec DP comprises data generated from 5 clinical studies: PTC-AADC-GT-002, AADC-010, and AADC-011 plus the long-term follow-up Study AADC-1602, and

Study AADC-CU/1601 – only the pivotal PTC-AADC-GT-002 study (N=13) conducted under IND 19653 involved the SmartFlow cannula device. The applicant did not observe any treatment-emergent adverse events (TEAE) that were related to the SmartFlow cannula. Of the TEAEs in all clinical studies, dyskinesia was the most commonly observed and attributed by the applicant's investigators to effects of initial de novo dopamine synthesis due to the gene therapy.

In addition to the assessment by Clinical review, the applicant's clinical safety assessment of the Smartflow device is acceptable from a CBER Device perspective for the following reasons:

- Of the 13 subjects studied in PTC-AADC-GT-002, no TEAEs were determined to be attributable to the intraparenchymal delivery device; there were also no new safety signals due to the device when compared to the applicant's "integrated supportive studies"
- AADC deficiency is an ultra-rare disease, so the expected use of the device is both limited and will be carried out by highly specialized neurosurgery centers
- The surgical procedure of intraparenchymal drug delivery is inherently risky; no SAEs were determined to be caused by the surgical procedure itself in Study PTC-AADC-GT-002
- The clinical data for intrasurgical brain MRI and brain CT during and after the surgical procedure did not note any major safety findings

V. Device Constituents of Combination Product

As noted throughout the BLA submission (Module 3.2.R) and per the applicant's clinical program, eladocogene exuparvovec is intended to be administered directly to the brain putamen via 1-time neurosurgical procedure that would be performed by trained neurosurgeons. Eladocogene exuparvovec will be delivered using the SmartFlow cannula device manufactured by ClearPoint Neuro and will involve the use of various ancillary device components – these ancillary device components include stereotactic equipment, a syringe, syringe accessories (filter needle, syringe cap), and a syringe infusion pump. The intended use of the delivery device system is to administer eladocogene exuparvovec directly to the putamen of the brain via 1-time bilateral infusion. Eladocogene exuparvovec is intended to be administered in the surgical suite under aseptic conditions by a qualified neurosurgeon.

Briefly, the eladocogene exuparvovec **cross-labeled combination product** comprises the following product constituents:

- **Biologic** (provides the primary mode of action in treating AADC deficiency) – eladocogene exuparvovec gene therapy
- **Device** (delivery of the gene therapy) – ClearPoint SmartFlow Cannula

Information for the SmartFlow cannula and ancillary devices used for eladocogene exuparvovec delivery are provided in Module 3.2.R.3 of the BLA submission. The applicant also includes a user related risk assessment (URRA) report in Module 5 of the BLA, which includes information to validate the safe and effective use of the eladocogene exuparvovec combination product user interface.

In the original BLA submission, the applicant provided a letter of authorization to cross-reference (b) (4) from ClearPoint Neuro, Inc. for the SmartFlow Neuro Ventricular Cannula.

CDRH notified CBER that the device manufacturer's de novo classification request was received on May 22, 2024, for the SmartFlow cannula for review under **DEN240023**. On May 29, 2024, the BLA applicant submitted a letter of authorization to allow cross-reference to **DEN240023** for relevant device-related information.

Review Comments:

The applicant's proposed product meets the definition of a 21 CFR Part 3 (cross-labeled) combination product, namely:

- (3) A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose [21 CFR 3.2(e)(3)]
- <https://www.fda.gov/media/90425/download>

In the original BLA submission, the applicant provides a Letter of Authorization to cross-reference (b) (4) is an active MAF within CDRH that houses information pertaining to the SmartFlow ventricular cannula device, which predates subsequent 510(k) clearances for the same ventricular cannulas. Hence, the information contained in the (b) (4) is generally redundant with K102101 and the applicant has indicated during preBLA discussions (IND 19653/48) that the device manufacturer will submit a de novo request submission for concurrent review to support cross-labeling.

Feedback was provided by FDA (CBER and CDRH) under IND 19653/48 (preBLA Type B) advising the applicant to work with their partnering device manufacturer (ClearPoint) to discuss regulatory pathway for the cross-labeled SmartFlow Cannula device directly with CDRH (with CBER involved) under a Q-Sub (b) (4) – this was due to the evolving internal policy discussions regarding the regulation of ventricular cannulas within CDRH given the use of such cannulas for intraparenchymal drug delivery.

Subsequently, the device manufacturer discussed the appropriate regulatory pathway for the cross-labeled SmartFlow cannula device with CDRH (and CBER) under (b) (4). It was determined that the submission of a De Novo Request would be most appropriate for the to-be-cross-labeled SmartFlow cannula due to the lack of suitable predicate device (i.e., indicated for parenchymal delivery of AAV-based gene therapy). The applicant and the device manufacturer, who were both present during these FDA interactions, were thoroughly advised that the approval timelines for the BLA and the device submission need to align – both stakeholders acknowledged that they understood this requirement.

CDRH notified CBER that the device manufacturer's de novo classification request for the SmartFlow cannula has been received on May 22, 2024 for review under **DEN240023**. On May 29, 2024, the BLA applicant submitted a letter of authorization to allow cross-reference to **DEN240023** for relevant device-related information. Since CDRH has jurisdictional purview over **DEN240023**, **CBER Device defers to CDRH for final review of the de novo request for the SmartFlow Cannula**; only relevant SmartFlow cannula device information provided by the BLA applicant will be reviewed in subsequent sections of this memo – information contained in cross-referenced (b) (4) is not reviewed because the information contained in **DEN240023** will be most relevant to the final cross-labeled SmartFlow cannula device.

1. SmartFlow Cannula (ClearPoint Neuro) – Cross-labeled Device Constituent of Combination Product

Regulatory Status

The applicant states that the SmartFlow cannula used with the eladocogene exuparvovec gene therapy is 510(k)-cleared under K102101 (21 CFR 882.4060, product code – HCD). While a signed letter of authorization is provided in the BLA authorizing cross-reference to (b) (4) for the SmartFlow cannula, the applicant indicates that the cannula device manufacturer (ClearPoint Neuro) will submit a de novo request to CDRH for concurrent review – as discussed under (b) (4), this was the

agreed approach between FDA (CBER and CDRH) and the applicants (ClearPoint Neuro and PTC Therapeutics).

Review Comments:

Per the applicant and the device manufacturer, the ventricular cannula used for DP delivery to the brain putamen is the same ventricular cannula device cleared under K102101 and classified under 21 CFR 882.4060, HCD (Ventricular Cannula) – however, the 510(k)-exemption status for 21 CFR 882.4060 (see FR 2019-27394) classified ventricular cannulas is not appropriate for the applicant's proposed cross-labeled combination product. **Refer to discussions and CDRH/CBER reviews under (b) (4)** – it was determined and agreed (between CDRH/CBER and both applicants) that the **appropriate regulatory pathway for the cross-labelled SmartFlow Cannula is a de novo classification request**. The use of the SmartFlow cannula for drug delivery to the brain parenchyma falls outside the regulatory scope (Class I general controls) of 21 CFR 882.4060 for ventricular cannulas

(<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=882.4060>).

Indeed, ventricular cannulas are now categorized as Class 1 devices that no longer require 510(k) premarket notification (84 FR 71815; ventricular cannulas under 21 CFR 882.4060 and product code HCD are only 510(k) exempt if they are made of medical grade stainless steel); however, the risks of administering novel AAV-based gene therapy using neuro-cannulas to the brain parenchyma involves increased risks when compared to such Class 1 devices. Other regulatory considerations included the following:

- Ventricular cannula devices regulated as Class I devices under 21 CFR 882.4060 are exempt from the premarket notification procedures in subpart E of part 807 of this chapter **subject to the limitations of § 882.9**: manufacturers of any commercially distributed class I or II device for which FDA has granted an exemption from the requirement of premarket notification must still submit a premarket notification to FDA ... when: 1) Device is **intended for a use different from the intended use of a legally marketed device** in that generic type of device (e.g., device is intended for a different medical purpose.... And 2) Modified device operates using **a different fundamental scientific technology** than a legally marketed device in that generic type of device....

Using (b) (4) (Product Code: HCA) as the primary predicate Class II device for a concurrent 510(k) submission to support cross-labeling of the SmartFlow cannula with the BLA would present a regulatory pain point. This is because cannula/catheter devices cleared under the HCA product code are intended for accessing cavities of the brain and not brain parenchymal tissue and therefore, establishing Substantial Equivalence to such legally marketed predicate devices would not be feasible.

Therefore, new special controls will need to be defined for neuro-cannulas delivering novel gene therapy products to brain parenchyma and the appropriate regulatory pathway to do so for the cross-labeled SmartFlow cannula is via the de novo classification request pathway (see Section 513(f)(2) of FD&C Act).

Only relevant information for the SmartFlow cannula is referenced from both (b) (4) and DEN240023, as needed. **CBER Device Review notes that the SmartFlow cannula device information contained in DEN240023 (and not (b) (4)) will be the most relevant to support cross-labeling with BLA 125722 – this information contained in DEN240023 falls under CDRH regulatory purview.**

Final decision for the SmartFlow Cannula under DEN240023 is deferred to CDRH since the device submission falls within the regulatory purview of CDRH – the regulatory decision for DEN240023 should occur concurrently and align with this BLA.

Device Description

Table 3. Description for SmartFlow Cannula

Component	Function/Intended Use	Description	Drug Product Contact
SmartFlow Cannula	Delivery of eladocogene exuparvovec to the putamen within the brain	MRI-compatible ventricular cannula model (NGS-NC-01, NGS-NC-02) <ul style="list-style-type: none">• Ceramic patient-contacting materials• (b) (4) product-contacting materials• Blunt tip with single bore 16-gauge OD, 200 µm ID, 18 mm tip length, 26.8 cm cannula body, 30.0 cm bore length, 4 ft or 10 ft overall length, 0.04-0.10 mL priming volume	Yes

To deliver the exadocagene exuparvovec DP to the brain putamen, the applicant intends to cross-label the DP as a combination product with the ClearPoint Neuro SmartFlow Cannula delivery device. The SmartFlow Neuro Cannula will not be co-packaged with eladocagene exuparvovec.

The SmartFlow Neuro Cannula consists of a ceramic body with an inner lumen that provides the conduit for injected/aspirated fluids. The inner lumen portion extending beyond the ceramic body is covered with protective flexible tubing; the tubing maintains a standard luer connector at the proximal end.

Key features of the device include:

- Cannula w/ through-lumen with a stepped tip design at distal end that enables convection-enhanced delivery (CED) of agents; the stepped tip design minimizes backflow of fluid outside the region of interest
- Rigid ceramic outer body to protect portion of the through lumen entering the brain; soft tubing protects the proximal portion of through lumen terminating with a female luer fitting
- Cannula is intended to be used with a supporting structure, such as a stereotactic guide tube and frame, for support/control during insertion into brain
- Certain cannula configurations (0.008" ID) that require guide tube to fit through the ClearPoint Neuro SmartFrame will include ClearPoint Neuro's 16 ga Guide Tube; other configurations without guide tubes "must use another form of supporting structure" for support/control during insertion

- The fluid-contacting central lumen is manufactured using non-reactive silica; cannula is MR-compatible – material composition includes (b) (4) ceramic (b) (4)
- Only patient-contacting materials are the (b) (4)
- Extension is either 4 ft (end of scanner bore) or 10 ft (outside of scanner 5 gauss line)
- Multiple configurations available to accommodate human brain variation and range of aspiration/delivery applications (e.g., different therapeutics to different brain regions)

Table 4. SmartFlow Cannula Components and Materials

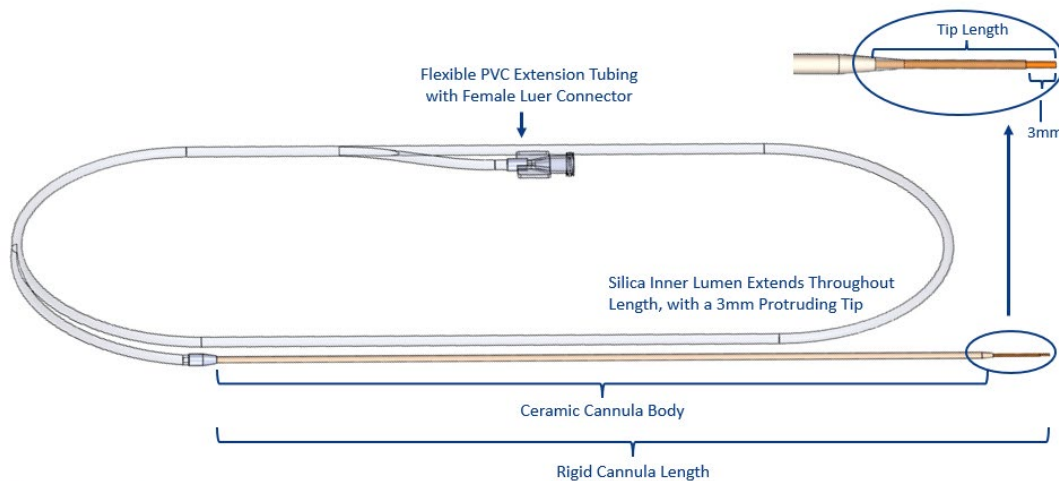
Component	Materials
Tip	(b) (4)
Intermediate step	(b) (4) ceramic
Cannula body	(b) (4) ceramic
Infusion lumen	Silica glass
Flexible tubing	Non-PVC, latex-free, DEHP-free
Abbreviations: DEHP, di-(2-ethylhexyl) phthalate, (b) (4) (b) (4) PVC, polyvinylchloride	

Other key design features of the SmartFlow Cannula include:

- (b) (4)
- Intended for single-patient use only; not to be re-sterilized
- (b) (4)

ClearPoint SmartFlow® Cannula

SmartFlow Cannula Construction



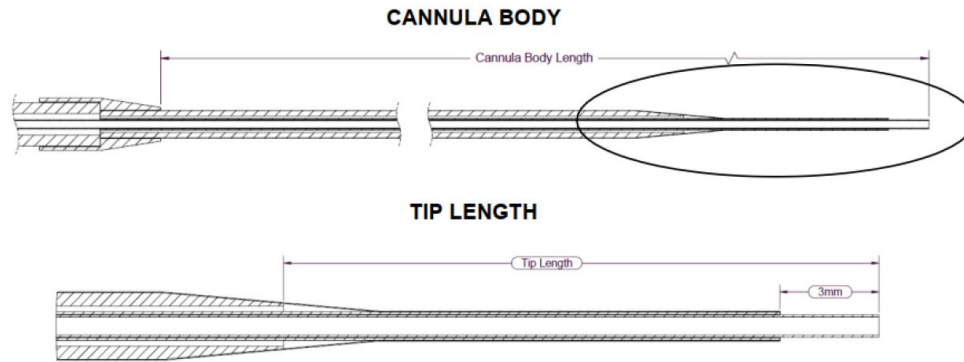


Table 5. Dimensions of Representative SmartFlow Cannula

Outer Diameter			Inner Diameter		Tip Length	Cannula Length	Bore Length	Total Length ^a	Priming Volume ^a
Ga	in.	mm	in.	µm	mm	cm	cm	ft.	mL
16	0.065	1.65	0.008	200	18	26.8	30.0	4 or 10	0.04 or 0.10

^a The cannula comes in 2 lengths, 4 ft and 10 ft. Total length includes the flexible tubing. For both sizes, all cannula dimensions are the same except for the total length and the corresponding priming volume.

On May 29, 2024, the BLA applicant submitted a letter of authorization to allow cross-reference to DEN240023 for relevant device-related information. Several SmartFlow cannula models are described in DEN240023

- **Indication for Use statement** – The SmartFlow Neuro Cannula is intended for intraputamen administration of the gene therapy eladocogene exuparvovec for the treatment of aromatic L-amino acid decarboxylase (AADC) deficiency.

Review Comments:

The applicant indicates throughout Module 3.2.R.3 that the composition, dimensions, and physical properties of the SmartFlow Cannula are referenced from the (b) (4) (held by ClearPoint Neuro) for the SmartFlow Cannula Device. However, the information from (b) (4) is not completely reflective of the SmartFlow Cannula version that will be cross-labeled with the DP under this BLA – this is because (b) (4) is a device MAF that contains information pertaining to various ventricular cannula configurations and versions of the SmartFlow Ventricular Cannula device that may not be applicable to the cross-labeled cannula design.

Although the applicant and device manufacturer both indicate that the SmartFlow Cannula to be included in the de novo request submission is essentially the same as the device cleared under K102101, the cross-referenced (b) (4) contains several significant amendments with updated design control information for the SmartFlow cannula that were submitted to CDRH in October 2021 and October 2023. It appears that the SmartFlow cannula device design control information has been updated since K102101 clearance review.

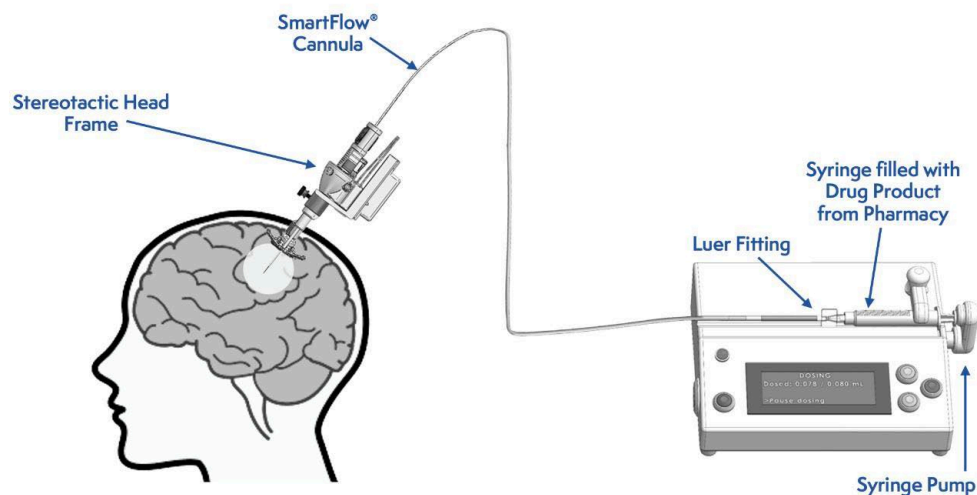
Hence, only relevant information pertaining to the cross-labeled SmartFlow Cannula from DEN240023 should be referenced/reviewed to support cross-labeling with eladocogene exuparvovec.

Final regulatory decision for DEN240023 falls within CDRH purview – On May 22, 2024, ClearPoint Neuro (SmartFlow cannula manufacturer) submitted a concurrent de novo request to CDRH to support cross-labeling with BLA 125722.

Defer to CDRH for final review of DEN240023.

Administration Procedure

The intraputamenal route of administration procedure comprises the following device(s) and general steps:



- Prepare DP dosing syringe (in pharmacy)
 - Thaw vials at room temperature (~15 minutes) and gently invert the vial 3 times to mix the solution
 - Inspect thawed vial for particular matter and discoloration
 - Gather supplies for DP syringe preparation, which include:
 - 1 mL or 5 mL sterile Luer-Lock **polycarbonate** or **polypropylene syringes** with **elastomer** plunger, lubricated with **medical-grade silicone oil**
 - Luer connector compatible with filter needle and cannula connector
 - 18- or 19-gauge sterile needle with 5 µm filter
 - Plastic bag and appropriate secondary container for delivery to surgical unit
 - Using sterile technique under aseptic conditions (in a BSC or isolator):
 - Attach filter needle to syringe; draw full volume of DP vial into syringe; draw air into syringe so that needle is emptied of DP; remove needle from syringe and purge air; cap syringe with syringe

- cap and place in plastic bag; seal plastic bag and place in secondary container for transport to the surgical suite at room temperature
- Thawed product can be stored at room temperature and used within 6 hours of thawing; product cannot be refreezed
 - Filled syringe for administration should be used immediately
- Eladocagene exuparvovec administration
 - Gather supplies for administration
 - Prepared syringe containing the DP
 - ClearPoint Neuro SmartFlow Cannula
 - Syringe Pump
 - Stereotactic system
 - Stereotactic mapping of the target anatomical site
 - Brain imaging for stereotactic planning and intraoperative navigation planning should be performed prior to surgery
 - Entry point on skull will be marked following stereotactic mapping
 - Connect DP syringe to SmartFlow cannula via luer lock connection; place in syringe pump
 - Insert SmartFlow cannula into stereotactic system via headframe (or frameless)
 - Target anatomical site for controlled injection(s); administer drug product **at a rate of 0.003 mL/minute**
 - Administer DP in one surgical session at two sites per putamen

Review Comments:

The administration procedure describes the steps necessary to conduct the intraparenchymal delivery of eladocagene exuparvovec and is intended for qualified neurosurgeons (and associated clinical staff) at specialized pediatric neurosurgical centers. The administration procedure information adequately describes the every step and the roles of the various device components required for drug delivery.

Refer to the final prescribing information for eladocagene exuparvovec for finalized instructions– see FINAL PRESCRIBING INFORMATION.

Manufacturer

SmartFlow Cannula is manufactured by ClearPoint Neuro, Inc. (120 S. Sierra Ave., Suite 100, Solana Beach, CA 92075, USA).

Route of Administration – Device

The cross-labeled SmartFlow Cannula intended for intraparenchymal DP administration leverages a similar ROA and patient contact category as the 510(k)-cleared SmartFlow Ventricular Cannula under K102101. Specifically, the SmartFlow Ventricular Cannula requires insertion of the cannula through a burr hole in the skull and tracked through brain parenchymal tissue to target ventricles. For the cross-labeled SmartFlow Cannula, the cannula will be inserted following an identical procedure and tracked through the

brain parenchymal tissue to reach the putamen. Delivery mechanism between the 510(k)-cleared cannula and the cross-labeled cannula remain the same.

Design Control Summary – Mechanical, Chemical, and Biological Properties

The applicant summarized information from (b) (4) for following chemical and biological property elements:

- Biocompatibility
 - The SmartFlow Cannula is evaluated for biocompatibility per (b) (4) according to its tissue contact category for the following endpoints:
(b) (4)
- Chemical Stability
 - Silica lumen of the SmartFlow Cannula is non-reactive
- Sterilization
 - The SmartFlow Cannula is sterilized by (b) (4)
 - Sterilization validation is completed per (b) (4)
- Bacterial Endotoxins
 - The SmartFlow Cannula is considered non-pyrogenic
 - The SmartFlow Cannula is tested using the (b) (4)
(b) (4)
 - Every lot of the SmartFlow Cannula device is subjected to (b) (4) testing and must meet acceptance criteria of (b) (4) /device
- Bench Performance Testing
 - The SmartFlow Cannula was subjected to (b) (4) testing,
(b) (4) testing, and (b) (4) testing
- (b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4) methodology are inert with negligible-to-low safety risk to patients.

- (b) (4) and conditions are tabulated below:

Table 6. (b) (4) Test Conditions for the SmartFlow Cannula

(b) (4)

Review Comments:

The applicant's summary of the design controls and design verification/validation testing for the SmartFlow Cannula in Module 3.2.R.3 generally relies upon information contained in (b) (4) (cross-referenced) and from K102101. The SmartFlow Cannula design verification/validation testing information provided in Module 3.2.R.3 is near-identical to the device information contained previously in (b) (4) for discussion with CDRH/CBER but with minor updates.

Per discussions with the applicant during the Pre-BLA Type B Meeting (IND 19653/48; December 2023) and (b) (4) (with ClearPoint Neuro), it was agreed upon and anticipated that information for the SmartFlow Cannula contained in the de novo request submission to CDRH will represent the most relevant device information to be reviewed.

- For parenchymal catheters/cannulas, the body contact category per FDA guidance on (b) (4) is generally considered to be tissue contact (direct and indirect) with the brain (and cerebral spinal fluid) for a limited duration (< 24 hours) and to be biological drug product contacting. Therefore, the recommended biocompatibility endpoints include (b) (4)

(b) (4)

The applicant's description of the SmartFlow Cannula biocompatibility testing indicates that appropriate biocompatibility endpoints (including neurotoxicity testing per (b) (4)) were assessed to support intraparenchymal administration of eladocogene exuparvovec DP. Biocompatibility testing information is **acceptable** from a CBER Device perspective – **defer to CDRH for final review of DEN240023**

- Although (b) (4) information for the SmartFlow cannula devices appear to be unchanged from K102101, **CBER Device defers to CDRH for final review of DEN240023**
 - (b) (4) testing will be performed for (b) (4) device (b) (4) in accordance with (b) (4) – **this is acceptable for CBER Device; defer to CDRH for final review of DEN240023, which should describe the device manufacturer’s management of design history records in accordance with 21 CFR Part 820.**
 - The (b) (4) results for the SmartFlow Cannula, as (b) (4) the same (b) (4) data for the SmartFlow Cannula reported in (b) (4) for CDRH/CBER discussion only identified (b) (4) under the same specified conditions
- ⇒ For (b) (4) testing of the SmartFlow Cannula, the applicant notes that none of the (b) (4) using (b) (4) were detected (b) (4) – it was reasoned that risks of patient exposure to such (b) (4) (b) (4) would be (b) (4) during gene therapy administration because the (b) (4) is similar to the gene therapy DP formulation (b) (4); however, the presence of (b) (4) in the DP (b) (4) could alter the (b) (4) – **Defer to CDRH for final review of DEN240023**
- ⇒ CDRH provided substantive feedback to ClearPoint Neuro re: the (b) (4) testing conditions under (b) (4) – **Defer to CDRH for final review of the SmartFlow cannula design control information contained in DEN240023**

2. Non-Cross-labeled Device Components – General Use Labeling

In addition to the SmartFlow Cannula, the intraputamenal administration of eladocogene exuparvovec also requires the stereotactic system, a syringe pump, a syringe, and syringe accessories (filter needle, syringe cap).

Such ancillary device components will leverage a general use labeling approach since these device components are commercially available and will be sourced by neurosurgeons – none of these device components will be provided with eladocogene exuparvovec.

A tabular summary of ancillary devices to be used with the SmartFlow Cannula for DP administration is provided below – the applicant also includes a discussion of each ancillary device in Module 3.2.R.3, as follows.

Device Description – Ancillary Devices

Table 7. Description for Ancillary Devices Used to Deliver Eladocagene Exuparvovec

Component	Function/Intended Use	Description	Drug Product Contact
Stereotactic System	For placement and guidance of the parenchymal cannula to administer DP to the target anatomical site of the brain putamen	<ul style="list-style-type: none"> Framed or frameless stereotactic guidance system E.g., (b) (4) Stereotactic guidance system 	No
Syringe Pump	To control the rate of DP administration from the syringe + cannula to the target anatomical site of the brain putamen	<ul style="list-style-type: none"> Syringe infusion pump that meets treatment flow rate requirements and performance attributes – 0.003 mL/min (0.18 mL/hr) 	No
Syringe	Contains DP after preparation from vial by the clinical site pharmacy; used in conjunction with the filter needle during DP withdrawal from vial; used in conjunction with the syringe pump during DP administration	<ul style="list-style-type: none"> 1-mL or 5-mL polycarbonate Luer-lock syringe with polypropylene plunger E.g., (b) (4) or other syringe models 	Yes
Syringe Cap	Maintains DP enclosed in the syringe after preparation and during transport from pharmacy to surgical suite	<ul style="list-style-type: none"> Polycarbonate or polypropylene Luer connector compatible with syringe connector 	No
Filter Needle	Withdraws DP from vial during dose preparation when used in conjunction with the syringe	<ul style="list-style-type: none"> 18- or 19-gauge, 1.5 in, stainless steel, non-coring, 5 µm filter, hypodermic needle E.g., (b) (4) or other filter needle models 	Yes

Stereotactic Guidance System – General Use Labeling

- Includes the framed or frameless equipment and used in combination with stereotactic software and brain imaging
- Facilitates the identification of target points in the dorsal putamen with high degree of accuracy via planned trajectories for cranial entry into the target points
- General Use labeling approach is used for the stereotactic system because they are commonly used by neurosurgeons as part of the specialized clinical practice; other reasons include:
 - Stereotactic systems are susceptible to procurement issues; therefore, a General Use labeling approach will mitigate difficulties in procuring specific stereotactic systems that may not be available
 - Stereotactic systems may be selected by neurosurgeons in accordance with their clinical practice per the BLA applicant's minimum requirements:
 - Stereotactic systems do not contact the eladocagene exuparvovec DP and will need to be compatible with the SmartFlow Cannula and compatible with mm to sub-mm accuracy; stereotactic systems will also need to be compatible with imaging systems (MRI, computed tomography scanner) used to plan surgical trajectory

Table 8. Examples of Representative Stereotactic Systems

Stereotactic System	510(k)	Compatible With SmartFlow Cannula	Compatible With Imaging Systems	Millimetric to Sub-millimetric Accuracy	Indicated for Neurological Procedures	Requirements for Eladocagene Exuparvovec Administration
(b) (4)		Yes	Compatible (b) (4) and (b) (4) MRI scanners	(b) (4)	Yes	Compatible with the SmartFlow cannula device and compatible with either MRI or CT scanners. Capable of accuracy (millimetric to sub-millimetric) sufficient to enable the distribution of the product
		Yes	Compatible with CT scanner		Yes	

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging

Review Comments:

The applicant's justification for adopting a general use labeling approach for the stereotactic system is acceptable. Additionally, the design controls of the SmartFlow Cannula will ensure compatibility with other stereotactic guidance devices to be used as part of the neurosurgery clinical workflow – **this information is reviewed by CDRH in DEN240023.**

Cleared Indications for Use (IFU) statements for the applicant's listed stereotactic frame examples in Module 3.2.R.3 include:

- (b) (4)

Based on the broad IFU of such 510(k)-cleared stereotactic frames for neurosurgery, the stereotactic system used in these procedures are being used in accordance with their cleared labeling – hence, the applicant's general use labeling approach for these components is **acceptable**.

Syringe Pump – General Use Labeling

- Controls the rate of eladocogene exuparvec DP administration to the targeted anatomical site of the brain putamen
- General Use labeling approach is used for the syringe pump because syringe pumps are commonly used devices as part of various medical procedures; other reasons include:
 - To provide flexibility for the neurosurgeon for selecting syringe pumps per the BLA applicant's minimum requirements:
 - The syringe pump will not contact the eladocogene exuparvec DP and will need to be able to administer the DP at an infusion rate of 0.003 mL/min (0.18 mL/hr); must be compatible with 1-mL and 5-mL syringes

Table 9. Examples of Representative Syringe Pumps

(b) (4)

Review Comments:

The applicant's justification for adopting a general use labeling approach for the syringe infusion pump is acceptable. While the SmartFlow Cannula design controls will ensure compatibility/interoperability with other device components of the intraparenchymal delivery system, syringe infusion pumps are general hospital use infusion devices that may not be specifically designed for the infusion of small volumes into the brain parenchyma. However, the applicant's general use labeling approach for the syringe infusion pump is supported by the commercial availability of 510(k)-cleared pumps that can fulfill the required technical specifications for the applicant's intraparenchymal DP administration and by adequate DP-device compatibility testing (**see review of Module 3.2.P.6 below**).

While many recent 510(k)-clearances of modern syringe infusion pumps include IFU statements that explicitly list specific routes of administration that are supported, the 21 CFR 880.5725 regulatory description for infusion pumps is generally very broad:

- *An infusion pump is a device used in a health care facility to pump fluids into a patient in a controlled manner. The device may use a piston pump, a roller pump, or a peristaltic pump and may be powered electrically or mechanically. The device may also operate using a constant force to propel the fluid through a narrow tube which determines the flow rate. The device may include means to detect a fault condition, such as air in, or blockage of, the infusion line and to activate an alarm.*

The example IFUs of commercially available infusion pumps identified by the applicant and/or used by the applicant in their US-based clinical study are broad enough to not raise any Outstanding Device Issues with respect to promoting off-label or inappropriate use. **To obtain alignment with CDRH on the general use labeling approach for the syringe infusion pumps, an ICCR was submitted to CDRH/OHT3 under ICCR#00983305 – see CDRH/OHT3 ICCR summary below.**

Cleared Indications for Use statements for the listed examples in Module 3.2.R.3 include:

- (b) (4)

- **Additional examples of cleared syringe infusion pumps were discussed with FDA (CDRH/CBER) under (b) (4) – these examples were shared by ClearPoint Neuro with CDRH for labeling assessment**

Due to the breadth of commercially available syringe pumps, it is essential that the applicant determine minimum required specifications for the delivery device system that are suitable for the intraparenchymal administration of eladocagene exuparvovec gene therapy. It was determined during DP-device compatibility testing that the minimum required performance specifications for the syringe pump, which fall within the operating essential performance requirements of the pumps, include:

- Flow rate of 0.003 mL/min (0.18 mL/hr)
- Compatibility with 1mL and 5mL syringes

This information is acceptable and will be included in the finalized prescribing information for eladocagene exuparvovec.

Syringe – General Use Labeling

- Withdraws DP from the vial when used in conjunction with the filter needle and administers the DP when used in conjunction with the syringe pump
- General Use labeling approach is used for the syringe because syringes are commonly used devices as part of various medical procedures and are widely available; other reasons include:
 - To provide flexibility for the neurosurgeon for selecting syringes per the BLA applicant's minimum requirements
 - Syringes must be **1-mL** or **5-mL** in size and certified sterile; materials of construction must be **polycarbonate** or **polypropylene** for the syringe barrel, and elastomer lubricated with silicone oil for the plunger; must have Luer-lock connection compatible with the filter needle and cannula connector
 - The syringe will contact the eladocogene exuparvovec DP and will indirectly contact the patients for a limited duration (<24 hrs)
 - Compliance with 21 CFR 820 and manufactured in facilities compliant with ISO 13485
 - Syringes must be: sterilized using validated method per ISO; evaluated for biocompatibility per (b) (4) ; non-pyrogenic (b) (4)
 - Similar hypodermic syringes have been used for administration of non-hypodermic therapeutic fluids, as an example, with ophthalmic products administered via subretinal or intravitreal injection (Luxturna® [BLA 125610] 2017; Lucentis® [BLA 125156] 2006) and neurologic products administered via ICV injection (b) (4) [BLA 761052] 2017). Most piston syringes are cleared for broad general use, eg, general aspiration and injection of fluids (BD Hypodermic Syringe [K203453]), rather than specific injection site indications.
 - Worst-case DP-syringe contact duration is 9 hours – the applicant indicates that the indirect patient contact is still limited (<24 hrs) and below the biocompatibility threshold for more stringent testing (i.e., (b) (4) testing per (b) (4) , neurotoxicity testing per (b) (4)); extraction conditions during biocompatibility testing for (b) (4) are sufficiently challenging for the intended duration of use

Table 10. Examples of Representative Syringes

Syringe	510(k)	Material of Construction	Sterility	Biocompatibility	Requirements for Eladocogene Exuparvovec Administration
1 mL (b) (4) Luer-Lock	(b) (4) (4)				Sterile; polycarbonate or polypropylene barrel; plunger stopper elastomer lubricated with medical-grade silicone oil; evaluated for biocompatibility as per (b) (4) and tested as per (b) (4) for (b) (4)
5 mL (b) (4) (b) (4) Luer-Lock					
5 mL (b) (4) Luer-Lock					
Abbreviations: (b) (4)					

Review Comments:

The applicant's justification for adopting a general use labeling approach for the piston syringes is acceptable. The SmartFlow Cannula design controls will ensure compatibility/interoperability with other device components of the intraparenchymal delivery system.

The applicant's general use labeling approach for the syringes is supported by the commercial availability of 510(k)-cleared syringes that can fulfill the required technical specifications for the applicant's intraparenchymal DP administration and by adequate DP-device compatibility testing (**see review of Module 3.2.P.6 below**).

Although piston syringes can be 510(k)-cleared under different FDA device product codes (e.g., FMF, QEH, QNQ) Piston syringes are Class II general hospital use infusion devices classified under 21 CFR 880.5860, which includes a broad regulatory definition for such piston syringes:

- *A piston syringe is a device intended for medical purposes that consists of a calibrated hollow barrel and a movable plunger. At one end of the barrel there is a male connector (nozzle) for fitting the female connector (hub) of a hypodermic single lumen needle. The device is used to inject fluids into, or withdraw fluids from, the body.*

The example IFUs of commercially available syringes identified by the applicant and/or used by the applicant in their US-based clinical study are broad enough to not raise any Outstanding Device Issues with respect to promoting off-label or inappropriate use. **To obtain alignment with CDRH on the general use labeling approach for the syringe**

infusion pumps, an ICCR was submitted to CDRH/OHT3 under ICCR#00983305 – see CDRH/OHT3 ICCR summary below.

Cleared Indications for Use statements for the listed examples in Module 3.2.R.3 include:

- (b) (4)

Due to the breadth of commercially available syringes, it is essential that the applicant determine minimum required specifications for the delivery device system that are suitable for the intraparenchymal administration of eladocogene exuparvovec gene therapy. It was determined during DP-device compatibility testing that the minimum required performance specifications for the syringe, which fall within the operating essential performance requirements of the pumps, include:

- Sterility
- Materials of construction that include – polycarbonate or polypropylene barrel, plunger stopper elastomer lubricated with silicone oil
- Evaluated for biocompatibility per (b) (4) and for (b) (4) per (b) (4)

Filter Needle – General Use Labeling

- Filter needle is only used during withdrawal of eladocogene exuparvovec DP from the vial and is not directly part of the final delivery device during DP administration
- General Use labeling approach is used for the filter needles because filter needles are commonly used devices as part of various medical procedures and are widely available; other reasons include:
 - To provide flexibility for the neurosurgeon for selecting filter needles per the BLA applicant's minimum requirements:
 - 18G or 19G; contains 5-µm filter; be certified sterile
 - Needle must be composed of stainless steel; needle hub must be composed of polycarbonate or polypropylene; must have Luer-lock connection compatible with the syringe and cannula connector
 - Compliance with 21 CFR 820
 - Filter needles must be: sterilized using validated method per ISO; evaluated for biocompatibility per (b) (4) ; (b) (4) per (b) (4) testing per (b) (4)

Table 11. Examples of Representative Filter Needles

Filter Needle	510(k)	Material of Construction	Sterility	Biocompatibility	Requirements for Eladocagene Exuparvovec Administration
(b) (4)					18G or 19G, sterile, stainless steel needle with 5-µm filter and polycarbonate or polypropylene hub; evaluated for biocompatibility as per (b) (4) and tested as per (b) (4) for (b) (4)

Abbreviations (b) (4)

Review Comments:

The applicant's justification for adopting a general use labeling approach for the filter needle is acceptable. The filter needle will only be used during preparation of the DP and will not be part of the delivery system during intraparenchymal DP administration.

Since the filter needle is DP-contacting and will therefore, be considered indirect patient-contacting, it is essential that the applicant determine minimum required specifications suitable for the intraparenchymal administration of eladocagene exuparvovec gene therapy. It was determined during DP-device compatibility testing that the minimum required performance specifications for the filter needle include:

- Compatibility with syringe and DP vial (i.e., 18G or 19G, 5 µm filter, luer-lock connection)
- Sterility
- Materials of construction that include – polycarbonate or polypropylene hub, stainless steel needle
- Evaluated for biocompatibility per (b) (4) and for (b) (4) per (b) (4)

The applicant's proposed minimum specifications and general labeling approach for this component is **adequate**. This is also in consideration of the fact that the filter needle is not part of the delivery system used to administer the DP during the surgical procedure.

Syringe Cap – General Use Labeling

- Only needed for capping the syringe after preparation in the pharmacy for transport of the DP to the surgical suite; there is **no DP contact** for the syringe cap component
- General Use labeling approach is used for the syringe cap because these components are commonly used devices as part of various medical procedures and are widely available; other reasons include:
 - To provide flexibility for the neurosurgeon for selecting syringe cap per the BLA applicant's minimum requirements:
 - Composed of either (b) (4)

- must have Luer-lock connection compatible with the syringe connector
- Syringe caps are Class I devices and are 510(k) exempt

Review Comments:

Due to the lower risk associated with the syringe cap component (commonly used in various medical procedures) and the fact that the component does not contact DP, the applicant's general labeling approach for this component is **adequate**.

Design Control Summary and Quality Systems – Ancillary Devices

Due the General Use labeling approach for the ancillary device components to be used with the SmartFlow Cannula, the applicant did not include a detailed description of the design controls (21 CFR 820.30) and other quality systems related elements for these components. However, minimum essential performance requirements were described in Module 3.2.R.3 for each of these ancillary components.

The applicant cites extractables and leachables testing from a device manufacturer for the following representative DP-contacting ancillary device components: 1-mL Luer-Lock syringe (b) (4), 5-mL Luer-Lock syringe (b) (4) 18G blunt filter needle (b) (4). Relevant details include:

- (b) (4)

; the applicant indicated that toxicological risk assessment was acceptable based on the intended use to delivery eladocogene exuparvovec DP

Additionally, the applicant's design verification and validation activities for the eladocogene exuparvovec combination product include a comprehensive DP-device compatibility study – this information is described in Module 3.2.P.2.6 and is summarized/reviewed in Section VI.5 of this memo.

Review Comments:

The applicant indicates that the clinically relevant extractables identified in the extractables/leachables study of the ancillary device components were subjected to a toxicological risk assessment per (b) (4) – the applicant reported that all identified extractables met toxicologically acceptable levels and/or adequate margins of safety based on levels lower than the calculated tolerable exposure values.

Considering that the applicant leverages a general use labeling approach for the commercially available ancillary device, the described extractables and leachables testing information for DP-contacting ancillary device components is **acceptable**.

Based on the device information contained in Module 3.2.R for the cross-labeled SmartFlow device and ancillary device components, the applicant does not describe how the eladocogene exuparvovec quality system ensures the quality of the

combination product as a whole; the applicant also does not describe how the eladocogene exuparvovec quality system ensures that all ancillary components meet minimum performance requirements – **IR COMMENT (August 2, 2024)**

- **UPDATE (August 9, 2024) – RESOLVED; See response to IR#18 (Appendix)**

CDRH/OHT3 ICCR# 00983305 – Review of General Use Infusion Devices and General Use Labeling Approach

Summary of internal discussions between CDRH and CBER: Based on internal discussions between CBER and CDRH, it was determined that the commercially available labeling/indications of the syringe pumps do not raise an Outstanding Device Issue and another device submission for the syringe and pump system is not needed.

Summary of CDRH/OHT3 Review Recommendation – [ICCR#00983305](#):

- CBER question for CDRH – Is the applicant's proposed general use labeling strategy and proposed minimum required specifications of the syringe pump, syringe, filter needle acceptable for the BLA?
 - The proposed labeling provided for eladocogene exuparvovec does not specify the tradename / proprietary name of the syringe pump or syringe intended to be used to deliver the biologic. The Applicant only includes information related to the syringe pump and syringe regarding the abilities of these components (e.g., flow rate, volume). **From a device perspective, this approach appears reasonable.** However, the draft labeling specifically cites use of the SmartFlow Cannula. The SmartFlow Cannula should be labeled with specific syringe pumps and syringes that align with the SmartFlow Cannula's intended use. We wanted to note that, at this time, there are no currently cleared syringes compatible with syringe pumps that are explicitly indicated for delivery of fluids into the neurological tissue and, therefore, most likely have not been assessed for neurotoxicity risk. As such, the labeling, compatibility of the syringe(s) and syringe pump(s), and benefit / risk assessment of the combination product will be deferred to the review of the De Novo.
 - In regard to labeling eladocogene exuparvovec with the SmartFlow Cannula, there is concern of stating "Administer BRANDNAME only with SmartFlow® Cannula (ClearPoint Neuro Part Number NGS-NC-01 or NGS-NC-02)." This specific labeling would preclude future devices from coming in for use with the drug product. If there is a reasonable belief that another device / system would have the ability to deliver eladocogene exuparvovec adequately, with the compatibility and clinical data necessary for a marketing application, this language may want to be revised to exclude specific use with "only" the SmartFlow Cannula.
- CBER question for CDRH – Based on the example devices listed and CDRH's analysis, is there an ODI for the infusion pump or syringe components given the applicant's proposed "general use" labeling strategy for the BLA?

- Any ODIs related to the syringe pump or syringe based on the proposed labeling strategy of the SmartFlow® Cannula **will be assessed during review of the De Novo**. Based on the review of the draft BLA labeling and the compatible syringe pumps and syringes listed as examples within the BLA, **we believe there are syringe pumps and syringes that are indicated / labeled broadly such that there is no outright ODI** - assuming the BLA labeling remains general as currently proposed (i.e., BLA labeling lists out the device characteristics that should be used to deliver the gene therapy and should not call out any specific devices by name). This feedback has been communicated previously through interactions within Q-Submissions with OHT5 (b) (4) as well as meeting requests through IND 19653.

Review Comments:

Based on internal discussions with CDRH and the CDRH/OHT3 review under ICCR# 983305, CDRH indicated that the applicant's general labeling approach for the general hospital use infusion devices (i.e., syringe pump, syringes, filter needles) is **acceptable** and does not present Outstanding Device Issues – **CDRH/OHT3 ICCR review is attached to this memo.**

3. Use-Related Risk Assessment

The applicant includes a use-related risk assessment (URRA) that includes all related risks associated with the intraputamen administration of eladocogene exuparvec DP with all devices – device design risk assessments for the SmartFlow Cannula were completed by ClearPoint Neuro.

The URRA was conducted per the FDA Guidance on human factors (2016; <https://www.fda.gov/files/about%20fda/published/Human-Factors-Studies-and-Related-Clinical-Study-Considerations-in-Combination-Product-Design-and-Development.pdf>), IEC 62366-1:2015, and ISO 14971:2019

Intended users of the eladocogene exuparvec combination product:

- Healthcare professionals (HCPs) – for DP preparation
 - Pharmacists, pharmacy technicians, doctors
 - Licensed for aseptic preparation of DP
- Neurosurgical team healthcare professionals – for DP administration and neurosurgery
 - Neurosurgeon, nurses, surgical technicians
 - Experts in the field of neurosurgery with rigorous training and vast experience in pediatric stereotactic neurosurgery and experience for variety of procedures
- Education level and training may vary between HCPs
 - Post-graduate degrees for pharmacists (e.g., PharmD) and doctors (e.g., MD)
 - Minimum of nursing degree for nurses

- Minimum of high-school diploma (or equivalent) and technician training program accreditation for pharmacy/surgical technicians

Intended use conditions and environments of the eladocogene exuparvovec combination product:

- During DP preparation – clinical setting, such as a hospital-based pharmacy
 - May vary in terms of size, personnel, ambient noise; brightly lit and equipped with dedicated aseptic area for drug preparation; equipped with temperature-controlled storage environments and drug preparation materials
- During DP administration – operating room (OR) within a clinical center specializing in pediatric stereotactic neurosurgery
 - May vary in terms of size, personnel, ambient noise; brightly lit by surgical lights; equipped with equipment, machines, supplies, monitors with sufficient space for surgery under sterile conditions; equipped with equipment needed for eladocogene exuparvovec DP administration

Tasks associated with use of the eladocogene exuparvovec combination product involves:

- Selection of compatible components (sterile syringes, needles, stereotactic navigation system, cannula, syringe pump)
- Preparation of the DP
 - Retrieve DP to thaw, withdraw DP vial contents into syringe, cap syringe for transport to the OR
- Performing stereotactic planning
 - Perform standard brain imaging to identify target points, mark target points, identify entry points
- Surgery and infusion
 - Make incisions at entry points, drill burr holes and open dura for access, fixate stereotactic frame (for frame-based systems), perform MR imaging
 - Connect syringe to SmartFlow cannula, load syringe into syringe pump, configure pump's syringe selection to match syringe, prime cannula using specified low flow rate per instructions, insert cannula to target point, infuse DP at specified infusion rate, incrementally withdraw cannula along intraputaminial track length, pause pump and leave cannula in place for 5 min – repeat these steps for each target point for DP administration
- Disposal of the used product and materials

Use-related errors/problems associated with the various device components of the eladocogene exuparvovec combination product were analyzed and determined by the applicant to be similar to errors/problems associated with various procedures requiring low infusion rates – these errors were also considered in the URRRA and known use problem analysis and generally include:

- Wrong preparation technique -> incorrect dose
- Flow continuity issues when using programmable syringe pumps -> larger deviations in delivered dose

- Use of incompatible syringes with pump -> inaccurate delivery, insufficient sensing
- Use of syringes that are too large for or incompatible with the prescribed DP -> inaccurate delivery, delay of therapy, delay of alarms, different residual volumes leading to inaccurate delivery
- Priming errors -> inaccurate delivery, over-priming, alarms
- Uncontrolled infusions at different infusion rates due to syringe pump errors (alarm issues, failure to confirm infusion rates) -> overdose
- Programming errors with the pump -> inaccurate delivery

Summary of the applicant's URRR report (PTC-AADC-URR-503) – additional key relevant details include:

- URRR report (PTC-AADC-URR-503) and related documentation are included in Module 5 of the BLA
- Per the product description, the eladocogene exuparvovec DP is cross-labeled with and should only be administered using the SmartFlow cannula (ClearPoint Neuro); none of the components required for DP preparation and administration are co-packaged with the product and users will be responsible for selecting appropriate components based on the applicant's labeling/prescribing information
- Failure mode effects analysis (FMEA)-based quantitative risk assessment tool was used for the URRR per ISO 14971:2019
 - Critical tasks were identified and involved tasks related to syringe/needle selection, stereotactic system selection, cannula selection, infusion pump selection, drug storage, drug preparation, perform stereotactic planning, perform neurosurgery, perform infusion, dispose of materials
- Risk control strategies include:
 - Instructions outlined in the US Prescribing Information and labeling for the eladocogene exuparvovec DP
 - Standard surgical procedures and medical practice of specialized treatment centers for pediatric neurosurgery
 - Device quality systems and risk management information from device manufacturers of other cleared/approved device components

Conclusions from the applicant's URRR:

- Residual risks of the eladocogene exuparvovec combination product user interface following mitigations implemented (as described in the URRR) were evaluated against the benefit of the therapy for the affected patients. General risk mitigation considerations of the eladocogene exuparvovec combination product include:
 - Clinical experience with devices used to deliver DP did not result in device-related use errors
 - HCPs are highly specialized and skilled in neurosurgery with extensive clinical experience; mock surgeries are performed in advance of surgeries
 - Clear instructions on dosing and administration in the US Prescribing Information (USPI), which covers the entire procedure from DP preparation to surgical procedure

- Verification of DP compatibility with representative device components according to DP-device compatibility studies
- Potential benefits outweigh risk for the ultra-rare disease with significant unmet medical need that outweighs overall risk

Review Comments:

ClearPoint Neuro, the partner device manufacturer, completed a risk assessment of the SmartFlow cannula as part of the device design controls – **this information is described in DEN240023 and is reviewed by CDRH**. Human factors validation (as part of a clinically relevant workflow) will also be included as part of the required special controls for these intraparenchymal cannulas and will be established as part of DEN240023 review. Additionally, CBER Device notes that the user interface of the current combination product comprising the SmartFlow cannula and eladocogene exuparvovec will be largely identical to the 510(k)-cleared SmartFlow cannula user interface under K102101 – this is because the neurosurgical procedure for intraparenchymal drug delivery using the SmartFlow cannula is essentially identical to the intraventricular delivery surgical procedure and involve all of the same components, exception for the final target location in the brain; the delivery mechanism between the two routes of administration are also the same.

The applicant also performed a comprehensive use-related risk assessment (URRA) to evaluate the risks associated with the combination product user interface and the delivery system as a whole, including ancillary device components. The applicant's URRA was conducted using a quantitative FMEA-based approach per FDA guidance (<https://www.fda.gov/media/171855/download>) and included a systematic evaluation of all tasks involved with the combination product user interface – this approach is **acceptable**.

The applicant's URRA also appropriately defined and considered the intended users, the intended patient population, the intended conditions of use (including use environment), and known/potential use problems. The URRA did not identify any new/novel critical tasks arising from the eladocogene exuparvovec and SmartFlow cannula combination product that would require additional human factors validation testing. Indeed, the identified critical tasks associated with the eladocogene exuparvovec and SmartFlow cannula combination product have already been addressed by the existing human factors validation for each device component. Additionally, the DEN240023 outlines the design controls for the SmartFlow cannula, which should include human factors validation considerations – **defer to final CDRH review of DEN240023 for the SmartFlow cannula**.

Collectively, CBER Device determines that the applicant's URRA for the eladocogene exuparvovec and SmartFlow cannula combination product is **acceptable** without the need for additional human factors validation testing for the following reasons:

- User interface of the SmartFlow cannula device and ancillary device components, even when used together as a system, for intraparenchymal drug administration is essentially unchanged from the existing user interface of these devices for

intraventricular drug administration – therefore, existing human factors validation information for these devices are still applicable

- No novel/new critical tasks associated with combination product user interface
- Intended users are highly specialized neurosurgeons that are well trained in pediatric neurosurgery; only “a few select institutions” will be administering the product to patients
- The intended patient population is very small, due to the ultra-rare nature of AADC deficiency disease

4. Relevant Preclinical Information – Delivery Device

Per Module 2.4, intraputamenal doses via SmartFlow cannula from MRI Interventions (now ClearPoint Neuro, Inc., Solana Beach, CA) were administered without issue or findings in 2 monkey studies (**1144-015** and **1144-023**). Per Module 2.6, the 4-week NHP study (**1144-023**) included evaluation of eladocogene exuparvovec biodistribution following intraputamenal infusion via the SmartFlow cannula:

- Applicant noted that there were no procedure-related adverse events after intraputamenal dosing using the SmartFlow cannula in the NHP model at 4-weeks
- In another NHP study reported in the literature (San Sebastian 2014), procedure-related microscopic findings at 9 months included gliosis and vacuolated macrophages observed around the cannula tract

For a detailed discussion of the intraputamenal route of administration, please see Module 2.6.2, Section 2.6.2.2.2.

Review Comments:

Based on the summary of nonclinical animal data from 1144-015 and 1144-023, use of the SmartFlow cannula for intraputamenal administration of DP (b) (4) did not result in major/novel safety concerns related to the surgical procedure.

Defer to Clinical and P/T Review for comprehensive safety assessment of the surgical route of administration.

5. Device Compatibility Testing with Eladocogene Exuparvovec

The applicant summarizes their device compatibility testing with the eladocogene exuparvovec DP in Module 2.3.P.2. The applicant indicates that 4 device compatibility studies were completed for the eladocogene exuparvovec DP submission, which include: two quality compatibility studies (Study 1,2), one microbiological compatibility study (Study 3), and one dose accuracy study (Study 4).

The eladocogene exuparvovec DP lots and delivery devices used for these compatibility studies are tabulated, as follows:

Table 12. Overview of Device Compatibility Studies with Eladocogene Exuparvovec

Component	Material	Actual Study Components
-----------	----------	-------------------------

Eladocagene exuparovec DP lots	DP – (b) (4) <i>Fill Configuration – (b) (4) in 2 mL glass vial</i>	(b) (4)
Syringe pump	Syringe infusion pump compatible with imaging systems, capable of an infusion rate of 0.18 mL/hr (0.003 mL/min) and compatible with 1-mL or 5-mL syringes. The syringe pump does not come into direct contact with eladocagene exuparovec.	(b) (4)
Syringe	1-mL polycarbonate , or 5-mL or 10-mL polypropylene , Luer lock syringe with polypropylene plunger.	(b) (4)
Needle	19-gauge, 1.5-inch, stainless-steel , non-coring, 5-µm filter, hypodermic needle.	(b) (4)
Cannula	Magnetic resonance compatible cannula. Product-contacting surfaces are comprised of silica (internal lumen).	(b) (4) ClearPoint Neuro SmartFlow ventricular cannula: <ul style="list-style-type: none"> • CE-marked in EU • K102101 in US

Overall objective of DP-device compatibility studies:

- To ensure ability to administer DP as 4 separate infusions of 80 µL each at an infusion rate of 3 µL/min (i.e., dose accuracy)
- To ensure that representative administration systems (comprising all relevant device components) does not have an adverse impact on DP quality during the clinical administration workflow/procedure

DP quality attributes measured to assess compatibility:

- Vector (b) (4) for quantifying vector (b) (4) (Module 3.2.S.4.2)
- (b) (4) potency assay (b) (4) – measurement of (b) (4) (Module 3.2.S.3.1)
- (b) (4) (Module 3.2.S.4.2)
- Bioburden – (b) (4)

(b) (4)

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

Review Comments:

For applicant's DP-device compatibility Study 1, 2 –

- The applicant used process demonstration lots of eladocogene exuparvovec DP for the DP-device compatibility studies, which is stated to be representative of the commercial manufacturing process (i.e., Process C) – **this is acceptable for CBER Device, but defer to CMC Review to confirm.**
- The ClearPoint Neuro SmartFlow cannula used in these studies are the intraventricular cannulas cleared under K102101 – DEN240023 is the de novo request to update the labeling of these intraventricular cannulas with information to support intraparenchymal administration of eladocogene exuparvovec; the SmartFlow cannulas between K102101 and DEN240023 are largely identical except for minor design updates as part of the product development lifecycle – **this is acceptable** from a CBER Device perspective, since the SmartFlow models tested here are highly representative of the device models that will be cross-labeled; specifically, the tested cannula models will translate to NGS-NC-01 and NGS-NC-02 described in DEN240023.
- Additionally, the experimental design of studies of Study 1 + 2 enable the assessment of DP exposure to (b) (4) SmartFlow cannula models – **this is acceptable for CBER Device.**
- The parallel procedure utilized in Study 2 with 5 mL polypropylene syringes is **acceptable** for the purpose of evaluating DP compatibility with polypropylene.

For applicant's DP-device compatibility Study 3 – Use of the (b) (4) to assess microbiological compatibility (i.e., contamination potential) with the device system is **acceptable** – this is because the (b) (4) alone is sufficient to detect any possible microbiological growth (see CMC review confirming no bacteriostatic/fungistatic properties) and the presence of DP does not impact this aspect. The modification to assess an (b) (4) is **acceptable** for the purpose of determining DP-device microbiological compatibility.

For applicant's DP-device compatibility Study 4 – (b) (4) dose delivery accuracy (via (b) (4) measurement) is **acceptable** – this is because the DP contents do not impact (b) (4) analysis of delivered volumes for aqueous solutions. The use of

Overall, the applicant's experimental design for DP-device compatibility studies do not necessarily apply rigorous statistical methods for the prospective estimation of sample sizes based on estimated effect sizes; however, rigorous statistical approaches for demonstrating DP-device compatibility is not required (unlike for demonstrating DP comparability between manufacturing changes) – hence, the applicant's DP-device compatibility study designs are **acceptable for CBER Device.**

For DP quality assessment, the applicant only measured critical quality attributes related to adsorption, inactivation, and degradation of the eladocogene exuparvovec DP, i.e., (b) (4), bioburden – **this is**

acceptable from a CBER Device perspective, but defer to CMC for the assays used to assess device impact on these product quality attributes – IR COMMENT

- UPDATE (May 13, 2024; July 23, 2024) – RESOLVED; See response to IR#15 and Filing Letter Items (Appendix)

For the sampling of the DP for device compatibility testing, (b) (4)



– IR COMMENT

- UPDATE (May 13, 2024; July 23, 2024) – RESOLVED; See response to IR#15 and Filing Letter Items (Appendix)

Results for Study 1 – Quality Compatibility Study

- DP (b) (4)

Table 15. DP Vector Titer Results for Quality Compatibility Study

(b) (4)

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

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Review Comments:

For applicant's DP-device compatibility Study 1, 2 –

- For Study 1 + 2, the applicant's assessment of DP quality following exposure to the delivery device system indicated that the device components did not adversely impact DP critical quality attributes for the (b) (4) DP lots tested (representative of commercial process); specifically, the delivery device system did not reduce genome titer, did not degrade DP potency, and did not cause aggregation – **defer to CMC for review** of the analytical procedures for evaluating DP quality and for final assessment of DP attributes; **IR COMMENT – UPDATE (May 13, 2024; July 23, 2024) – RESOLVED; See response to IR#15 and Filing Letter Items (Appendix)**
- For Study 1 + 2, the applicant's internal control group (i.e., (b) (4))

noted above, this sampling approach would inadvertently neglect the initial impact of the syringe and filter needle materials on the DP during prep and relies on overall DP stability (defer to CMC review of DP stability); **IR COMMENT – UPDATE (May 13, 2024; July 23, 2024) – RESOLVED; See response to IR#15 and Filing Letter Items (Appendix)**

- For Study 1 + 2, the applicant's data indicate that (b) (4) Cannula models did not adversely impact measured DP quality attributes (comparing results for (b) (4)) – **this is acceptable for CBER Device.**

For applicant's DP-device compatibility Study 3, the applicant's data indicate no impact of delivery device system exposure to the DP on bioburden results – **this is acceptable for CBER Device.**

For applicant's DP-device compatibility Study 4, the applicant's data indicate approximately (b) (4) recovery of initial DP dose from the delivery device setup using the 5 mL syringe + compatible infusion pump and a dose accuracy of (b) (4) . The applicant's data also highlighted diminished dose accuracy (b) (4) with larger syringe sizes (i.e., 10 mL). Since smaller syringe sizes will be much more accurate when used with compatible syringe pumps, **the applicant's DP-device compatibility data support up to 5 mL syringe sizes** – general clinical practice recommends the selection of smallest reasonable syringe size for pediatric patients, which is per practice of medicine; doi: 10.1097/PCC.0b013e3181a0e2e9). **This is acceptable for CBER Device.**

Overall, the applicant's DP-device compatibility studies acceptably demonstrated DP compatibility with the following device materials and/or parameters:

- 1 mL and 5 mL syringe sizes; polypropylene or polycarbonate materials
- 19-gauge filter needle – stainless steel cannula, polycarbonate hub, (b) (4)
- (b) (4) SmartFlow cannula models (b) (4) gauge); with (b) (4) – NGS-NC-01, NGS-NC-02 were tested; however, models (b) (4) described in DEN240023 have technical specifications that are also covered by the DP-device
- Multiple infusion pumps (e.g., (b) (4)) with infusion rate of 0.003 mL/min

VI. Draft Labeling – DP Prescribing Information

The applicant's draft labeling document for Eladocadene exuparvovec includes the following statements pertaining to the route of administration and the delivery device(s):

- “Administer a total dose of 1.8×10^{11} vg (0.32 mL total volume) delivered as four 0.08 mL (0.45×10^{11} vg) infusions (two sites per putamen-anterior and posterior) at a rate of 0.003 mL/minute (0.18 mL/hour) for a total of 27 minutes per site, administered in a single stereotactic surgery using a cannula that is cleared by FDA for intraparenchymal infusion. (2.2, 2.4)”

- “Administer KEBILIDI only using an FDA-cleared cannula for intraparenchymal infusion (i.e., ClearPoint Neuro SmartFlow® Cannula Part Number NGS-NC-01-EE or NGS-NC-02-EE).”
- “Use of the syringe (i.e., connecting the syringe to the syringe pump and priming of the cannula) should begin within 6 hours of starting product thaw.”
- “KEBILIDI is intended to be administered with an infusion pump capable of infusing at a rate of 0.003 mL/min.”
“KEBILIDI is administered as four intraputamen infusions in a single stereotactic neurosurgical procedure as per the recommended dose shown in Table 1. “

Total Recommended Dose	1.8x10 ¹¹ vg (0.32 mL)
Total number of infusions	4
Volume (dose) per infusion	0.08 mL (0.45x10 ¹¹ vg)
Location of infusions	2 in anterior putamen, 2 in posterior putamen
Infusion rate at each target point	0.003 mL/min
Dose duration for infusion at each target point	27 minutes

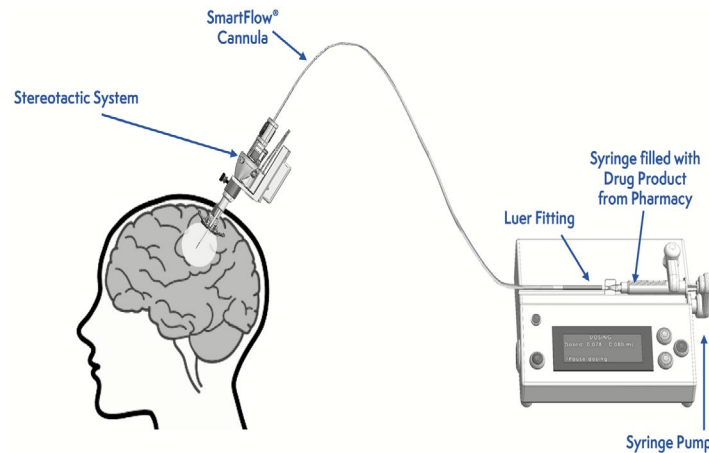
The items listed as supplies for administration in the draft labeling include:

- SmartFlow® Cannula
- Syringe pump, capable of an infusion rate of 0.003 mL/min and compatible with 1 mL or 5 mL syringe sizes
- Stereotactic system

Component	Material of Construction
1mL lubricated sterile Luer-lock syringe with elastomer plunger Or 5mL lubricated sterile Luer-lock syringe with elastomer plunger	Silicone, PC; Silicone, PP Silicone, PP
18 or 19 G sterile needle with 5µm filter	Stainless steel, PC hub; Stainless steel, PP hub
Sterile Luer-lock syringe cap	-
Plastic bag for delivery into surgical unit	-
Secondary container for delivery into surgical unit	-

Abbreviations: PC=Polycarbonate; PP=Polypropylene

Procedures for intraputamen administration are described in the draft labeling and only refer to the SmartFlow Cannula by brand name. Schematics depicting the administration setup are also provided:



In the original BLA submission, the applicant also provided foreign labeling for eladocagene exuparvovec (Upstaza) – relevant statements include the following:

- “Each vial is for single use only. This medicinal product should only be infused with the SmartFlow ventricular cannula.”
- Delivery device is referred to as the “intracranial cannula” or “infusion cannula”; other device components include:
 - “5-mL syringe [5 mL, polypropylene syringes with latex-free elastomer plunger, lubricated with medical-grade silicone oil]”
 - 18- or 19-gauge filter needle (1.5-inch, stainless steel, 5µm filter), syringe cap
 - Syringe pump – Upstaza is infused at a rate of 0.003 mL/min
- Listed additional risk mitigation measures include:
 - • Presence of or affiliation with a neurosurgeon experienced in stereotactic neurosurgeries and capable of administering Upstaza;
 - • Presence of a clinical pharmacy capable of handling and preparing adeno-associated virus vector-based gene therapy products;
 - • Ultra-low temperature freezers ($\leq -65^{\circ}\text{C}$) available within the treatment centre pharmacy for treatment storage.

The sponsor’s request for proprietary name review, UPSTAZA, also includes references to delivery device to be used with the drug product. Specifically, the request for proprietary name review includes an instruction for use section indicating that UPSTAZA can only be administered using the SmartFlow cannula.

Reviewer Comments:

This information was based on the version of the draft labeling dated October 29, 2024. Refer to the final version of the DP prescribing information.

It was determined during BLA review that the proprietary name for eladocagene exuparvovec will be KEBILIDI.

VII. Appendix – Information Requests

1. Response to IR # 18 (Device, SN0027) – August 2, 2024

1. *Although you are the owner of only the eladocogene exuparvovec gene therapy constituent of the combination product, your current good manufacturing practice (CGMP) operating system should take into account considerations for the combination product as a whole, as appropriate. You provide device information in Module 3.2.R for the cross-labeled SmartFlow Cannula device constituent and you cross-reference both (b) (4) and DEN240023 for relevant additional details. You also describe the minimum requirements for ancillary device components (stereotactic system, syringe pump, syringe, filter needle, syringe cap) required for administering eladocogene exuparvovec. However, you do not describe how your quality system for eladocogene exuparvovec ensures that the quality of the combination product as a whole is maintained. Please provide additional information in a revised Module 3.2.R to describe how your quality system ensures quality of the combination product as a whole, as well as ensuring all ancillary device components needed for product administration meet minimum performance requirements. For more information regarding application of CGMP requirements to combination products, please refer to FDA’s 2017 guidance “Current Good Manufacturing Practice Requirements for Combination Products” (<https://www.fda.gov/media/90425/download>).*

Applicant Response

PTC Therapeutics (PTC) is providing an updated Section 3.2.R.3 Device with this response. PTC’s established quality system, and adherence to cGMP, ensure the quality of the eladocogene exuparvovec combination product as a whole. PTC addresses “Question 1” in three parts:

- Part 1 will discuss the combination product – [key summary details]:
 - The SmartFlow Cannula is the only device that is specifically cross-labeled. Therefore, the cross-labeled combination product consists of only 2 “constituent parts” (as defined in the FDA guidance “Current Good Manufacturing Practice Requirements for Combination Products”): the eladocogene exuparvovec DP and the SmartFlow Cannula device.
 - Per the 2017 FDA guidance, constituent parts of cross-labeled combination products need only comply with the requirements otherwise applicable to that type of product. Consequently, PTC (as the responsible party for the eladocogene exuparvovec constituent part) conforms to drug cGMP and CLPT (as the manufacturer of the device constituent part) complies with the device quality system regulation and applicable International Organization for Standardization (ISO) standards.
 - The PTC quality system for eladocogene exuparvovec ensures that the quality of the combination product as a whole is maintained.... PTC takes into account considerations for the combination product through the PTC vendor management system which includes: Quality Technical Agreements (QTAs), risk-based vendor assessments, and audits.

- In summary, the QTA, risk-based vendor assessment, and audits serve to ensure that PTC's quality system adequately ensures the quality of the combination product as a whole.
- Part 2 will discuss the ancillary devices – [key summary details]:
 - Ancillary devices are cleared devices independent of the combination product – *As PTC is not the manufacturer of any of the ancillary devices, and as they are not constituent parts of the cross-labeled combination product, they do not fall under the purview of PTC's quality system.... However, PTC has described specific requirements in the USPI that the ancillary devices must meet when they are selected for use by the site administering the therapy.*
 - *USPI is a key instrument in ensuring minimum performance requirements are met – Clear instructions on dosing and administration of eladocogene exuparvovec are provided in the USPI. Requirements for the key attributes for the ancillary devices are described to clearly instruct the choice of these components. Specialized and highly trained surgeons perform the surgery....*
 - *Ultra-rare disease requiring specialized (ultra-competent) treatment centers – PTC has worked, and will work, extensively with the teams that will treat patients, providing education and contributing to training.... Representatives of PTC and CLPT will be present during mock surgeries and actual surgeries to provide any support that may be requested. The above provide assurance that the ancillary devices will be selected, handled, and ultimately used correctly, thereby helping ensure that minimum performance requirements are met.*
 - *Robust device compatibility studies have been carried out*
 - *A risk-based approach to ancillary devices – PTC commits to monitoring public sources of information (eg, company websites, FDA websites, etc) on a monthly basis to look for any pertinent and/or concerning information regarding the representative ancillary devices used by the specialized treatment centers (eg, recalls, parts changes, firmware updates, etc). PTC will conduct a risk assessment to determine the potential impact of these events. The assessment will inform any action that may be necessary.*
- Part 3 will replicate (for convenience) the updates made to Section 3.2.R.3 Device. These updates capture key elements discussed in Parts 1 and 2.

Reviewer of Response:

The applicant's response and updates to Module 3.2.R.3 indicate that PTC Therapeutics will have procedures and plans in place to ensure quality of the cross-labeled device constituent of the eladocogene exuparvovec combination product and the ancillary device components – PTC's overall quality system will also ensure that the DP and device components will remain compatible in accordance with the validated/qualified specifications reviewed under BLA 125722 and DEN240023.

The applicant's response also highlight that PTC is aware that they maintain overall responsibility for the eladocogene exuparvovec combination product as the BLA applicant.

The applicant also provides a Quality Technical Agreement that establishes quality responsibilities (and GMP compliance) of each constituent party and provides the necessary notifications to the other party in the event of any design/quality changes.

This response is **acceptable**.

2. *Your CGMP operating system should ensure consideration of whether manufacturing or design changes to one constituent part could affect performance and/or interaction with the other constituent part(s) and, if so, whether the safety and effectiveness of the combination product could be impacted. You should have procedures in place to be informed by both manufacturers of changes made to the individual constituent parts that may affect the safety or effectiveness of the cross-labeled combination product, and to confirm that the specifications for the respective constituent parts remain appropriate or are updated as needed to ensure that the combination product remains safe and effective. Quality agreements with constituent part manufacturer(s) are one way to ensure that changes to a constituent part are transparent to a combination product manufacturer or owner. Please submit the established quality agreement between you and the device constituent part manufacturer and confirm that it includes notification of any design changes that may affect the safety or effectiveness of the combination product.*

Applicant Response

The quality agreement between PTC and CLPT is provided with this response (ClearPoint Neuro PTC QTA – Medical Devices). The QTA establishes the responsibilities of each party to comply with all relevant Good Manufacturing regulations. PTC confirms that the QTA includes clear responsibilities for the notification of any design/manufacturing changes that may affect the safety or effectiveness of the combination product. The QTA includes a Design Control and a Change Control section. The Design Control process at CLPT feeds into the Change Control process such that any potential changes will undergo impact assessment and PTC will be notified, as described in the QTA. A summary of some of the pertinent sections of the QTA is provided in Table 1.

(b) (4)

Reviewer of Response:

The applicant also provides a Quality Technical Agreement that establishes quality responsibilities (and GMP compliance) of each constituent party and provides the necessary notifications to the other party in the event of any design/quality changes.

This response is **acceptable**.

2. Response to IR # 15 (CMC/Device, SN0022/SN0023) – July 23, 2024

1. *You have provided a description of the additional device compatibility study (Study 5) and the test results in an amendment (SN 0022) submitted on July 22, 2024, in response to the potential review issue #5 in the Filing Notification Letter. Please submit a finalized study report for device compatibility Study 5.*

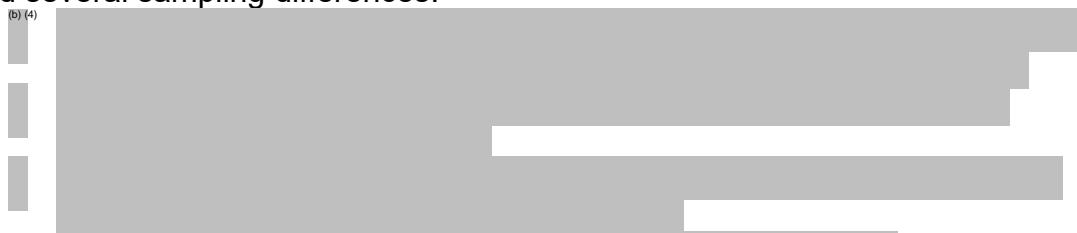
Applicant Response

The previously submitted device compatibility study report has been updated to include Study 5 data and is submitted for review (US AADC Summary of Eladocagene Exuparvovec In-use Commercial Delivery System Compatibility Studies). Following the submission of the Response to RSI – IR #10 - Q1 (SN 0022, submitted on 22Jul2024), additional data for a (b) (4) drug product (DP) lot (b) (4) has been obtained for (b) (4) endotoxin. These additional Study 5 data further support and confirm the conclusion as was described in Response to RSI – IR #10 - Q1 and previously submitted with DP (b) (4) data.

Procedure for Study 5 – Quality Compatibility 4

- New compatibility data collected using the (b) (4) assay is summarized in this section
- Study procedure mimics the procedures of DP-device compatibility Study 1+2, with the same experimental design differences from intended clinical procedure and several sampling differences:

(b) (4)



- Analytical methods included (b) (4) (Module 3.2.S.4.2), (b) (4) (Module 3.2.S.4.2), (b) (4) bacterial endotoxin test

Table 24. Device Components Evaluated with Eladocagene Exuparvovec for Compatibility Study 5

(b) (4)

1 page has been determined to be not releasable: (b)(4)

(b) (4)

Review of Response:

The applicant's additional DP-device compatibility Study 5 (i.e., Quality Compatibility Study 4) provides additional evidence to support eladocogene exuparvovec DP compatibility with the proposed intraputamenal administration delivery devices (and/or technical parameters). When combined with existing DP-device compatibility studies, the applicant's overall DP-device compatibility study data **acceptably demonstrate DP compatibility with the following device materials and/or parameters:**

- 1 mL and 5 mL syringe sizes; polypropylene or polycarbonate materials
- 19-gauge and 18-gauge filter needle – stainless steel cannula, polycarbonate hub, (b) (4)
- (b) (4) SmartFlow cannula models (b) (4) NGS-NC-01, NGS-NC-02 were tested; however, models (b) (4) described in DEN240023 have technical specifications that are also covered by the DP-device
- Multiple infusion pumps (e.g., (b) (4)) with infusion rate of 0.003 mL/min; compatibility of such infusion pumps with 1 mL and 5 mL syringes
- Bacterial endotoxin limits from both DP and device components meet threshold for (b) (4)

In SN0023, the applicant provides an updated DP-device compatibility study report (Document No. PROC-PTCHPW-00003 v3.0 | Approved Date: 25 Jul 2024) that incorporates the "Quality Compatibility Study 4" data – **additionally, CMC and Device collectively reviewed this compatibility study report as part of ICCR#00998901 from CDRH to support DEN240023; the CBER ICCR memo is attached to this memo.**

3. Response to IR # 10 (CMC/Device, SN0013) – June 25, 2024

In your May 31, 2024, response to the potential review issue # 5 in the Filing Notification Letter dated May 13, 2024, you indicate that you will redo the device compatibility testing using the (b) (4) assay. You also indicate that the test results will be provided by the end of July 2024. Please provide an update on when you will be able

to submit these data for our review. To facilitate our concurrent review and a contemporaneous decision for the De Novo application for the SmartFlow Cannula and the BLA for eladocagene exuparvovec, we request that you submit the new device compatibility data collected using the (b) (4) assay by July 22, 2024 or sooner, if possible. We also ask that you inform your device partner, ClearPoint Neuro, the date that you intend to submit the device compatibility data to the BLA such that the new data can be referenced during substantive review of the De Novo application.

Applicant Response

The testing for the device compatibility using the (b) (4) assay is currently ongoing. PTC Therapeutics agrees with a target submission date of 22 July 2024. Our device partner, ClearPoint Neuro, will be informed of the target submission date for the device compatibility data to the BLA for reference during the substantive review of the De Novo application.

Review of Response:

The applicant will be redoing the DP-device compatibility study using the (b) (4) assay (validated) for testing and plans to submit data for FDA review by the end of July 2024.

- **This information was received in SN0022/SN0023 on July 23, 2024, and reviewed by CMC and Device disciplines– see the review of IR response above.**

4. Response to Filing Letter Items (CMC/Device, SN0007) – May 13, 2024

1. *In the Application Orientation Meeting held on April 23, 2024, you indicated that ClearPoint Neuro, Inc. will submit the De Novo application for the SmartFlow cannula to the Center for Devices and Radiological Health (CDRH) in Q2 2024 to support the cross-labeling with eladocagene exuparvovec as a combination product in the BLA. Please be aware that the therapeutic product (i.e., eladocagene 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. Since the BLA has been submitted and is under a priority review, we are concerned that any potential delay in the De Novo submission and approval for the administration device could impact the timely approval of the BLA for the therapeutic product. We strongly urge you to work closely with your administration device partner to align with your submission timelines to permit adequate review time of the device submission in CDRH and to facilitate the contemporaneous approval of the BLA and the De Novo. Please submit the Letter of Authorization (LOA) enabling cross-reference to relevant information in the device submission as soon as feasible.*

Applicant Response

ClearPoint Neuro, Inc. submitted their De Novo 510 (k) Classification Request DEN240023 to CDRH on 22 May 2024. A Letter of Authorization from ClearPoint Neuro, Inc. enabling crossreference to DEN240023 is being provided with this submission. This

submission also includes the updated Statement of Right of Reference section 1.4.2 to include ClearPoint Neuro, Inc. De Novo 510 (k) Classification Request DEN240023.

Review of Response:

The de novo classification request to support cross-labeling of the SmartFlow cannula with eladocagene exuparvovec has been confirmed as received by CDRH on May 22, 2024, and is filed under DEN240023.

As part of this response, the applicant provided a signed LOA from ClearPoint Neuro to permit cross-reference to DEN240023 to support the review of BLA 125722. Since CDRH has jurisdictional purview over DEN240023, the CBER Device review team is coordinating with CDRH to align the review of DEN240023 for a contemporaneous regulatory decision to be made with BLA 125722.

The applicant's response is **acceptable** to resolve this item.

2. *You indicated during the April 10, 2024 Qsub meeting (240111) that you intend to provide a LOA to ClearPoint Neuro, Inc. to cross-reference the device compatibility data in the BLA to support their De Novo application for the SmartFlow Cannula. We have the following concerns regarding your device compatibility data provided in Section 3.2.P.2.6 of the BLA:*
 - a. *Based on the readout of the potency values (i.e., vg/cell) provided in Table 11, it appears that your device compatibility testing used the (b) (4) potency method instead of the current (b) (4) method. The potency data showed substantial variability (i.e., up to (b) (4) differences) among (b) (4), possibly due to the high variability of the (b) (4) method. Please redo the study using the (b) (4) method.*
 - b. *It appears that you intend to include syringes of two sizes (1 mL and 5 mL) and two materials (polycarbonate and polypropylene) as part of the general use approach for labeling. However, you only assessed product (b) (4)*
(b) (4) Please provide data to support product compatibility with 5 mL polycarbonate syringes.
 - c. *In our Additional Comment #3 in the Type C Meeting Summary dated November 3, 2022 and our Non-hold Comment #8cii in the Clinical Hold Letter dated April 22, 2020 for your IND 019653, we asked that the starting Drug Product (DP) material used for device compatibility testing (b) (4)*
(b) (4) DP lot used in the study and included in side-by-side testing. However, the (b) (4)
(b) (4) With this approach, you have not assessed the potential loss of product due to (b) (4)
(b) (4). Please explain why you did not include the (b) (4) in the testing and provide data to ensure that there is no substantial loss of (b) (4)
(b) (4) following exposure to the (b) (4) during product administration.
 - d. *Please submit your device compatibility study report to the BLA.*

Applicant Response

- a. PTC is redoing the study using the (b) (4) assay for testing. The (b) (4) results are expected to be provided by the end of July 2024.
- b. PTC initially considered qualifying syringes in both materials of construction (MOC), polypropylene and polycarbonate, to provide flexibility in sourcing of materials, hence the results of Study 1, Study 2, and Addendum to Study 2. However, in retrospect, the ubiquity of polypropylene syringes in hospital pharmacies (most 5 mL syringes are polypropylene) means PTC no longer sees the need to include polycarbonate MOC for the 5 mL syringe. Consequently, PTC will specify in the United States Prescribing Information (USPI) that the material of construction for 5 mL syringes is to be polypropylene.
- c. With regards to FDA's request to explain why PTC did not include the (b) (4) in the testing and provide data to ensure that there is no substantial (b) (4) during product administration, PTC will clarify DP sampling methods below and provide the supporting data. PTC notes that the control samples tested in the device compatibility studies were sampled from (b) (4). These samples were described as S1 in the IND 019653 and Section 3.2.P.2.6 of the BLA. (b) (4) are the methods used commonly to aliquot samples from DP vials. When the (b) (4) results for these S1 compatibility testing samples (taken from lots (b) (4)) are compared to (b) (4) stability data collected at (b) (4), it is clear that the results are comparable ie, within the variability of the assay (Table 10). Therefore, there does not appear to be any loss of product due to the (b) (4) method from the (b) (4) during device compatibility testing. Consequently, the (b) (4) samples can be considered to be equivalent to a sample derived from an (b) (4).
- d. The device compatibility report (Summary of Eladocagene Exuparvovec In-use Commercial Delivery System Compatibility Studies) is being provided with this submission.

(b) (4)

(b) (4)

Review of Response:

The applicant will be redoing the DP-device compatibility study using the (b) (4) assay (validated) for testing and plans to submit data for FDA review by the end of July 2024.

- **This information was received in SN0022/SN0023 on July 23, 2024, and reviewed by CMC and Device disciplines – see the review of IR response above.**

The applicant no longer sees a need to assess 5 mL polycarbonate syringes for DP compatibility and plans to remove this information from the DP prescribing information. This is also due to the ubiquity of polypropylene syringes (over polycarbonate syringes) – **this is acceptable; final prescribing information will be reviewed.**

In response to FDA comments requesting side-by-side testing with (b) (4) in DP-device compatibility tests, the applicant justifies that the (b) (4) samples are highly similar in (b) (4) compared to stability data from the same lots (that have (b) (4); Table 10) indicating (b) (4) – **this explanation is acceptable from a CBER Device perspective; defer also to CMC review for additional product quality perspective.**

The device compatibility report that the applicant provides is identical to the study report included in the original BLA submission.