

CMC REVIEW MEMO: GTB2/DGT1/OGT

ICCR Number:	00998901
De Novo Number:	DEN240023
De Novo Applicant:	ClearPoint Neuro
Device Information:	SmartFlow Neuro Cannula
Indications for Use	The SmartFlow Neuro Cannula is intended for intraputamenal administration of gene therapy eladocogene exuparvovec for the treatment of aromatic L-amino acid decarboxylase (AADC) deficiency.
De Novo Application Submission Date:	5/22/2024
Gene Therapy Product Information:	Eladocogene exuparvovec
BLA Number:	125722
BLA Submission Date:	3/15/2024
BLA Action Due Date:	11/13/2024
Device Compatibility Reviewer:	Bo Liang
CBER Device Reviewer:	Johnny Lam
CBER OTP/OGT/DGT1 Director:	Andrew Byrnes
Review Date:	7/23/2024
ICCR Due Date:	7/29/2024

Executive Summary:

This consult review is conducted to assess the device compatibility of eladocogene exuparvovec with SmartFlow Neuro Cannula to support CDRH's review of a De Novo application for the SmartFlow Neuro Cannula. The De Novo application is intended to support cross-labeling of SmartFlow Neuro Cannula as the designated administration device for eladocogene exuparvovec as a device/product combination product. Most device compatibility data were submitted in the original BLA submission. Additional device compatibility data were provided in an amendment to address potential concerns on the sampling strategy and assessment of product potency. These concerns have been resolved. The device compatibility studies are adequate to support intraputamenal administration of eladocogene exuparvovec using the SmartFlow Neuro Cannula.

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Background

The ClearPoint SmartFlow Neuro Cannula initially received 510(k) clearance K102101 in January 2011. The indications for use in the initial 510(k) clearance are intended for injection of Cytarabine or removal of CSF from the ventricles during intracranial procedures. The purpose of the De Novo submission is to gain FDA's approval of a new indication of the device for intraputamen administration of eladocogene exuparvovec, an adeno-associated virus (AAV) vector-based gene therapy product, to support cross-labeling of the SmartFlow Neuro Cannula and eladocogene exuparvovec as a combination product.

Eladocogene exuparvovec is a sterile, parenteral formulation containing a recombinant AAV serotype 2 (AAV2) vector with the human dopamine decarboxylase (DDC) gene that encodes the human aromatic L-amino acid decarboxylase (AADC). Eladocogene exuparvovec is injected into four sites of bilateral putamen using the SmartFlow Neuro Cannula following a stereotactic neurosurgical procedure, at a total dose of 1.8×10^{11} vector genome (vg) in a total volume of 320 μL , i.e., 80 μL per injection site, at an infusion rate of 3 $\mu\text{L}/\text{min}$.

Question for consult

Please review drug / device compatibility report to be provided by PTC Therapeutics in response to Issue 5 in BLA 125722 Filing Notification Letter.

Review

Product and device preparation and administration procedures:

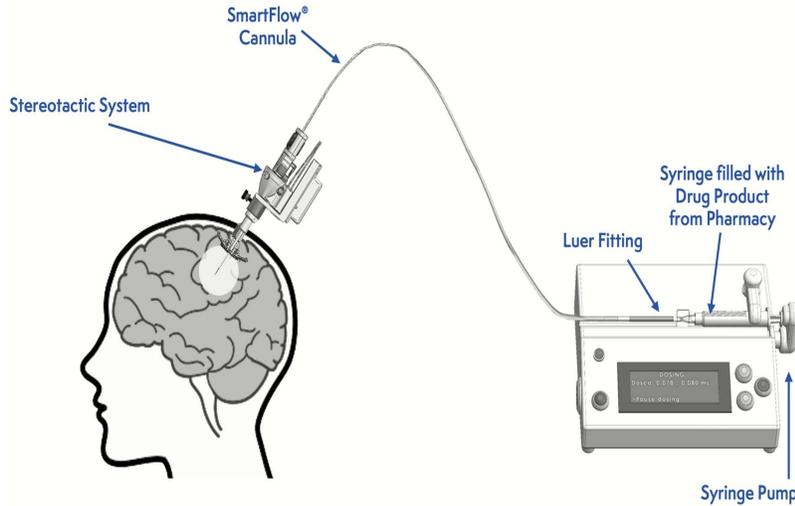
The draft eladocogene exuparvovec package insert (PI) contains information on administration device components, product preparation, and administration procedures are described. A summary of the information on device and product preparation/administration procedure is provided below.

Administration device:

The setup of the infusion delivery system is illustrated in Figure 1 below.

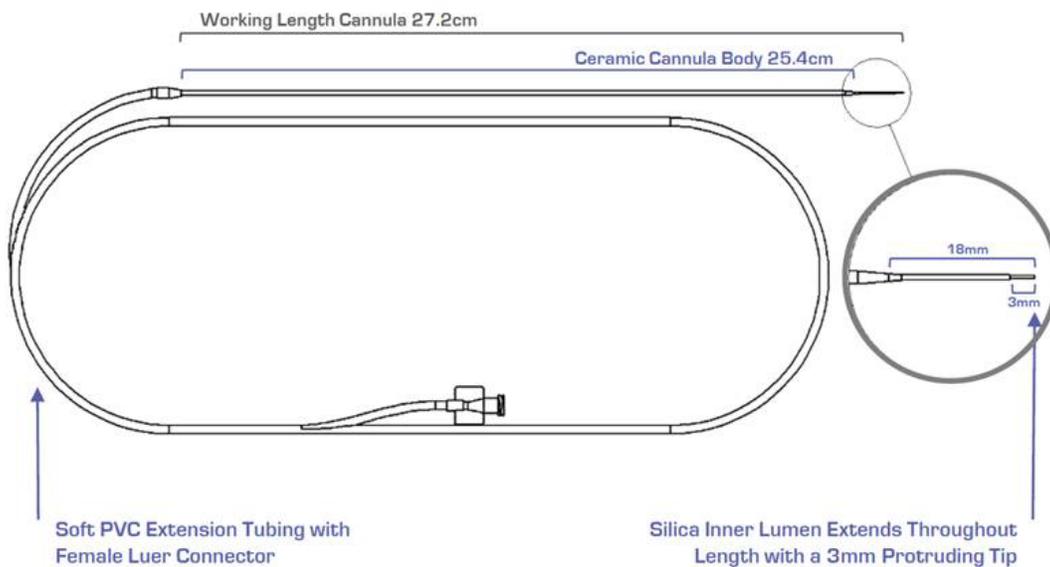
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Figure 1. Infusion delivery system



The draft PI specified two configurations of SmartFlow Cannula (Part Number NGS-NC-01 or NGS-NC-02) that can be used for product administration. Note that SmartFlow Cannula has numerous configurations of different sizes and parameters in design. An illustrative diagram for SmartFlow cannula system is provided in Figure 2. The two configurations of the SmartFlow system used in the compatibility testing are provided in Table 1.

Figure 2. Illustrative Diagram of SmartFlow Neuro Cannula



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Table 1. Summary of Cannula Dimensions Used for the Study

Outer Diameter			Inner Diameter		Tip Length	Cannula Body Length	Bore Length	Overall Length	Priming Volume
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

Reviewer comments: NGS-NC-01 is 16 ga, .008" ID x 4 ft x 15mm tip. NGS-NC-02 is 16 ga, .008" ID x 10 ft x 15mm tip. The only difference between NC-01 and 02 is the length. The device compatibility testing included both configurations. Note that the priming volume is different with different lengths. The priming volume was accounted for in the compatibility testing as priming at the defined infusion rate was part of the test procedure. This is acceptable.

According to draft product PI, 1 mL or 5 mL sterile Luer Lock polycarbonate or polypropylene syringe with elastomer plunger, lubricated with medical grade silicone oil and 18- or 19-gauge sterile needle with 5 µm filter are used for preparation and/or injection of the product.

Reviewer comments: The device compatibility testing only included 1 mL polycarbonate and polypropylene syringe and 5 mL polypropylene syringe. In response to an IR by CBER, PTC indicates that most 5 mL syringes in hospital pharmacy are polypropylene; therefore, there is no need to include 5 mL polycarbonate syringes in the testing. PTC also committed to specify in the PI labeling that the material of construction for 5 mL syringe should be polypropylene. This is acceptable.

In the draft PI labeling for the AAV product, there is no information on specific requirement for the syringe pump.

Reviewer comments: Specific information on selecting compatible syringe pump and syringe components for use with the SmartFlow cannula will be defined in labeling of the cannula under De Novo.

Preparation procedure (in the draft PI):

- Product vial is thawed at room temperature, which takes approximately 15 min.
- Thawed product is visually inspected for particulates, cloudiness, or discoloration and drawn into a syringe through a filter needle.
- Remove the needle and cap the syringe with a sterile Luer Lock syringe cap.
- Place the syringe in a sealed plastic bag.
- Place the sealed bag in a secondary container for delivery to the surgical suite at room temperature.
- Thawed product can be stored at room temperature for no more than 6 hours.

Administration procedure (in the draft PI):

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- Connect the syringe containing the product to the cannula.
- Load the syringe to the syringe pump.
- Prime the cannula at the rate of 3 μ L/min until the first drop of the product can be seen at the tip of the needle.
- Insert the cannula through a burr hole into the putamen and infuse 80 μ L at a rate of 3 μ L/min into the target site, which takes 27 minutes.
- After the first infusion, withdraw the cannula and then re-insert at the next site, repeating the same procedure for the other 3 sites.

Reviewer comments: In the device compatibility testing, the infusion time, hold, and the time needed for the insertion and withdraw of the cannula at four target sites were included in the study procedure. The flowrate used in the compatibility testing is the same as indicated in the PI.

Compatibility testing

A total of five studies were conducted to support the compatibility of eladocagene exuparvovec with the device. A report for the first four (4) studies was provided in the initial BLA submission. Study 5 was conducted after submission of the BLA to address FDA's review issue #5 conveyed in the BLA Filing Notification Letter dated May 13, 2024. A major issue addressed in Study 5 is assessment of product potency using a (b) (4)

- Study 1: Quality compatibility study 1
- Study 2: Quality compatibility study 2
- Study 3: Microbiological comparability study
- Study 4: Dose accuracy study
- Study 5: Additional quality comparability study

Table 2. Components Tested with Eladocagene Exuparvovec for Administration

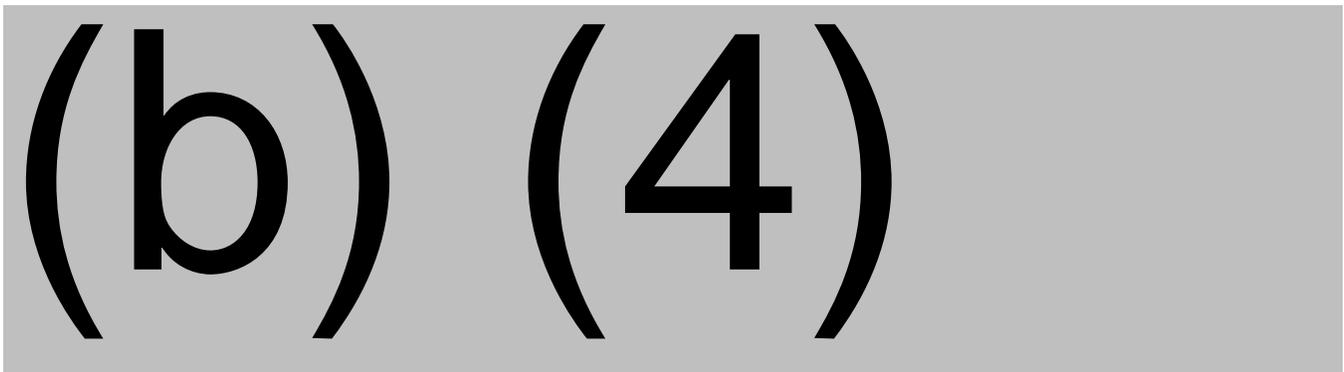
Component	Material	Actual Study Component Used
Syringe pump	Syringe infusion pump compatible with imaging systems, capable of an infusion rate of 0.18 mL/hr (0.003 mL/min) and compatible with 1-mL or 5-mL syringes. The syringe pump does not come into direct contact with eladocagene exuparvovec.	(b) (4)
Syringe	1-mL polycarbonate, or 5-mL (b) (4) polypropylene, Luer lock syringe with polypropylene plunger.	(b) (4)
Needle	19-gauge, 1.5-inch, stainless-steel, noncoring, 5- μ m filter, hypodermic needle.	(b) (4)

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		(b) (4)
Cannula	Magnetic resonance compatible cannula. Product-contacting surfaces are comprised of silica (internal lumen).	(b) (4)

The test articles used in the compatibility testing are process demonstration lots manufactured using the commercial manufacturing process (Study 1, 2, and 5), (b) (4) (Study 3), (b) (4) (Study 4) (Table 3).

Table 3. Eladocagene Exuparvovec (b) (4) Lots for In-Use Delivery System compatibility studies



Study 1

Study 1 was conducted following the procedure described in Table 4. This study included (b) (4)



Reviewer comments: The modifications of the administration procedure for compatibility testing are acceptable.

Table 4. Summary of Commercial Administration Procedure for the Quality Compatibility Study 1

Step	Procedure	Administrati on Duration (minutes)

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

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(b) (4)

Study 2

A second quality compatibility study, Study 2, was conducted to (b) (4)

The test procedure of Study 2 was similar to Study 1. (b) (4)

(b) (4)

(b) (4)

(b) (4)

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(b) (4)

Study 3

Study 3 was conducted using (b) (4) to assess the risk of the microbial contamination during product preparation and administration. The test procedure mimicked all steps of product preparation and infusion including the device components, hold duration, infusion flow rate, and volume of infusion. (b) (4)

Reviewer comment: This study and test result is acceptable. Risk of microbial contamination during administration using the device is adequately assessed.

Study 4

(b) (4)

(b) (4)

(b) (4)

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with the syringe size, indicating ability to choose interoperable device components. This is acceptable.

Study 5

PTC conducted Study 5 to address FDA's potential review issue #5 in the Filing Notification Letter. Potency was initially assessed in Study 2 using the (b) (4) [redacted], which was used during clinical development. The (b) (4) [redacted] assay was highly variable and deemed not suitable to assess the potency for commercial product. PTC has developed and validated a more precise (b) (4) [redacted] assay for commercial product. In the Filing Notification Letter, FDA asked PTC to re-do the compatibility study and use the (b) (4) [redacted] assay to evaluate the impact to potency after (b) (4) [redacted]

In the May 31, 2024 response (Amendment 6) to the comment in the Filing Notification Letter, PTC committed to re-do the device compatibility study using the (b) (4) [redacted] assay and submit the data by the end of July, 2024. To align with CDRH review timeline of substantive review decision date on August 5, 2024, CBER asked PTC (in an IR communicated on June 25, 2024) to submit the device compatibility data by July 22, 2024. PTC agreed and submitted a summary of the test procedures and results of Study 5 on July 22, 2024. The test procedure and results are summarized below.

Study 5 was also conducted mimicking the product administration procedure in the clinic. There are only (b) (4) [redacted] major differences compared to clinical procedure: (b) (4) [redacted]

Study 1 and Study 2, (b) (4) [redacted] product was drawn into (b) (4) [redacted] 5-mL polypropylene syringe, which is same as the clinical procedure. A summary of the administration procedure for Study 5 is shown in Table 8.

Table 8. Summary of Commercial Administration Procedure for the Quality Compatibility

Step	Procedure	Administration Duration (minutes)
(b) (4)	(b) (4)	Unlikely

(b) (4)

Reviewer comments: The (b) (4) data indicate that there was no detectable reduction of product potency following the administration of the product with (b) (4)

The (b) (4) The difference between (b) (4) is within the range of assay variability. These data in combination with the (b) (4) data and the (b) (4) assay potency data in Study 1 and Study 2 are adequate to demonstrate the compatibility of eladocagene exuparvovec with the product contacting device components that include SmartFlow Neuro Cannula, 1-mL and 5-mL polypropylene syringes, 1-mL polycarbonate syringe, 18-gauge and 19-gauge filter needles.

In addition, PTC also tested the level of (b) (4) samples according to (b) (4). The results indicated that (b) (4), which is within the DP specification of (b) (4) and also within the acceptable limit of (b) (4) specified by (b) (4).

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