

CBER CMC BLA Review Memorandum

BLA STN 125722

**eladocagene exuparvovec-tneq
KEBILIDI**

Reviewers

**Bo Liang, PhD, OTP/OGT/DGT1/GTB2
Susan Butler, PhD, OTP/OGT/DGT1/GTB1
Jacob Bitterman, PhD, OTP/OGT/DGT1/GTB3**

1. BLA#: STN 125722

2. APPLICANT NAME AND LICENSE NUMBER

PTC Therapeutics, Inc., License No. 2168

3. PRODUCT NAME/PRODUCT TYPE

- a. Non-Proprietary/Proper/USAN: eladocagene exuparvovec-tneq
- b. Proprietary Name: KEBILIDI
- c. Company codenames: (b) (4)-AADC, rAAV2-AADC, rAAV2-CMV-AADC, (b) (4)
- d. UNII Code: S51J6N56M7
- e. NDC Code (vial): 52856-601-011
NDC Code (carton): 52865-601-01
- f. Chemical Abstract Service Name (registry number): 2098615-91-7

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

- a. Pharmacological category: Adeno-associated virus vector-based gene therapy
- b. Dosage form: Suspension for injection
- c. Strength/Potency: 5.6×10^{11} vector genome (vg)/mL
- d. Route of administration: Intraputaminial infusion
- e. Indication(s): Treatment of adult and pediatric patients with aromatic L-amino acid decarboxylase (AADC) deficiency

5. MAJOR MILESTONES

- a. Received: March 15, 2024
- b. Filed: May 13, 2024
- c. Mid-cycle communication: July 8, 2024
- d. Late-cycle communication: August 29, 2024
- e. PDUFA action due: November 13, 2024

6. CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Bo Liang, PhD, OTP/OGT/DGT1/GTB2	Elucidation of structure, comparability, container closure system, formulation, device compatibility, labeling, clinical virus shedding and immunogenicity assays, environmental assessment
Susan Butler, PhD, OTP/OGT/DGT1/GTB1	Manufacturing process and process controls, process validation, process development, control of materials
Jacob Bitterman, PhD, OTP/OGT/DGT1/GTB3	Analytical methods, validation of analytical methods, justification of specification, batch analysis, stability, clinical CSF neurotransmitter assays
Johnny Lam, PhD, OTP/OCTHT/DCT1/CTTB	Product administration devices including SmartFlow cannula (ClearPoint Neuro), syringes, syringe pumps, and filter needles

Andrey Sarafanov, PhD, OTP/OPPT/DH/HB2	Extractable and leachables
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7. INTER-CENTER CONSULTS REQUESTED

Reviewer/Affiliation	Section/Topic	In agreement with consult recommendations (Yes/No)
Kyran Gibson CDRH/OHT3	Section 3.2.R.3: “General use” labeling approach for syringe pumps, syringes, and filter needles used for product preparation and administration in the clinic.	Yes
Gregg Kittlesen CDRH/OHT5	Section 3.2.R.3: Cross- labeling of the SmartFlow cannula used for product administration as supported by a De Novo application.	Yes

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/Status
03/15/2024	125722/0	Original submission
5/31/2024	125722/0.6	Response to IR #5 dated 5/22/2024
6/14/2024	125722/0.8	Response to IR #6 dated 6/6/2024
6/26/2024	125722/0.10	Response to IR #7 (part 1) dated 6/12/2024
6/27/2024	125722/0.12	Response to IR #10 (part 1) dated 6/25/2024
7/9/2024	125722/0.13	Response to IR #10 (part 2) dated 6/25/2024
7/12/2024	125722/0.17	Response to IR #13 dated 7/2/2024
7/22/2024	125722/0.20	Response to IR #14 dated 7/11/2024
7/22/2024	125722/0.21	Response to IR #10 (part 3) dated 6/25/2024
7/26/2024	125722/0.22	Response to IR #15 dated 7/23/2024
8/6/2024	125722/0.25	Response to IR #16 (part 1) dated 7/26/2024
8/9/2024	125722/0.26	Response to IR #18 dated 8/2/2024
8/12/2024	125722/0.27	Response to IR #19 dated 8/6/2024
8/15/2024	125722/0.28	Response to IR #7 (part 2) dated 6/12/2024
8/23/2024	125722/0.30	Response to IR #21 dated 8/16/2024
9/6/2024	125722/0.32	Response to IR #16 (part 2) dated 7/26/2024

9/23/2024	125722/0.40	Response to IR #27 dated 9/16/2024
9/24/2024	125722/0.41	Response to IR #31 dated 9/19/2024
9/25/2024	125722/0.42	Response to IR #26 dated 9/13/2024
9/30/2024	125722/0.46	Response to IR #33 dated 9/26/2024
10/4/2024	125722/0.48	Response to IRs #10, 16, 21, 22 (dated 9/29/2024), 27, and 31
10/7/2024	125722/0.49	Response to IR #36 dated 10/2/2024
10/8/2024	125722/0.50	Response to IR #37 dated 10/3//2024
10/11/2024	125722/0.51	Response to IR # 34 dated 10/1/2024
10/11/2024	125722/0.52	Response to IR # 38 (part 2) dated 10/9/2024
10/15/2024	125722/0.53	Response to IR # 38 (part 1) dated 10/9/2024
10/18/2024	125722/0.54	Response to IR #40 dated 10/15/2024
10/29/2024	125722/0.60	Response to IR #45 dated 10/25/2024
10/29/2024	125722/0.61	Response to IR #47 dated 10/25/2024
10/31/2024	125722/0.62	Response to IR #48 dated 10/28/2024

9. Referenced REGULATORY SUBMISSIONS

Submission Type & #	Holder	Referenced Item	LOA	Comments/Status
MAF # ^{(b) (4)} (510(k))	ClearPoint Neuro Inc.	SmartFlow Cannula	Yes	The device information is submitted in the BLA Section 3.2.R. A De Novo application to support cross-labeling has been submitted and reviewed by CDRH.
MF5 # ^{(b) (4)}	^{(b) (4)}	Platform analytical method validations	Yes	LOA is provided in Amendment 6 in response to IR #5. Assays performed by ^{(b) (4)} for in-process and lot release tests are listed in response to IR #5 Question 6 in Amendment 6 (Table 3). Validation of assays performed by ^{(b) (4)} are reviewed by OGT and DBSQC.

DMF (b) (4)	(b) (4)	Drug Product glass vial	Yes	No DMF review required, information pertinent to container closure is provided in the BLA.
DMF (b) (4)	(b) (4)	Drug Product vial stopper	Yes	No DMF review required, information pertinent to container closure is provided in the BLA.
DMF (b) (4)	(b) (4)	(b) (4) sterilization of the stoppers	Yes	No DMF review required, information pertinent to container closure is provided in the BLA.
DEN 240023	ClearPoint Neuro Inc	SmartFlow Cannula	Yes	De Novo application for SmartFlow Cannula for the new indication is review by CDRH.

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

Based on the review of the information provided in the initial submission and subsequent information requests received throughout the review period, the CMC review team concludes that the manufacturing and controls for eladocogene exuparvovec-tneq (KEBILIDI) are capable of yielding a product with consistent quality attributes deemed acceptable for commercial manufacturing under the BLA.

Description of the product

Eladocogene exuparvovec-tneq is a recombinant adeno-associated virus serotype 2 (AAV2) vector expressing human aromatic L-amino acid decarboxylase (AADC). The drug product is supplied as a sterile, frozen suspension containing eladocogene exuparvovec-tneq in a phosphate-buffered saline with 0.001% poloxamer 188 in a 2 mL borosilicate glass vial. The drug product is sterile and contains no preservative. It is stored frozen at $\leq -65^{\circ}\text{C}$. After product thaw, each vial contains an extractable volume of 0.5 mL, for a single dose only.

Manufacturing and quality

Eladocogene exuparvovec-tneq is produced by (b) (4)
adherent human embryonic kidney (b) (4) cells (HEK (b) (4) cells) (b) (4)

(b) (4)

To manufacture the drug product, (b) (4), filter sterilized, and filled into borosilicate glass vials. Each vial of drug product contains an extractable volume of 0.5 mL with a labeled nominal concentration of 5.6×10^{11} vg/mL. The drug product formulation also contains (b) (4) potassium chloride, (b) (4) potassium dihydrogen phosphate, 337.0 mM sodium chloride, (b) (4) disodium hydrogen phosphate, 0.001% (w/v) poloxamer 188, and Water for Injection. Finished drug product is 100% visually inspected, packaged, and frozen. Frozen vials are labeled (process validated), packaged individually into cartons, and stored frozen at ≤ -65 °C.

The manufacturing process is controlled by (1) raw material and reagent qualification programs, (2) in-process monitoring and in-process control testing, (3) validation of the manufacturing process, and (4) validated lot release tests. The manufacturer accepts raw materials based on verification of raw material specifications and routine in-coming acceptance tests. Suppliers are qualified and audited according to established supplier qualification programs. Raw materials derived from animals and humans are appropriately qualified to ensure the absence of microbial or viral contamination. The manufacturing process control strategy includes setting acceptable limits for process parameters and testing the in-process materials, drug substance, and drug product for microbial and vial contaminants, identity, purity, strength, and potency. (b) (4) drug product are controlled by lot release tests. These include quantitative assays that measure (b) (4) product potency, and process- and product-related impurities, etc. Potency is a measure of the capability of the product to (b) (4). All in-process and lot release assays are validated.

Drug substance and drug product manufacturing process validation included the production of (b) (4) process performance qualification (PPQ) lots at the (b) (4). Criticality of process parameters and attributes was determined through failure modes and effects analysis (FMEA). Operation ranges for process parameters and attributes were established by process development and process characterization studies. The controls of process parameters and process attributes were monitored on each PPQ run per process validation protocol. Selected operation ranges were tightened during process validation for improved process control. All (b) (4) PPQ batches met pre-defined acceptance criteria. Sanitary processing capability was

demonstrated by consistently meeting in-process (b) (4) acceptance criteria. Additional validation studies, including aseptic processing simulation and shipping validation studies, were also performed. Process consistency will continue to be monitored and assessed post-approval according to the continuing process validation (CPV) plan.

Stability

The drug substance is stable for (b) (4) when stored (b) (4). The drug product is stable for 48 months when stored frozen ($\leq -65^{\circ}\text{C}$). Once thawed, drug product can remain at ambient temperature for a maximum of 10 hours, including the time for preparation and infusion.

Comparability

Throughout clinical trials, the manufacturing process was changed twice. The current manufacturing process produces drug product deemed not comparable to those used in supportive clinical trials. However, the current manufacturing process was utilized to manufacture the product used in the pivotal clinical study and is the commercial process.

Combination product

KEBILIDI and the SmartFlow Neuro Cannula are a cross-labeled combination product. A De Novo classification request to support the use of the SmartFlow Neuro Cannula to deliver KEBILIDI submitted by ClearPoint Neuro was reviewed and granted by CDRH (DEN 240023). Specific models of SmartFlow cannula that should be used to administer KEBILIDI are described in the USPI of KEBILIDI. Other accessory administration device components, including the stereotactic system, syringe pump, syringe, and filter needles are labeled in the USPI as general use.

B. RECOMMENDATION

I. APPROVAL

This Biological License Application (BLA) provides an adequate description of the manufacturing process and characterization of the drug product eladocagene exuparvovec-tneq. The CMC review team has concluded that the manufacturing process and associated test methods and control measures can yield a product with consistent quality characteristics. This information, along with Post-Marketing Commitments (PMCs) from PTC Therapeutics, Inc., satisfies the CMC requirements for biological product licensure per the provision of section 351(a) of the Public Health Service (PHS) Act controlling the manufacture and sale of biological products.

Post-Marketing Commitments (PMCs)

PMC #1

PTC commits to reassessing the acceptance criteria for release testing of eladocagene exuparvovec drug substance and drug product based on manufacturing experience and revising the acceptance criteria, if appropriate. A final acceptance criteria reassessment report will be submitted as a “Postmarketing Study Commitment – Final Study Report” within 60 days after release (under either the European license or US license) of the 10th commercial batch.

Final study report submission: May 31, 2028

PMC #2

PTC commits to reevaluating the in-process acceptance criterion for the (b) (4) assay. PTC will submit the test results and revise the acceptance limit with justification based on the data as a Postmarketing Study Commitment – Final Study Report within 60 days after the 10th commercial batch is released under either the European license or US license.

Final study report submission: May 31, 2028

PMC #3

PTC commits to reevaluating the in-process acceptance limit for (b) (4) based on data from commercial batches tested using the (b) (4) from (b) (4). PTC will submit the test results and revise the acceptance limit with justification based on the data as a Postmarketing Study Commitment – Final Study Report within 60 days after release (under either the European license or US license) of the 10th commercial batch tested using the (b) (4) from (b) (4).

Final study report submission: May 31, 2028

PMC #4

PTC commits to perform additional robustness assessments for the (b) (4) assay, including variations in the number of (b) (4) and (b) (4). The final report will be submitted as a “Postmarketing Study Commitment – Final Study Report”.

Final study report submission: May 31, 2025

PMC #5 (Requested by Hsiaoling Wang, DBSQC/OCBQ)

PTC commits to re-assessing the accuracy, precision, and linearity of the (b) (4) (b) (4) assay to cover the range of (b) (4) and including at least (b) (4) or more data points for assessment of linearity. The updated assay validation report and the validation protocol will be submitted as a “Postmarketing Study Commitment – Final Study Report”.

Final study report submission: May 31, 2025

PMC #6 (Requested by Yen Phan, DBSQC/OCBQ)

PTC commits to evaluating suitability with (b) (4) as environmental isolates post-BLA approval/PMC to provide additional assurance your sterility test method can detect this known environmental isolate in addition to the indicated USP microorganisms.

Final qualification suitability will be submitted to CBER in Annual Report on January 31, 2026.

II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Bo Liang Staff Fellow; OTP/OGT/DGT1/GTB2	Concur	
Jacob Bitterman Biological Reviewer; OTP/OGT/DGT1/GTB3	Concur	
Susan Butler Staff Fellow; OTP/OGT/DGT1/GTB1	Concur	
Andrew Byrnes Division Director; OTP/OGT/DGT1	Concur	
Denise Gavin Office Director; OTP/OGT	Concur	

Review of CTD

Table of Contents

1. BLA#: STN 125722.....	i
2. APPLICANT NAME AND LICENSE NUMBER.....	i
3. PRODUCT NAME/PRODUCT TYPE	i
4. GENERAL DESCRIPTION OF THE FINAL PRODUCT	i
5. MAJOR MILESTONES	i
6. CMC/QUALITY REVIEW TEAM	i
7. INTER-CENTER CONSULTS REQUESTED	ii
8. SUBMISSION(S) REVIEWED	ii
9. Referenced REGULATORY SUBMISSIONS.....	iii
10. REVIEWER SUMMARY AND RECOMMENDATION	iv
A. EXECUTIVE SUMMARY.....	iv
B. RECOMMENDATION	vi
I. APPROVAL.....	vi
II. SIGNATURE BLOCK	viii
Module 3	15
3.2.S DRUG SUBSTANCE	15
3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties	15
3.2.S.2 Manufacture	16
3.2.S.2.1 Manufacturer(s).....	16
3.2.S.2.2 Description of Manufacturing Process.....	18
3.2.S.2.3 Control of Materials	21
3.2.S.2.4 Controls of Critical Steps and Intermediates	30
3.2.S.2.5 Process Validation and/or Evaluation.....	41
3.2.S.2.6 Manufacturing Process Development.....	52
3.2.S.3 Characterization	58
3.2.S.3.1 Elucidation of Structure and Other Characteristics.....	58
3.2.S.3.2 Impurities.....	63
3.2.S.4 Control of Drug Substance	65
3.2.S.4.1 Specification(s) and 3.2.S.4.5 Justification of Specification(s)	65
3.2.S.4.5 Justification of Specifications	66
3.2.S.4.2 Analytical Procedures and 3.2.S.4.3 Validation of Analytical Procedures.....	75
3.2.S.4.4 Batch Analyses.....	94
3.2.S.5 Reference Standards or Materials	94
3.2.S.6 Container Closure System.....	100
3.2.S.7 Stability.....	101
3.2.S.7.1 Stability Summary and Conclusion and 3.2.S.7.3 Stability Data	101
3.2.S.7.2 Post-Approval Stability Protocol and Stability Commitment	106
3.2.P DRUG PRODUCT.....	107
3.2.P.1 Description and Composition of the Drug Product.....	107
3.2.P.2 Pharmaceutical Development.....	109
3.2.P.2.1 Components of the Drug Product	109
3.2.P.2.2 Drug Product	109
3.2.P.2.2.2 Overages	110

3.2.P.2.3 Manufacturing Process Development.....	111
3.2.P.2.4 Container Closure System	121
3.2.P.2.5 Microbiological Attributes	122
3.2.P.2.6 Compatibility	123
3.2.P.3 Manufacture	128
3.2.P.3.1 Manufacturer(s).....	129
3.2.P.3.2 Batch Formula	129
3.2.P.3.3 Description of Manufacturing Process.....	130
3.2.P.3.4 Controls of Critical Steps and Intermediates	133
3.2.P.3.5 Process Validation and/or Evaluation.....	134
3.2.P.4 Control of Excipients	139
3.2.P.4.1 Specifications	140
3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures	140
3.2.P.4.4 Justification of Specifications	140
3.2.P.4.5 Excipients of Human or Animal Origin.....	140
3.2.P.4.6 Novel Excipient.....	140
3.2.P.5 Control of Drug Product.....	140
3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s).....	140
3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures	147
3.2.P.5.4 Batch Analyses.....	147
3.2.P.5.5 Characterization of Impurities.....	148
3.2.P.6 Reference Standards or Materials.....	148
3.2.P.7 Container Closure System.....	148
3.2.P.7.1. Primary Container	148
3.2.P.7.2 Secondary container	149
3.2.P.8 Stability.....	150
3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data	150
3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment	156
3.2.A APPENDICES.....	157
3.2.A.1 Facilities and Equipment	157
3.2.A.2 Adventitious Agents Safety Evaluation	157
3.2.A.3 Novel Excipients.....	160
3.2.R Regional Information (USA).....	160
Executed Batch Records	160
Method Validation Package	161
Combination Products	161
Comparability Protocols.....	162
Other eCTD Modules	162
Module 1	162
A. Environmental Assessment or Claim of Categorical Exclusion	162
B. Reference Product Designation Request	162
C. Labeling Review.....	162
Full Prescribing Information (PI):	162
Carton and Container Label:.....	164

Modules 4 and 5	165
5.3.1 Analytical Procedures and Validation of Analytical Procedures for Assessment of Clinical and Animal Study Endpoints	165
Neurotransmitter Metabolites in CSF	165
qPCR assay for detection of vector in patient samples	168
(b) (4) detection of anti-drug antibodies against AAV2 in juvenile human serum ..	171
Cell-based assay for detection of anti-AAV2 neutralizing antibodies in juvenile human serum.....	173
Cell-based assay to measure AAV2 neutralizing antibodies in human serum samples (used in supportive studies)	175
(b) (4) assay to detect immune activation to AAV2 capsid and AADC transgene in primary human PBMCs	176
Quantification of AAV2-hAADC viral vector in human blood and urine using (b) (4) (used in supportive studies).....	178
Quantification of anti-AAV2 antibodies in human serum using (b) (4) (used in supportive studies)	178

List of Tables

Table 1. Nomenclature	15
Table 2. Active genetic elements of the (b) (4)	16
Table 3. Manufacturers of Eladocagene Exuparvovec Drug Substance	16
Table 4. (b) (4) Specifications	21
Table 5. Characterization of (b) (4)	24
Table 6. (b) (4)	25
Table 7. Characterization of (b) (4)	27
Table 8. DS In-Process Control Strategy: (b) (4)	32
Table 9. CPAs Monitored	33
Table 10. Critical Process Parameters Identified in DS Manufacture	35
Table 11. Analytical Method and Validation Details for In-Process Controls for the Drug Substance	37
Table 12. Revisions Made in the Process Control Strategy in DS Manufacturing Process during PPQ.....	43
Table 13. Drug Substance Release Results for PPQ Runs.....	47
Table 14. Historical Data Runs Used for In-Process Studies/Limits	52
Table 15. Comparison of the (b) (4) Methods.....	55
Table 16. Comparison of the (b) (4) Methods.....	56
Table 17. Comparison of Validation Parameters	56
Table 18. (b) (4)	57
Table 19. (b) (4) Study Results	58
Table 20. Analytical methods used in characterization studies.	58
Table 21. Summary Of (b) (4) Data	61
Table 22. Summary Results of (b) (4) Analysis by (b) (4)	62

Table 23. (b) (4) Assay Results	62
Table 24. (b) (4) Potency Results.....	63
Table 25. Drug Substance Specifications.....	65
Table 26. Summary of Batches Included to Support the Drug Substance Specifications	66
Table 27. Validation of (b) (4) Assay	76
Table 28. Validation of (b) (4) Assay.....	79
Table 29. Validation of (b) (4) Assay for In-Process Controls	81
Table 30. Qualification of (b) (4) Assay for (b) (4)	81
Table 31. Validation of (b) (4) Assay.....	83
Table 32. Validation of (b) (4) Assay	86
Table 33. Validation of (b) (4) Assay	90
Table 34. Validation of General rcAAV Procedure	92
Table 35. Product Specific Validation of rcAAV Assay	93
Table 36. Summary of DS Batches	94
Table 37. Qualification Results for (b) (4) ..	95
Table 38. Qualification Results for (b) (4)	97
Table 39. Qualification Results for (b) (4)	98
Table 40. Characterization Tests for the Qualification of Future Reference Standard Lots	99
Table 41. Summary of DS Stability Batches and Stability Studies	102
Table 42. DS Stability Specifications.....	102
Table 43. (b) (4) Stability Results.....	105
Table 44. (b) (4)	106
Table 45. DS Post-Approval Stability Testing Plan	107
Table 46. Quantitative Composition of Drug Product	108
Table 47. Comparison of Nonclinical/Clinical and Commercial Eladocagene Exuparvovec Drug Product Formulations.....	109
Table 48. Target And Actual Vg (b) (4) Of PPQ And Commercial Launch Lots	111
Table 49. Fill Weight Statistics	113
Table 50. Batches manufactured using Processes A, B, and C.....	116
Table 51. Analytical comparability assessment based on lot release assays.....	117
Table 52. Analytical comparability assessment based on characterization assays.....	118
Table 53. (b) (4) results from (b) (4)	119
Table 54. Components and Materials Used in Device Compatibility Studies	125
Table 55. Vector (b) (4) Results from Study 1.....	126
Table 56. (b) (4) Results from Study 5	128
Table 57. Manufacturer(s) of Drug Product	129
Table 58. Representative Batch Formula for Drug Product.....	130

Table 59. Critical Process Parameters and Critical Process Attributes for Drug Product	133
Table 60. Revisions Made in the Process Control Strategy During DP PPQ	136
Table 61. Drug Product Release Test Results	138
Table 62. Specifications for (b) (4) Excipients.....	140
Table 63. Drug Product Release Specifications	140
Table 64. Summary of DP Vector (b) (4) and DP Release Results	143
Table 65. Statistical Analysis of DP Vector (b) (4) Release and Stability Data	144
Table 66. (b) (4) Results for Process B and Process C batches	146
Table 67. Summary of DP Lots	147
Table 68. Components of DP container closure system.....	148
Table 69. Summary of DP Stability Studies.....	150
Table 70. Attributes and Acceptance Criteria for DP Stability Testing.....	151
Table 71. DP Post-Approval Stability Testing Protocol.....	157
Table 72. Summary of Log Reduction	159
Table 73. Validation of (b) (4) Assay for Neurotransmitter Metabolites in CSF ...	166
Table 74. Validation of (b) (4) Assay for Neurotransmitter Metabolites in CSF ...	167
Table 75. Summary of Validation Results for the qPCR Assay	169
Table 76. Summary of Validation Results for Total Anti-AAV2 Assay	172
Table 77. Summary of Validation Results for Anti-AAV2 Neutralizing Antibody Assay	175
Table 78. Summary of Validation Results for (b) (4) Assay	177

List of Figures

Figure 1. Diagram of Eladocagene Exuparvovec (b) (4)	15
Figure 2. Drug Substance Manufacturing Process Diagram	18
Figure 3. AAV Transgene Plasmid (b) (4)	23
Figure 4. AAV Capsid (b) (4)	24
Figure 5. (b) (4)	30
Figure 6. Classification and Hierarchy of Process Parameters and Attributes	31
Figure 7. Overview of Process Control Strategy	42
Figure 8. AVB Statistical Results - (b) (4)	54
Figure 9. (b) (4) Statistical Results - (b) (4) Potency at (b) (4)	54
Figure 10. (b) (4)	60
Figure 11. (b) (4) and Results for Process Performance Qualification Batch (b) (4)	61
Figure 12. Justification of DS (b) (4)	68
Figure 13. Justification of DS (b) (4)	69
Figure 14. Justification of Specifications for DS (b) (4)	70
Figure 15. Justification of Specification for DS (b) (4)	71

Figure 16. Justification of Specifications for (b) (4)	71
Figure 17. Justification of Specifications for (b) (4)	72
Figure 18. Justification of Specifications for (b) (4)	72
Figure 19. Justification of Specification for (b) (4)	73
Figure 20. Justification of Specification for (b) (4)	73
Figure 21. Stability Analysis of DS (b) (4)	103
Figure 22. Stability Analysis of DS (b) (4)	104
Figure 23. Stability Analysis of DS (b) (4)	104
Figure 24. Content Uniformity Results - Normalized Values	113
Figure 25. An illustrative diagram of SmartFlow Neuro Cannula	124
Figure 26. Infusion delivery system	124
Figure 27. Overall Drug Product Manufacturing Flow Diagram	131
Figure 28. Justification of (b) (4)	141
Figure 29. Justification of Specification for (b) (4)	142
Figure 30. Justification of Specifications for DP Capsid (b) (4)	143
Figure 31. Justification of Specifications for (b) (4)	145
Figure 32. DP Vector Genome (b) (4) Stability Data	153
Figure 33. DP (b) (4) Stability Data	153
Figure 34. DP (b) (4) Potency Data	154
Figure 35. DP (b) (4) Potency Data	154
Figure 36. DP Capsid (b) (4) Stability Data	155


Module 3

3.2.S DRUG SUBSTANCE


3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties

(Reviewed by BL)


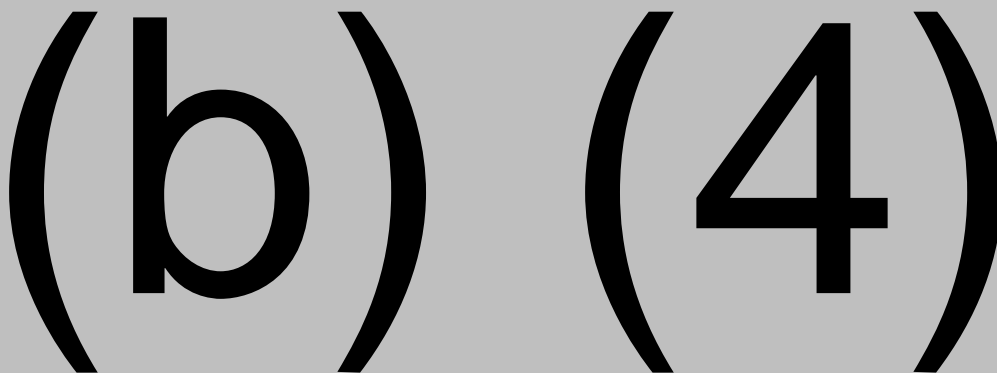
(b) (4)

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(b) (4)

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3.2.P DRUG PRODUCT

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

(Reviewed by BL)

The Drug Product (DP) of eladocagene exuparvovec-tneq is a sterile, clear to slightly opaque, colorless to faint-white solution, packaged in a single-dose 2-mL Type (b) (4) borosilicate glass vial. The DP vial stopped with a siliconized, 13-mm chlorobutyl stopper with (b) (4) and sealed with a 13-mm aluminum/plastic (b) (4) cap.

The DP is formulated at a target vector genome (vg) concentration of (b) (4) in a solution consisting of (b) (4) potassium chloride (KCl), (b) (4) potassium dihydrogen phosphate (KH_2PO_4), 337.0 mM sodium chloride (NaCl), (b) (4) disodium hydrogen phosphate (Na_2HPO_4), and 0.001% (w/v) poloxamer 188 in Water for Injection (WFI) with (b) (4). The quantitative composition of the DP in different unit formats is shown in Table 46.

The DP label indicates that each vial of DP contains an extractable volume of 0.5 mL with a total of 2.8×10^{11} vector genome copies, with a vg concentration of 5.6×10^{11}

vg/mL, ensuring delivery of a single dose of 1.8×10^{11} vg in a total dose volume of 0.32 mL.

DP has an (b) (4), as it is formulated at a vg concentration (i.e., (b) (4) vg/mL) (b) (4) than the labeled concentration (i.e., 5.6×10^{11} vg/mL) to account for the variability of the assay and manufacturing process.

Reviewer's Comments: This (b) (4) is deemed acceptable. Please refer to the discussion in 3.2.P.2.2.2 (b) (4).

The labeled extractable volume is 0.5 mL. But the target fill volume for DP is (b) (4) mL, with an (b) (4) the label claim.

Reviewer's Comments: The target filled volume is (b) (4) the recommended (b) (4) volume of (b) (4) for a label claim volume of 0.5 mL according to (b) (4). Considering the relatively small volume of administration, (b) (4) and that this product will be administered by experienced neurosurgeons, the chance of overdosing (b) (4) is low. This is acceptable.

Table 46. Quantitative Composition of Drug Product

Component	Quality standard	Function	mg/mL	mM	mg/unit ^a	mg/dose ^b
Eladocagene exuparvovec	In-house	Active substance	(b) (4)	N/A	(b) (4)	(b) (4)
KCl	(b) (4)	Buffer/stabilizer tonicity	(b) (4)	(b) (4)	(b) (4)	(b) (4)
KH ₂ PO ₄	(b) (4)	Buffer/stabilizer tonicity	(b) (4)	(b) (4)	(b) (4)	(b) (4)
NaCl	(b) (4)	Buffer/stabilizer tonicity	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Na ₂ HPO ₄	(b) (4)	Buffer/stabilizer tonicity	(b) (4)	(b) (4)	(b) (4)	(b) (4)
poloxamer 188	(b) (4)	Manufacturing aid, non-ionic surfactant	0.01	N/A	(b) (4)	(b) (4)
WFI	(b) (4)	Solvent	Q.S	N/A	Q.S	Q.S

^a Based on extractable volume of 0.5 mL.

^b Based on a dose volume of (b) (4).

^c Note that these values are different compared to labeled values in the initial version of the USPI due to the (b) (4) in DP formulation.

N/A: not applicable

Q.S.: quantum satis (the amount that is sufficient)

(b) (4)

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

(Reviewed by BL)

3.2.P.2.1.1 Drug Substance

(b) (4)

3.2.P.2.1.2 Excipients

Excipients used in DP formulation, their respective monographs, and functions are described in Table 46. No excipients of human or animal origin are used. Compatibility of DS with excipients is demonstrated by DS and DP stability data.

3.2.P.2.2 Drug Product

(Reviewed by BL)

3.2.P.2.2.1 Formulation Development

Eladocagene exuparvovec-tneq DP is formulated in a hypertonic, phosphate buffer solution with (b) (4) and a non-ionic surfactant (Table 46). None of the excipients in DP formulation are novel. The commercial DP formulation was developed based on the formulation of Process B Lot 2004-101 that was used in supportive clinical studies AADC-010 and AADC-011, as well as a GLP toxicology study AADC-003 (Table 47).

(b) (4)

poloxamer 188 to prevent adsorption and aggregation during manufacturing process. Except for poloxamer 188 and KH_2PO_4 , the amount of each excipient in the formulation for commercial eladocagene exuparvovec is (b) (4)-fold (b) (4) compared to that in other FDA approved medicinal products (i.e., Brineura, Spinraza, and Cytarabine) administered through intraventricular or intrathecal route.

Table 47. Comparison of Nonclinical/Clinical and Commercial Eladocagene Exuparvovec Drug Product Formulations

Component (CAS #)	Lot PBR-0045-001, Process A (AADC-1601)		Lot 2004-101, Process B (AADC-003 ^a , AADC-010, AADC- 011)		Commercial, Process C (PTC-AADC-GT-002)	
Concentration	mM	mg/mL	mM	mg/mL	mM	mg/mL

KCl (b) (4)	(b) (4)						
NaCl (b) (4)	(b) (4)			337.0	(b) (4)	337.0	(b) (4)
KH ₂ PO ₄ (b) (4)	(b) (4)						
Na ₂ HPO ₄ , (b) (4)	(b) (4)						
Poloxamer 188 (b) (4)	(b) (4)						0.01
(b) (4)	(b) (4)						

^a 6-month GLA toxicology study

NA: not applicable

3.2.P.2.2.2 Overages

DP has (b) (4), as it is formulated at a target concentration of (b) (4), which is (b) (4) than the labeled concentration of 5.6×10^{11} vg/mL.

Reviewer's comments: In IR #7 sent on 6/12/2024, we asked the Applicant for a rationale for the (b) (4). In Amendment 10 submitted on 6/26/2024, the Applicant clarified that the target (b) (4) was set (b) (4) than the label claim to account for (b) (4) (b) (4) and did not represent (b) (4). They also indicated that PPQ (b) (4) lot targeted a vg concentration of (b) (4) and the other (b) (4) PPQ lots targeted (b) (4) (Table 48). However, PPQ (b) (4) before administration, and there will be (b) (4) step for administration of commercial product. For the commercial product, because there is (b) (4) will result in a (b) (4) dose than labeled.

This issue was further discussed with the Applicant at the mid-cycle meeting (CMC Discussion Topic a.). During the mid-cycle meeting, we asked whether the Applicant had investigated the source of process variability. The Applicant indicated that there was nothing with the process that contributed to the variability; it was mainly due to (b) (4). The Applicant further clarified that they have improved the assay precision by testing (b) (4) (Note: For the (b) (4) assay used for lot release, there are (b) (4) sample (b) (4) In Amendment 20 submitted on 7/22/2024 in response to a follow-up IR #14 sent on 7/11/2024, the Applicant indicated that the change of vg (b) (4) assay for (b) (4) was implemented from PPQ (b) (4) Table 48). Based on data provided in Amendment 10 and Amendment 20 and additional data from (b) (4) post-PPQ lots (b) (4) requested during Pre-License Inspection, this approach did result in the manufacturing process meeting the target (b) (4) more closely than before (Table 48). Considering that the process has been improved to meet the target titer of (b) (4) more closely, we recommended in IR #21 sent on 8/16/2024 before the late-cycle meeting that the Applicant tighten the upper limit of the acceptance criterion from their initially proposed (b) (4), so that the final DP titer would not (b) (4) of

the labeled titer of 5.6×10^{11} vg/mL. Because the (b) (4) lot release assay is (b) (4), the tightened upper limit of the DP lot release AC would be (b) (4) of the labeled concentration. In Amendment 30, the Applicant agreed to narrow the upper limit of DP lot release specification to (b) (4).

Considering the improved (b) (4) process, the variability of lot release assay, and the narrowed acceptance criterion, the (b) (4) of DP target of (b) (4) the label claim is acceptable. The concentration of DP will be (b) (4) of the label claim of 5.6×10^{11} vg/mL, which is reasonable.

Table 48. Target And Actual Vg (b) (4) Of PPQ And Commercial Launch Lots

DP Lot	Targeted Vector (b) (4) (vg/mL)	Actual vector (b) (4) (vg/mL)	%Difference compared to target (b) (4)	%Difference compared to label claim 5.6×10^{11} vg/mL
(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)	(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)

3.2.P.2.2.3 Physicochemical and Biological Properties

The DP is identical to (b) (4), if needed. The physicochemical and biological properties of the DP are the same as those described for (b) (4) in 3.2.S.3 Characterization.

3.2.P.2.3 Manufacturing Process Development

(Reviewed by SB [sections 1-4] and BL [section 5])

3.2.P.2.3.1 DP Manufacturing Overview

Three different processes were used during clinical trials and the comparability of these processes is commented on more in depth in 3.2.P.2.6 Compatibility. The pivotal clinical material and commercial process are called Process C.

3.2.P.2.3.2 – 3.2.P.2.3.3 Definition and Development of DP Process Control Strategy

As done with the (b) (4), the applicant used a criticality hierarchy to ensure consistent monitoring and control of the DP process shown in Table 59 below. Process

Parameters are aspects of the process that should be within an appropriate limit, range, or distribution to ensure desired product quality in accordance with ICH Q8(R2). From historical manufacturing data these elements were divided into critical (CPPs) or non-critical (key process parameters (KPPs) or monitored process parameters (MPPs)) using a similar FMEA risk assessment as detailed 3.2.S.2.4 Controls of Critical Steps and Intermediates for (b) (4) manufacture. The resultant critical process parameters and critical process attributes are detailed in 3.2.P.3.4 Control of Critical Steps and Intermediates Table 59.

3.2.P.2.3.4 Process Development

(b) (4) studies were conducted for the DP manufacturing's process's effects on (b) (4). These and the DP (b) (4) evaluation study are reviewed below.

(b) (4)

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

Therefore, the analytical comparability of Process A, Process B, or Process C is not established.

3.2.P.2.3.6 Extractables and Leachables Study of Product Contact Materials

In the original submission, the Applicant conducted risk assessment on extractables from all product contact materials used in product manufacturing using extractable data from vendors. During filing review, Andrey Sarafanov (OTP/OPPT) determined that the leachable/extractable data were not adequate, and that additional leachable study should be conducted. Request of additional leachable study was communicated in the Filing Notification Letter dated 5/13/2024 and was followed-up in IR #5 dated 5/22/2024, IR #14 dated 7/11/2024, and IR #31 dated 9/19/2024. The requested leachable study data was submitted in Amendment 45 received on 9/27/2024. The data was reviewed by Andrey Sarafanov. The toxicological assessment of leachables was reviewed by Mondona McCann (OTP/OPT). These are deemed acceptable to support the BLA. No additional study is needed. Please refer to Andrey Sarafanov's review memo for additional details.

3.2.P.2.4 Container Closure System

(Reviewed by BL)

DP is vialled in a 2 mL Type^{(b) (4)} borosilicate glass vial, stopped with a siliconized (b) (4), 13 mm grey chlorobutyl stopper with (b) (4), and sealed with a 13 mm aluminum/plastic (b) (4) cap. Type^{(b) (4)} glass vials are designed to withstand the storage condition of the DP at -65 °C and are commonly used for frozen liquid biologics. The Type^{(b) (4)} borosilicate glass vials are in conformance with (b) (4). The chlorobutyl stoppers are (b) (4)) that minimize the possibility of interaction between the DP and the stopper closure because of its sorption resistance properties. The chlorobutyl rubber stoppers comply with (b) (4). The aluminum/plastic seals are non-product contact and serve to ensure that the stopper remains in place and provide tamper-evidence.

An initial extractables study was performed using various (b) (4) conditions with the container closure system components to identify the extractable compounds. A risk assessment was performed on the identified extractable compounds exceeding a specific threshold to determine potential safety risk associated with the extracted compounds. The Applicant also performed a comprehensive risk assessment and determined that extracted compounds posed no significant safety risk to patient and that product-specific leachable studies were not needed. However, FDA determined that a simulated leachable study including all product contacting component/equipment/container closure system (b) (4) is required. This request was communicated in the Filing Notification Letter dated

5/13/2024. The Applicant conducted such simulation leachable study and submitted data in Amendment 45 as noted above. Please refer to Andrey Sarafanov's review memo for additional detail of the extractables/leachables assessment.

Shipping validation studies demonstrated that the DP container closure system is suitable to maintain product integrity during shipping. Shipping validation studies were reviewed by DMPQ. Please refer to DMPQ reviewer memo for additional details.

Reviewer's Comment: The DP container closure system is suitable for its use.

3.2.P.2.5 Microbiological Attributes

(Reviewed by BL)

Control of microbiologic attributes includes controls during manufacturing process, controls at the manufacturing facility, routine lot release and stability testing, and the control of container closure system.

In the DP manufacturing process, (b) (4)

[REDACTED]

DP vials under a validated aseptic filling process. This aspect of the filling process is reviewed by DMPQ and deemed acceptable.

DP manufacturing process is conducted in a Grade (b) (4) environment. (b) (4)

[REDACTED]

Filled DP is tested for sterility per (b) (4) and endotoxin per (b) (4) for lot release. In addition, container closure integrity is assured by CCIT using (b) (4) vials as part of the stability plan. The DP container closures are supplied pre-sterilized using validated sterilization processes and tested for sterility and endotoxin.

3.2.P.2.6 Compatibility

(Reviewed by BL)

Eladocagene exuparvovec is injected into four sites of bilateral putamen using a SmartFlow Cannula following a stereotactic neurosurgical procedure at a total dose of 1.8×10^{11} vg in a total volume of 320 μ L, i.e., 80 μ L per injection site, at an infusion rate of 3 μ L/min. In the proposed USPI, two models of SmartFlow Cannula, i.e., P/N NGS-NC-01, and NGS-NC-02, which correspond to 4 feet and 10 feet in length, respectively, can be used for administration (Figure 25). A 1 mL or 5 mL sterile Luer Lock polycarbonate or polypropylene syringe with siliconized elastomer plunger and an 18-gauge or 19-gauge stainless steel filter needle with 5 μ L filter are used for preparation and injection of the product. The infusion rate is controlled by a syringe pump (Figure 26). Injection into each site will take approximately 27 minutes. After the first injection, the cannula is withdrawn and re-inserted into the next site. This is repeated for the three other injection sites.

The SmartFlow Neuro cannula and eladocagene exuparvovec are regulated as a cross-labeled combination product. Selected models of SmartFlow Neuro cannula specified in the USPI of eladocagene exuparvovec should be used for administration of the drug product. ClearPoint Neuro, the SmartFlow cannula manufacturer, submitted a De Novo application (DEN240023) to CDRH to support cross-labeling of the device. Other 510(k) cleared product accessory devices used for product preparation and administration, including syringe pumps, syringe, and filter needles are labeled with a general use approach.

Device information in addition to the device compatibility studies is reviewed by the device reviewer, Johnny Lam (OTP/OCTHT). Two ICCRs were requested by Johnny Lam to obtain consult review of the cross-labeled cannula and other accessory devices for general use labeling approach. Please refer to Johnny Lam's review memo for additional details on devices and their labeling approaches.

Figure 25. An illustrative diagram of SmartFlow Neuro Cannula

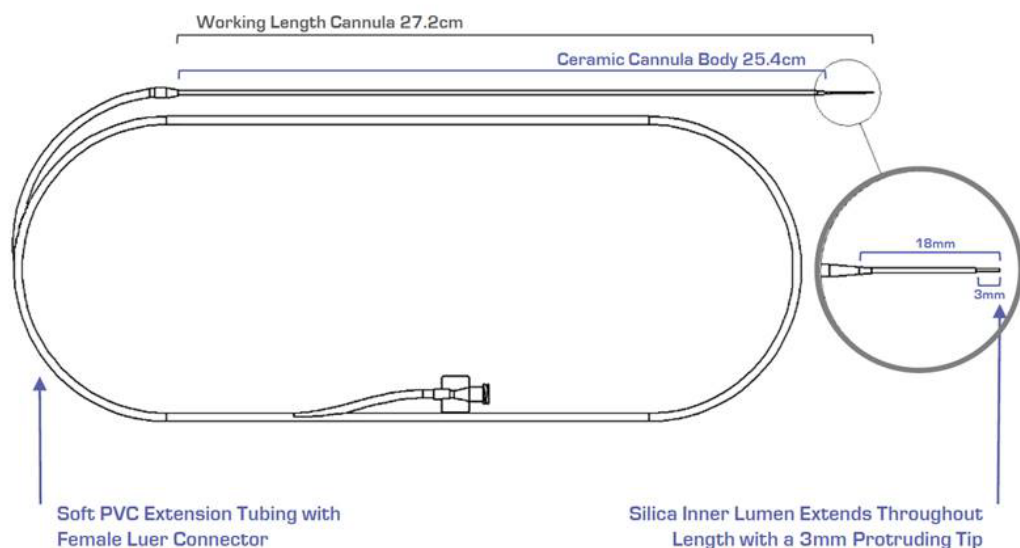
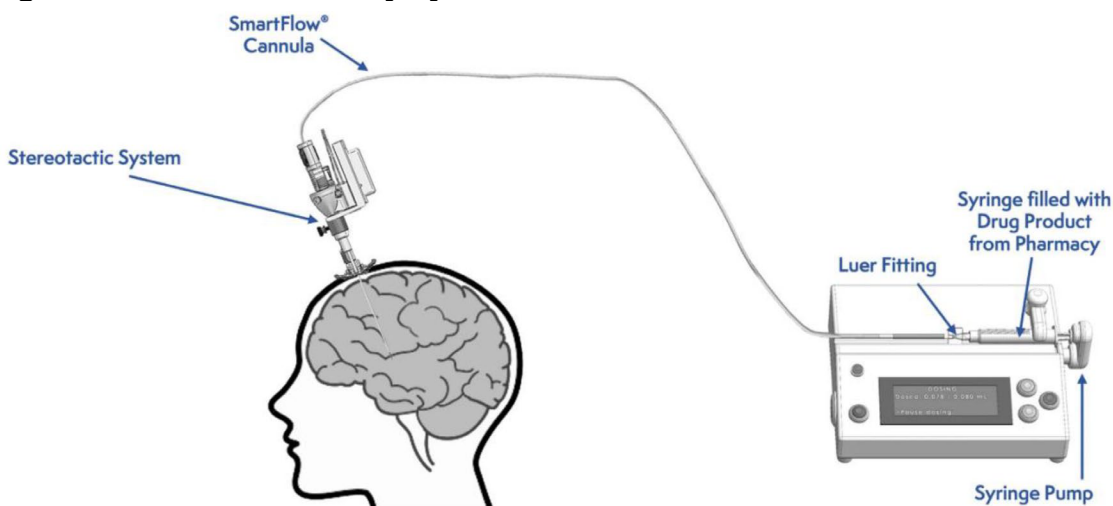


Figure 26. Infusion delivery system.



To support the device compatibility, PTC conducted a total of five studies. A report for the first four (4) studies was provided in the initial BLA submission. Study 5 was conducted during BLA review, in response to FDA's review issue #5 communicated in the May 13, 2024 Filing Notification Letter. The purpose of Study 5 was to assess the potential impact to product potency during administration using the (b) (4) assay. An updated report with results from all five studies was submitted to 3.2.R. Components and materials used in these studies are shown in Table 54.

- 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 54. Components and Materials Used in Device Compatibility Studies

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

(b) (4) process demonstration lots manufactured using commercial manufacturing process were used in compatibility studies (Studies 1, 2, and 5). (b) (4) was used in Study 3 to assess the risk of microbial contamination. (b) (4) was used in Study 4 to assess the accuracy of injection volume.

(b) (4)

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

Reviewer's Comments: *There was a concern that (b) (4)*

In Amendment 6 received on 5/31/2024, PTC indicated that (b) (4), i.e., (b) (4) is in the upper range of 48 months stability data for this lot, i.e., (b) (4). There is no substantial (b) (4) based on comparison with (b) (4) values from lot release and stability testing. There is no notable adsorption to the administration device. This is acceptable.

Study 2 was conducted to assess (b) (4) following administration. The testing procedure of Study 2 was nearly identical as Study 1. The (b) (4)

Reviewer's Comments: *This supports the use of 5 mL polypropylene syringe. No study was performed using 5 mL polycarbonate syringe. In response to an IR in the May 13, 2024 Filing Notification Letter, PTC indicates in Amendment 6 dated May 31, 2024 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 USPI labeling that the material of construction for 5 mL syringe should be polypropylene. This is acceptable.*

Study 5 was conducted similarly as Study 1 and Study 2. A major difference is that (b) (4)

Table 56. (b) (4) Results from Study 5

(b) (4)

Reviewer's Comments: The (b) (4) data indicate that there was no detectable (b) (4) following the administration of the product with (b) (4) assay is (b) (4). The difference between (b) (4) These data in combination with the (b) (4) data and the (b) (4) assay (b) (4) 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.

Study 3 was performed using (b) (4) to assess the risk of microbial contamination during product preparation and administration. The collected (b) (4) was tested for (b) (4). The test results from (b) (4)

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

Study 4 was conducted using (b) (4) to test accuracy of the injection volume using (b) (4) setups were able to accurately deliver (b) (4) volume.

Reviewer's Comments: The 5 mL syringe with (b) (4) pump combination is more accurate than the other combination with (b) (4) syringe. The relatively less accuracy with (b) (4) syringe is expected as it's the worst-case scenario with a (b) (4) in the syringe. Only 1 mL and 5 mL syringes can be used for administration of commercial product. It is also noted that the syringe pump selection was tailored for compatibility with the syringe size, indicating ability to choose interoperable device components. This is acceptable.

Overall Reviewer's Assessment of Section 3.2.P.2:

- The device compatibility data are acceptable.
- ClearPoint Neuro cross-referenced the device compatibility data to support the De Novo application for the SmartFlow Cannula as a cross-labeled combination product. CBRE provided consult review for CDRH on the device compatibility.

3.2.P.3 Manufacture
(Reviewed by SB)

3.2.P.3.1 Manufacturer(s)

The names and addresses of the facilities used in the manufacturing and testing of drug product are summarized below in Table 57 below.

Table 57. Manufacturer(s) of Drug Product

Manufacturer	FEI and DUNS	Responsibilities
(b) (4) (b) (4) (b) (4) (b) (4)	FEI: (b) (4) DUNS: (b) (4)	Manufacturing of drug product
(b) (4)	FEI: (b) (4) DUNS: (b) (4)	Release testing, stability testing and storage of drug product <ul style="list-style-type: none"> – Release and Stability: Appearance, (b) (4) – Stability only: (b) (4)
(b) (4)	FEI: (b) (4) DUNS: (b) (4)	Release testing of drug product <ul style="list-style-type: none"> – (b) (4) Endotoxin; Sterility
(b) (4) (b) (4) (b) (4) (b) (4)	FEI: (b) (4) DUNS: (b) (4)	Stability testing of drug product <ul style="list-style-type: none"> – Container Closure Integrity
(b) (4) (b) (4) (b) (4)	FEI: (b) (4) DUNS: (b) (4)	Secondary packaging, labeling and storage of drug product <i>Reviewer Notes: Adds label to product vial</i>
(b) (4) (b) (4) (b) (4) (b) (4) (b) (4)	FEI: (b) (4) DUNS: (b) (4)	Storage of drug product <i>Reviewer Notes: Labeled Drug Product</i>

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

3.2.P.3.2 Batch Formula

A unique batch number is generated and is used to identify each batch of DP. The DP has the product designation of (b) (4), the product code is (b) (4), and the unique lot identifier is a sequential (b) (4)

The Batch Formula for the Drug Product is comprised of (b) (4). Table 58 shown below details the components comprised in the (b) (4) as individual items (b) (4).

Table 58. Representative Batch Formula for Drug Product

Component/ Ingredient	Quality	Function/Purpose	Quantity (mg/mL)	Quantity per batch (mg) ^a
Eladocagene Exoparvovec (b) (4)	In house	(b) (4) /Active Ingredient	(b) (4)	(b) (4)
Potassium chloride (KCl)	(b) (4)	Buffer/stabiliser, tonicity	(b) (4)	(b) (4)
Potassium dihydrogen phosphate, (b) (4) (KH ₂ PO ₄)	(b) (4)	Buffer/stabiliser, tonicity	(b) (4)	(b) (4)
Sodium chloride (NaCl)	(b) (4)	Buffer/stabiliser, tonicity	(b) (4)	(b) (4)
Disodium hydrogen phosphate, (b) (4) (Na ₂ HPO ₄)	(b) (4)	Buffer/stabiliser, tonicity	(b) (4)	(b) (4)
Dibasic sodium phosphate, (b) (4) (Na ₂ HPO ₄)	(b) (4)			
Poloxamer 188	(b) (4)	Non-ionic surfactant, stabiliser	0.01	(b) (4)
Water for injection	(b) (4)	Solvent	Q.S.	NA

Abbreviations: KH₂PO₄, potassium dihydrogen phosphate, (b) (4); NA, not applicable; Na₂HPO₄, disodium hydrogen phosphate, (b) (4). Q.S., quantum satis (the amount that is sufficient); vg, vector genome.

^a Based on a batch size of (b) (4) vials (filling of (b) (4) total volume).

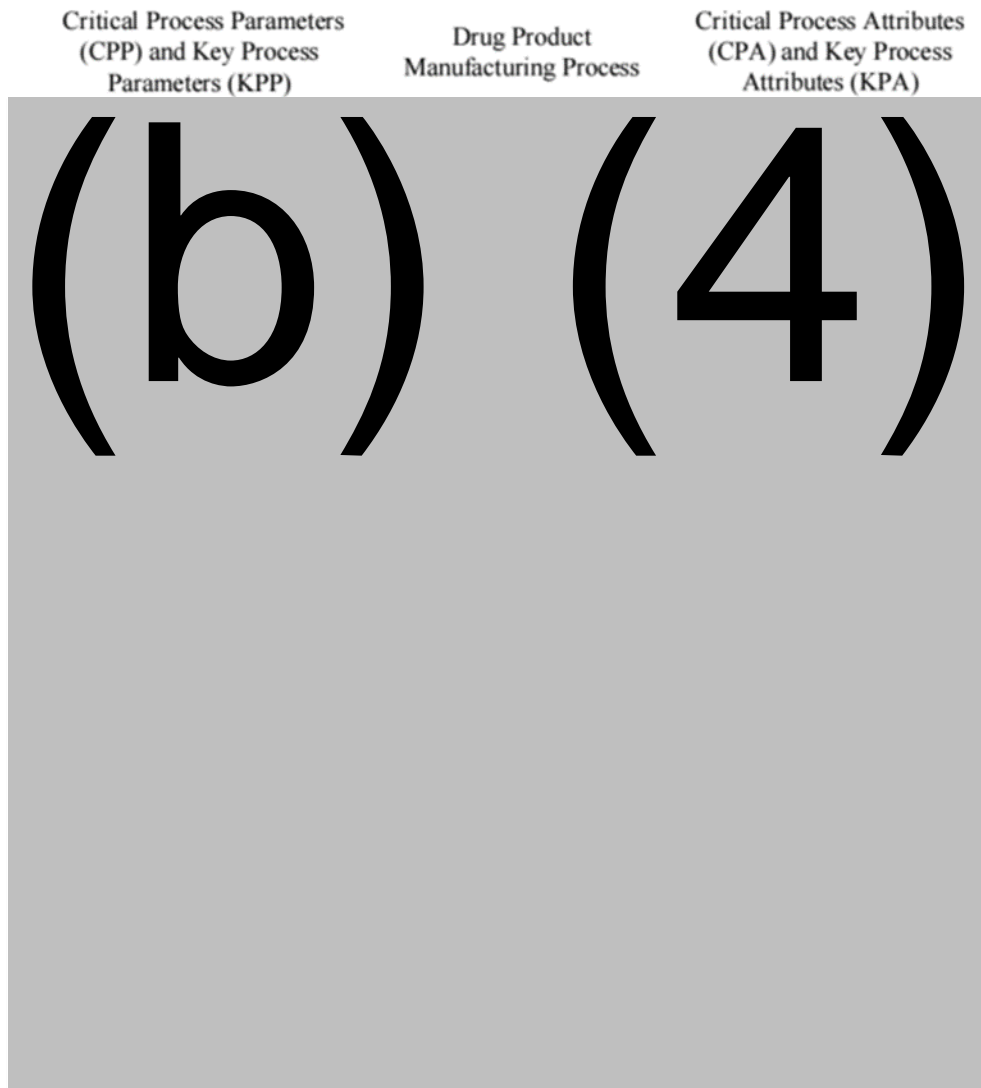
Overall Reviewer's Assessment of Sections 3.2.P.3.1 and 3.2.P.3.2:

No novel excipients are used, and the information provided is acceptable.

3.2.P.3.3 Description of Manufacturing Process

Applicant provides a combined DP manufacturing process diagram and identifier of CPP, KPP, CPA, and KPAs copied in Figure 27 below. A summarized description of the applicants' (b) (4) steps is compiled below.

Figure 27. Overall Drug Product Manufacturing Flow Diagram



(b) (4)

(b) (4)

(b) (4)

[REDACTED]

[REDACTED]

(b) (4) Inspection and Freeze: The sealed vials are 100% visually inspected. The unlabeled vials are stored in a sealed labeled box until they can be labeled by another vendor. (b) (4)

The vials are sampled for testing and frozen at $\leq -65^{\circ}\text{C}$. (b) (4)

Reviewer's comments:

During pre-license inspection, it was learnt that the frozen DP vials are shipped to (b) (4) facility (Table 57) for long-term storage. When needed, a (b) (4) from a batch stored at (b) (4) (Table 57), where vials are manually labeled and packaged under frozen conditions. Labeled and packaged vials are (b) (4) for storage and distribution (Table 57). The labeling and packaging processes are validated to ensure that the processes will maintain temperatures to support labeling and packaging of frozen vials. The shipping process is also validated. These were reviewed by DMPQ and deemed acceptable.

In response to review issue #3 noted in the Filing Notification Letter, the Applicant committed in Amendment #6 received on 5/31/2024 that a sample of labeled vial will be (b) (4) to confirm the identity of labeled DP using the (b) (4) test. In IR #7 dated 6/12/2024, we suggested that DP identity should be confirmed using an assay with specificity for the (b) (4). In Amendment 10 received on 6/26/2024, the Applicant agreed to confirm the identity using (b) (4) assay that (b) (4) to confirm the DP identity after vial labeling. This is acceptable.

In a follow-up IR #38 dated 10/9/2024, the FDA asked the Applicant to submit a lot release protocol for each subplot labeled separately for CBER lot release. We also requested that DP identity should be confirmed for each subplot as noted above and that the result should be reported on the lot release protocol for each subplot. The Applicant agreed in Amendment 52 received on 10/11/2024. This identity test for labeled drug product is included in the Lot Release Protocol under a section for Labeled Drug Product Lot Release Protocol submitted in Amendment 62 dated 11/31/2024.

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

- ☐ Description of the manufacturing process is appropriate.

3.2.P.3.4 Controls of Critical Steps and Intermediates

The CPPs and CPAs of the drug manufacture process are detailed with their action ranges in Table 59.

Table 59. Critical Process Parameters and Critical Process Attributes for Drug Product

Process Step	Process Parameter	CPP or CPA?	Action Range
--------------	-------------------	-------------	--------------

(b) (4)			
---------	--	--	--

(b) (4)

The test methods for the In-process test are referenced in this section. Except for the (b) (4) assays, they are (b) (4). The (b) (4) assay is referenced to be the same as that used for release test. A in-process (b) (4) is validated and is reviewed by DBSQC Hsiaoling (Charlene) Wang. Validation of this method is deemed acceptable by DBSQC.

Overall Reviewer's Assessment of Section 3.2.P.3.4:

- This is acceptable with CPV plan to tighten parameters and hold times as they gain manufacturing experience.

3.2.P.3.5 Process Validation and/or Evaluation

Similar to the process described in 3.2.S.2.5 Process Validation and/or Evaluation, the Applicant has divided the validation of the drug product into (b) (4) main stages including a division of (b) (4) as detailed for the (b) (4) above. This section will contain information specific to the DP.

(b) (4)

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

Table 61. Drug Product Release Test Results

Quality Attribute Category	Quality Attribute	Method	Acceptance Criteria
Potency	(b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)
Identity	(b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)
Safety	Sterility	(b) (4)	No Growth
	Endotoxin (EU/mL)	(b) (4)	(b) (4)
	Container Closure Integrity ^c	(b) (4)	Pass
Purity	Purity (%)	(b) (4)	(b) (4)
Quality	Appearance (post-thaw)	Visual Inspection (b) (4)	Clear to slightly opaque, colorless to faint white solution, free of visible particulates
	(b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)

^a The test for (b) (4) has been replaced with the test for (b) (4) performed using (b) (4) and tested. (b) (4)

^b Deviation Occurred, see report PTCIN-CO-012020=002

^c Container closure integrity testing was

^d Deviation Occurred, see report QE-001120 ^e (b) (4) vials were (b) (4)

(b) (4)

Reviewer's Comments:

There was a concern about a deviation in the PPQ^{(b) (4)} DP lot release sterility testing (b) (4) where the sterility/endotoxin test samples were (b) (4) under excursion temperature conditions. The intended (b) (4) temperature is (b) (4) but temperature in the (b) (4) was up to (b) (4) for a total duration of (b) (4) during (b) (4). PTC conducted risk assessment and concluded that the temperature excursion had no impact to validity of sterility and endotoxin tests. The risk assessment was based on product stability data and published literature about bacteria viability after storage in (b) (4). These are not adequate to prove the validity of the test result. This concern was discussed with the SEMs during prior-approval inspection. The Applicant committed to conduct (b) (4) study to demonstrate the validity of the sterility test results for samples stored under simulated excursion (b) (4) conditions and to re-test the (b) (4) for endotoxin. After inspection, we sent a follow-up request of the study plan in IR # 31. The Applicant provided a description of the proposed study in Amendment 41 dated 9/24/2024. The endotoxin re-test plan is acceptable, but details on the (b) (4) study for validity of sterility result on the (b) (4) level, inclusion of a facility environmental isolate, i.e., (b) (4), the number of replicates, test acceptance criteria, were not provided. A follow-up request of those details and a study protocol was sent in IR # 40. In Amendment 54 received 10/18/2024, the Applicant indicated that they intended to (b) (4) at a level of (b) (4) according to (b) (4) level did not survive) and include (b) (4) for each test articles. (b) (4) will be also included in the (b) (4) study. The acceptance criteria will include valid controls and growth with samples stored under both the intended condition and the simulated excursion conditions. In IR #45 dated 10/25/2024, we asked the Applicant to submit the finalized study protocol in a Product Correspondence for us to review when the development study on (b) (4) level is completed before conducting the (b) (4) study and submit the (b) (4) study results in a PAS to support the release of PPQ^{(b) (4)} lot. We also advised that if needed, the Applicant can request an expediated review of the PAS to facilitate timely release of the product for commercial distribution. The Applicant agreed in Amendment 60 dated 10/29/2024.

3. **Continued Process Verification:** The intended system for continual process verification is similar to that of the (b) (4) mentioned above.

Overall Reviewer's Assessment of Section 3.2.P.3.5:

- ☐ This is acceptable with CPV plan to tighten parameters and hold times as they gain manufacturing experience.

3.2.P.4 Control of Excipients

(Reviewed by BL)

3.2.P.4.1 Specifications

All the excipients in DP are (b) (4) grade. A list of the excipients and compendial references are provided in **Error! Reference source not found..**

Table 62. Specifications for (b) (4) Excipients

Component	Quality Standard
KCl	(b) (4)
KH ₂ PO ₄ , (b) (4)	
NaCl	
Na ₂ HPO ₄ , (b) (4)	
Poloxamer 188	
Water for Injection	
Abbreviations: (b) (4)	

3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures

All excipients are (b) (4). Analytical methods for testing of excipients are compliant with the corresponding (b) (4).

3.2.P.4.4 Justification of Specifications

Specifications for excipients are based on the current (b) (4).

3.2.P.4.5 Excipients of Human or Animal Origin

No excipients are of human or animal origin.

3.2.P.4.6 Novel Excipient

Not applicable.

Overall Reviewer's Assessment of Section 3.2.P.4:

Information on excipients in the DP is acceptable.

3.2.P.5 Control of Drug Product

(Reviewed by JB)

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

The DP release specifications are shown in Table 63.

Table 63. Drug Product Release Specifications

Quality Attribute	Analytical Procedure	Acceptance Criteria
Appearance	Visual Inspection	Clear to slightly opaque, colorless to faint white solution, free of visible particulates
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)

(b) (4)		
Endotoxin	(b) (4)	
Sterility	(b) (4)	No growth

Appearance

The appearance test is a visual inspection of the (b) (4) to test for clarity, color, and particulates. All (b) (4) DP lots have met the acceptance criterion of “clear to slightly opaque, colorless to faint white solution, free of visible particulates”.

Reviewer’s Comment: The proposed AC are acceptable.

(b) (4)

(b) (4)


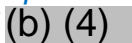



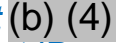

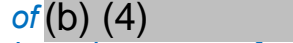


(b) (4)

(b) (4)

(b) (4)

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

(b) (4)**(b) (4)****(b) (4)****(b) (4)**

Reviewer's Comments: The applicant initially proposed an acceptance range of (b) (4)  vg/mL, which encompassed (b) (4)  of the proposed label claim of 5.6×10^{11} vg/mL. We initially asked the sponsor for justification for targeting a DP (b) (4)  of (b) (4)  vg/mL (b) (4)  the label claim) in IR #7. In Amendment 10 (received 06/26/2024), the applicant replied that the target (b) (4)  for DP is set to account for process and analytical variability. In subsequent IRs, we requested additional information to better understand the performance of the (b) (4)  assay for in-process control and release testing, and to understand when the changes described above were implemented. This information was provided in Amendment 20 (received 07/22/2024) and Amendment 25 (received 08/06/2024). During the inspection of (b) (4)  facility, the reviewers on inspection noted that additional lots of DP have been manufactured after PPQ (b) (4) . The data from lots PPQ (b) (4)  on, after the changes to



the in-process control, show better control of the DP (b) (4) at release (see 3.2.P.2.2.2 (b) (4)). In IR #21, we requested that the applicant lower the upper limit of the specification to (b) (4) vg/mL. The applicant agreed in Amendment 30 (received 08/23/2024). A revised Justification of Specifications document was provided in Amendment 48 (received 10/4/2024). The upper limit of the revised AC, i.e., (b) (4) vg/mL is (b) (4) than the target (b) (4) in the DP formulation process (i.e., (b) (4) vg/mL) and (b) (4) than the labeled (b) (4) (i.e., 5.6×10^{11} vg/mL). The revised AC can help ensure that the (b) (4) of DP is within an acceptable range supported by the pivotal clinical study.

(b) (4)

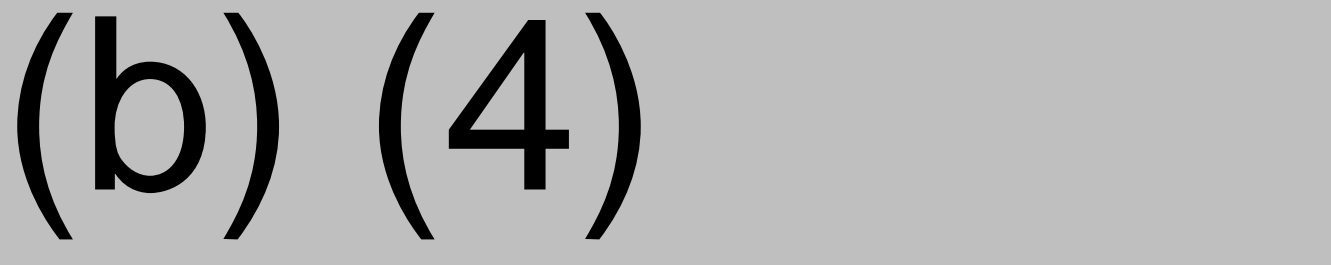
(b) (4)

(b) (4)


(b) (4)




(b) (4)



(b) (4)



(b) (4)



Endotoxin

The endotoxin acceptance criterion was set to conform to (b) (4) limits as described in 3.2.S.4.5 Justification of Specifications.

Sterility

The acceptance criterion of “no growth” conforms to (b) (4) and confirms that the DP is free of microbiological contamination.

Overall Reviewer’s Assessment of Sections 3.2.P.5.1 and 3.2.P.5.6:

In response to FDA IRs, PTC narrowed the DP lot release criterion for (b) (4). They have agreed to re-assess all lot release criteria after 10 commercial batches have been manufactured as PMC #1. The finalized DP lot release specifications are acceptable.

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures

The analytical methods used for both (b) (4) DP release testing are described in 3.2.S.4.2 Analytical Procedures and 3.2.S.4.3 Validation of Analytical Procedures. The analytical methods used only for DP lot release testing, including tests for (b) (4) endotoxin, and sterility, are reviewed by DBSQC and are deemed acceptable. Please refer to the DBSQC review memo for those methods used only for DP lot release testing.

Overall Reviewer’s Assessment of Sections 3.2.P.5.2 and 3.2.P.5.3:

All DP lot release testing methods are acceptable.

3.2.P.5.4 Batch Analyses

DP lots used in non-clinical studies, clinical studies, process validation, and PPQ are summarized in Table 67. Lot release test results for these DP batches are submitted in the BLA. The information provided represent the analytical methods, acceptance criteria and data reporting used at the time of lot release. The release testing results for the PPQ lots are shown in Table 61.

(b) (4)

(b) (4)

3.2.P.5.5 Characterization of Impurities

Applicant states that impurities are tested at the (b) (4) stage and the impurities present in the drug product are the same as the (b) (4) (see section 3.2.S.3.2 above). They refer to the stability program for tracking of aggregation and degradation products.

3.2.P.6 Reference Standards or Materials

(Reviewed by JB)

Please refer to 3.2.S.5 Reference Standards or Materials.

3.2.P.7 Container Closure System

(Reviewed by BL)

3.2.P.7.1. Primary Container

The DP container closure system (CCS) consists of a 2-mL borosilicate glass vial, a siliconized chlorobutyl elastomer stopper, and an aluminum/plastic (b) (4) cap (Table 68). All three components of the DP CCS are supplied by (b) (4). The glass vials are manufactured by (b) (4). Stoppers and caps are manufactured by (b) (4). All three components of the DP CCS are sterilized by (b) (4) using validated sterilizing processes.

Table 68. Components of DP container closure system

Component	Description	Grade	DMF Number (Manufacture)	Supplier
Vial	Clear, colorless, Type (b) (4) borosilicate glass serum vials, 2 mL	(b) (4)	DMF (b) (4) (b) (4)	(b) (4)
Stopper	Type (b) (4) siliconized (b) (4) chlorobutyl elastomer stoppers with (b) (4)	(b) (4)	DMF (b) (4)	(b) (4)
Cap	Aluminum/plastic (b) (4) cap, (b) (4)	NA (non-product contact)	NA (b) (4)	(b) (4)

Vial

Specification for incoming release of the class vial includes conformance to (b) (4) for Type (b) (4) glass containers, identity by visual (part number and supplier match), dimension verification (b) (4)

visual inspection for defects, sterility per (b) (4) endotoxin of less than (b) (4)

according to the (b) (4)

method in (b) (4)

Stopper

Specification for incoming release of the stopper includes conformance to (b) (4) for Type (b) (4) elastomeric closure requirements for injections, identity by visual (part number and supplier match), dimension verification (b) (4) fits on vial, (b) (4), visual inspection for defects, (b) (4), sterility per (b) (4)

and (b) (4)

according to the (b) (4) method in (b) (4)

Cap

Cap is not a product contact component. Specification for incoming release of the cap includes visual (part number and supplier match), fits to vial and stopper, visual inspection for defects, and sterility per (b) (4)

Reviewer's Comments:

The DP container closure system is acceptable. Validation of vial and stopper sterilization process is reviewed by DMPQ. Container closure integrity test (CCIT) is part of the DP lot release specification and stability plan. CCIT was reviewed by DMPQ. Representative COAs for three components of the DP CCS were submitted in Amendment 6 in response to IR #5. The Applicant indicates that the part number for each component may change with different quantity; therefore, the part number is not included in 3.2.P.7. This is acceptable.

Summary of L/E assessment

The Applicant provided extractables/leachable study data for the DP container closure system in the original submission in 3.2.P.2.4 Container Closure System. Additional leachable studies were requested by Andrey Sarafanov (OTP/OPPT). The data were provided in Amendment 45 received on 9/27/2024. Andrey Sarafanov reviewed the extractables/leachable data. Mondona McCann from OTP/OPT reviewed the toxicological risk assessment. These data are deemed adequate to support the BLA. Please refer to Andrey's review for additional information.

3.2.P.7.2 Secondary container

The secondary container consists of a 4"×2.75"×1.75" single vial folding carton sealed with a tamper evident label.

Overall Reviewer's Assessment of Section 3.2.P.7:

DP container closure system and the qualification plans for all components are acceptable.

3.2.P.8 Stability

(Reviewed by JB)

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

The DP is stored at the recommended long-term condition of $\leq -65^{\circ}\text{C}$. DP stability studies were performed in the long-term storage conditions, stressed conditions (b) (4) accelerated conditions (b) (4) and in a freeze-thaw stability study. The container closure for DP stability studies is the same vials used as the final container closure as described in 3.2.P.7 Container Closure System. Additional stability data is provided for the reference standard lot (b) (4), which is stored in (b) (4). A summary of the stability studies that are completed and in progress is shown in Table 69.

Table 69. Summary of DP Stability Studies

(b) (4)

The analytical procedures used for the stability study are a subset of the DP lot release analytical procedures. The acceptance criteria are set to align with the DP lot release acceptance criteria as shown in Table 70.

Long-Term Stability Data

Stability data at the long-term storage condition is available is provided for (b) (4) DP lots as described in Table 69. The applicant assigns a shelf-life of 48 months based on the stability data.

The results from all batches met the acceptance criteria for all quality attributes. There were no apparent trends, and no statistical analysis performed for appearance, purity, (b) (4). The results for the remaining quality attributes are discussed below.

(b) (4)

All lots met the acceptance criteria at the time of testing for available stability study timepoints. As noted in 3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s), the target (b) (4). This makes it challenging to perform a combined statistical analysis of (b) (4) results. The applicant provided an analysis performed according to the (b) (4) procedure for (b) (4) results through (b) (4) which estimates a shelf-life of (b) (4) months (with the confidence interval crossing the upper limit of the AC). They note that long-term stability results for (b) (4) DP lots at 48 months are within the acceptance criteria, and thus support a 48-month shelf life.

Reviewer's Comments: I attempted to perform the (b) (4) analysis using the full data set, but the variability of the assay and the (b) (4) made the analysis not possible. In Figure 32, I show a fit of the mean (b) (4) over time (solid black line), and the 95% confidence interval around the mean (gray shading). The AC are shown as black dotted lines. The apparent trend in the data is that the (b) (4) over time, which is likely due to variability of the assay. (b) (4) appears to remain stable for up to 48 months in the long-term storage condition.

(b) (4)

(b) (4)




(b) (4)

Potency

The (b) (4) potency assay was the original potency assay performed as part of the stability testing program. All lots met the acceptance criteria throughout the stability studies. Statistical analysis predicts a shelf-life of (b) (4) -months based off of the available (b) (4) potency data and an acceptance criterion of (b) (4) vg/cell for (b) (4) potency.

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

(b) (4)



***Reviewer's Comments:** The original BLA submission did not contain any information on (b) (4) of the DP. We requested (b) (4) information in IR #19, and received a response in Amendment 27 (received August 12, 2024). We requested an additional risk assessment covering light exposure during dose preparation and administration in IR #27 and received a response in Amendment 40 (received September 23, 2024). Although the (b) (4) study did show (b) (4) of the DP, we agree with the Applicant's risk assessment that the risk to DP is low given the limited light exposure and the existing lot release, stability, and compatibility data for the DP.*

3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment

The ongoing stability studies as described in Table 69 will be completed as planned. The post-approval stability studies will be completed as described in Table 71. (b) (4) (b) (4) (unless none are produced that (b) (4) will be included in the stability program.

Table 71. DP Post-Approval Stability Testing Protocol

Test	Acceptance Criteria	Timepoints (Months)						(b) (4)
		0	6	12	24	36	48	
Appearance (post-thaw): Visual inspection	Clear to slightly opaque, colorless to faint white solution, free of visible	X	X	X	X	X	X	(b) (4)
(b) (4)	(b) (4)	X	X	X	X	X	X	
		X	X	X	X	X	X	
		X	X	X	X	X	X	
		X	X	X	X	X	X	
Purity (b) (4)	(b) (4)	X	X	X	X	X	X	
(b) (4)	(b) (4)	X	X	X	X	X	X	
		X	X	X	X	X	X	
		X	X	X	X	X	X	
		X	NA	X	X	X	X	
Container closure integrity: (b) (4)	Pass	X	NA	X	X	X	X	

Overall Reviewer's Assessment of Section 3.2.P.8:

- ❑ Primary stability studies for DP include long-term stability at $\leq -65^{\circ}\text{C}$, accelerated conditions of (b) (4) stressed conditions of (b) (4) and up to (b) (4) (b) (4). Long-term stability data was provided for 48 months for (b) (4) process demonstration lots and (b) (4) PPQ lot. The remaining (b) (4) PPQ lots had data provided for 36, 12, and 9 months. The provided long-term storage stability data support the proposed shelf-life of 48 months when stored at $\leq -65^{\circ}\text{C}$.
- ❑ (b) (4) data was not included in the original BLA, but was provided in response to IRs and found to be acceptable.
- ❑ The upper limit for (b) (4) was revised in the stability program to align with the revised DP lot release criteria.
- ❑ The applicant plans to enroll (b) (4) in the post-approval stability program (b) (4) (unless none are produced that (b) (4)).

3.2.A APPENDICES**3.2.A.1 Facilities and Equipment**

Reviewed by DMPQ.

3.2.A.2 Adventitious Agents Safety Evaluation*(Reviewed by SB)*

The control strategy for adventitious agents comprises of:

- Ensuring that there are adequate controls on (b) (4) and raw and starting materials used in manufacture. More information is provided on this element of control in 3.2.S.2.3 Control of Materials.
- Routine testing will be performed on (b) (4) to ensure that the exclusion of adventitious agents is maintained in the (b) (4).
- Viral clearance evaluation studies were performed in accordance with (b) (4) that is detailed below using (b) (4) viruses.

Viral Clearance Studies

Viral clearance evaluation study were performed where viral clearance was expected to be possible ((b) (4)) using three model viruses:

(b) (4)

(b) (4)

(b) (4)

***Reviewer's Comments:** Original submission only denotes (b) (4), which was not sufficient. On inspection and through IR response received 2024-08-12 (eCTD 0028) it was learned that (b) (4) model viruses are evaluated for clearance. The Viral Clearance Report is now uploaded in 3.2.R. This is acceptable.*

(b) (4)

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

(b) (4)

(b) (4)

(b) (4)

Overall Reviewer's Assessment of Section 3.2.A.2:

- ☐ With the information added in amendment eCTD 0028, the information is sufficient to mitigate risks for endogenous or exogenous adventitious agents.

3.2.A.3 Novel Excipients

No novel excipients are used in manufacture of the DP.

3.2.R Regional Information (USA)

Executed Batch Records

(Reviewed by SB)

Executed batch records have been provided in 3.2R that are organized via the 3.2 R Executed Batch Records Cover Page for the (b) (4) PPQ runs (b) (4)

. A list of master batch records is also provided for the (b) (4) drug product along with historical batch records referenced in the process development sections above.

Reviewer's Comments: The batch record storage procedure was found to be inadequate on inspection. Form 483 includes mention of how physical batch records for (b) (4) have been previously lost for 8 months duration and that an inadequate paper log is used when the online copy of the batch records need be amended. In response to 483, PTC is instituting a (b) (4)

This is appropriate and the online system is adequate.

Method Validation Package

(Reviewed by JB)

Method validation is described in 3.2.S.4.2 Analytical Procedures and 3.2.S.4.3 Validation of Analytical Procedures and 3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures.

Combination Products

(Reviewed by BL)

Eladocagene exuparvovec and the SmartFlow Neuro Cannula are cross-labeled combination products. A De Novo Classification Request application for the SmartFlow Neuro Cannula by ClearPoint Neuro was reviewed and granted by CDRH to support the cross-labeling approach. Specific models of SmartFlow cannula that can be used to administer KEBILIDI are described in the USPI. Other accessory administration device components, including the stereotactic system, syringe pump, syringe, and filter needles are labeled in the USPI as general use. Device review is conducted by Johnny Lam (OCTHT/OTP). Please refer to his review memo for the SmartFlow Cannula and other accessory administration device components. The device compatibility is documented in 3.2.P.2.6 Compatibility. It is concluded that the data from the 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.

Overall Reviewer's Assessment of Combination Products Section:

The device information submitted to the BLA is adequate to support the cross-labeling of eladocagene exuparvovec and the SmartFlow Cannula as a combination product.

Comparability Protocols

No comparability protocol is submitted.

Other eCTD Modules

Module 1

(Reviewed by BL)

A. Environmental Assessment or Claim of Categorical Exclusion

The applicant submitted an environmental assessment (EA) pursuant to 21 CFR part 25.20(l). The EA provided an assessment of KEBILIDI environmental exposure based on the characteristics of the parental adeno-associated virus type 2 (AAV2), the genetic modifications to the AAV2 vector, the replication-incompetent and self-limiting nature of the vector, non-clinical and nonclinical data regarding the toxicity of the vector and transgene insert, vector biodistribution and shedding data, the likelihood of transmission to animals and releasing into the environment, and the product transportation, handling, storage, preparation, and administration procedures. The Agency determined that approval of KEBILIDI will not result in any significant environmental impact. A Finding of No Significant Impact (FONSI) memorandum has been prepared.

B. (b) (4)

The applicant has requested (b) (4) in section 1.3.5.3 of the CTD.

Reviewer's Comments: (b) (4)

C. Labeling Review

Full Prescribing Information (PI):

3. Dosage Forms and Strength

KEBILIDI is a sterile suspension for intraputaminial infusion. Each single-dose vial contains 2.8×10^{11} vg/0.5 mL (nominal concentration of 5.6×10^{11} vg/mL) of KEBILIDI and each 2 mL vial contains an extractable volume of 0.5 mL. Following product thaw, the suspension for infusion is a clear to slightly opaque, colorless to faint white liquid, free of visible particulates.

Reviewer's Comments: *In the original submission, the product was described as a solution. The applicant was asked to change the description of the product as a suspension. In addition, the original description of thawed DP did not include "free of visible particulates". We asked the applicant to add this description because it is an acceptance criterion for 100% visual inspection and an acceptance criterion for the appearance test for DP lot release. These changes are included in the revised PI labeling.*

11. Description

KEBILIDI is provided in a single-dose 2 mL vial containing a clear to slightly opaque, colorless to faint white liquid, free of visible particulates following thaw from its frozen state. The excipients include potassium chloride (3 mM), sodium chloride (337 mM), potassium dihydrogen phosphate (2 mM), disodium hydrogen phosphate (8 mM), and poloxamer 188 (0.001%).

16. How Supplied/Storage and Handling

KEBILIDI is stored and transported frozen at $\leq -65^{\circ}\text{C}$ (-85°F). The DP vial should be kept in the supplied carton during long-term storage. Thaw KEBILIDI vial upright at room temperature prior to administration. The content of the vial will thaw in about 15 minutes at room temperature. Do not thaw or warm the vial any other way. Gently invert the vial 3 times. Do not shake the vial. If not used immediately after thaw, store at room temperature (up to 25°C [77°F]) and use within 6 hours of starting product thaw. Do not refreeze vial once thawed.

2. Dosage and Administration

KEBILIDI should be administered using an FDA-cleared cannula for intraparenchymal infusion (e.g., ClearPoint Neuro SmartFlow Cannula Part Number NGS-NC-01-EE or NGS-NC-02-EE) with an infusion pump capable of infusing at a rate of 0.003 mL/min. User should coordinate the timing of KEBILIDI thaw and infusion. KEBILIDI should be used within 6 hours of starting product thaw. As infusion takes 4 hours, the maximum time from thaw to completion of infusion should be no more than 10 hours.

Reviewer's Comments:

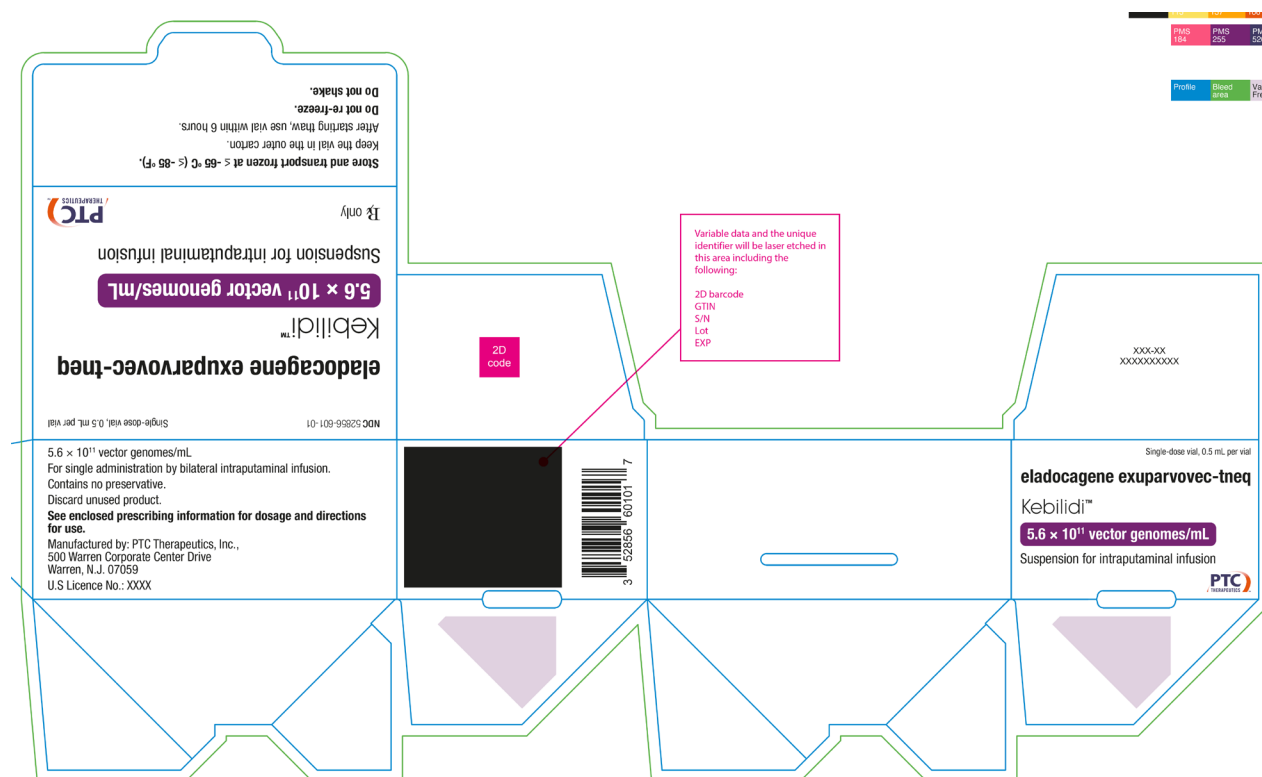
In the original PI, there was no information on the duration of infusion. In the device compatibility study, a duration of 4 hours of infusion (including the infusion time and the time between two infusions) and a maximum of 6 hours hold and drug preparation at room temperature, i.e., a total of 10 hours from thaw to completion of the administration, was tested to demonstrate in-use and in-device stability of the DP. Therefore, the applicant was asked to include 6 hours of preparation before use, 4 hours of infusion, and a total duration of 10 hours from thaw to completion of administration in the PI. This was revised.

The information on the devices, including syringe and sterile filter needles, used for preparation of the product for administration was also revised to align with the specific types of devices tested in the device compatibility studies and to include the specific requirements of those devices, including the materials of construction, sizes, etc. The review team also asked the applicant to present this information in a tabulated format for a clearer demonstration of those requirements. For the SmartFlow cannula, a language of "using an FDA-cleared cannula for intraparenchymal infusion..." was added to align with the cross-labeling combination product approach. Two specific models of the SmartFlow cannula are indicated in the PI label. Both models are supported by the

device compatibility studies and are supported by the revised device labeling in the De Novo application to support cross-labeling.

Carton and Container Label:

Carton label

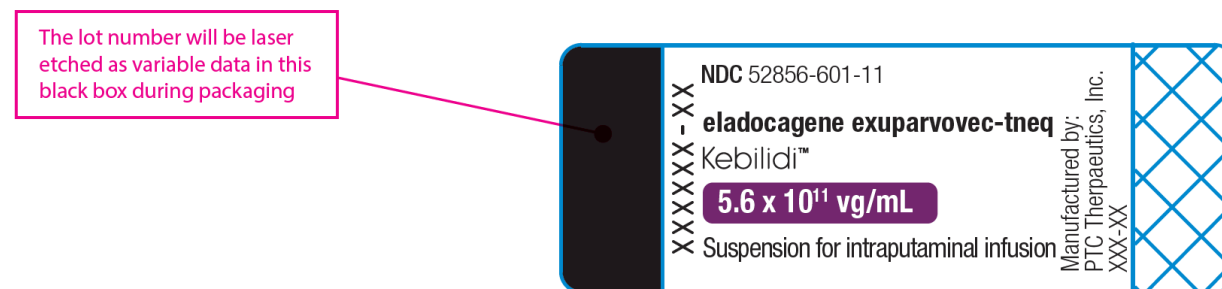


Reviewer's Comments:

In the originally proposed package label, information on product identifier data, including NDC number, serial number, lot number, and expiration date, were not included. In response to IR #26 sent on 9/13/2024, in Amendment 42 received on 9/25/2024, the applicant indicates that these will be included in the black box on the carton. In Amendment 42, the applicant also agreed to include an instruction of “Do not shake” per our request in IR #26. A 2D barcode is included on the carton label.

We had a concern about the manufacturer's information on the label. The originally proposed container label indicated that KEBILIDI is “Manufactured for PTC” and included PTC's address and a space for PTC's license #. No information on (b) (4) is included. In response to a request to add manufacturer's information, the applicant proposes to replace the words “Manufactured for PTC” with the words “Manufactured by PTC”. The applicant does not intend to include the name or address of (b) (4) on the label. The applicant justifies this approach by claiming the full responsibility of product manufacturing based on 21 CFR 600.3(t). This is acceptable.

Container label

**Reviewer's Comments:**

In response to a request of the missing information required for a full container label in IR #26, the applicant claimed for a partial label due to the small size of container label. A partial container label is acceptable. Per 21CFR 610.60(c), a partial label must include product name, name of manufacturer, and lot number. Lot number was not included. In response to IR #26, the applicant indicated that the lot number will be printed in the black box region. This is acceptable.

In the originally proposed labels, the container and carton shared the same NDC number. Because container and package should use different NDC numbers, we asked for a different NDC for the container label. In Amendment 42 dated 9/25/2024, the applicant changed the NDC # on the container to 52865-601-11. The NDC on the carton remains 52865-601-01. This is acceptable.

As noted above, the applicant claimed that PTC is the manufacturer of KEBILIDI according to 21CFR600.3(f) and changed the "Manufactured for PTC" to "Manufactured by PTC". This is acceptable.

Modules 4 and 5

(Reviewed by JB [CSF neurotransmitter assays] and BL [virus shedding and immunogenicity assays])

5.3.1 Analytical Procedures and Validation of Analytical Procedures for Assessment of Clinical and Animal Study Endpoints**Neurotransmitter Metabolites in CSF**

Throughout product development, two assays were used to measure the neurotransmitter metabolites homovanillic acid (HVA), (b) (4) in human cerebrospinal fluid (CSF). For supportive studies AADC-CU/1601, AADC-010, and AADC-011, and (b) (4) method was used. For the pivotal study PTC-AADC-GT-002 an LC-MS/MS method was used. The methods and their validations are described below.

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


Reviewer's Comment: This assay is suitably validated for the analysis of study/subject samples.

LC-MS/MS Method

Assay Description: The LC-MS/MS method (b) (4)



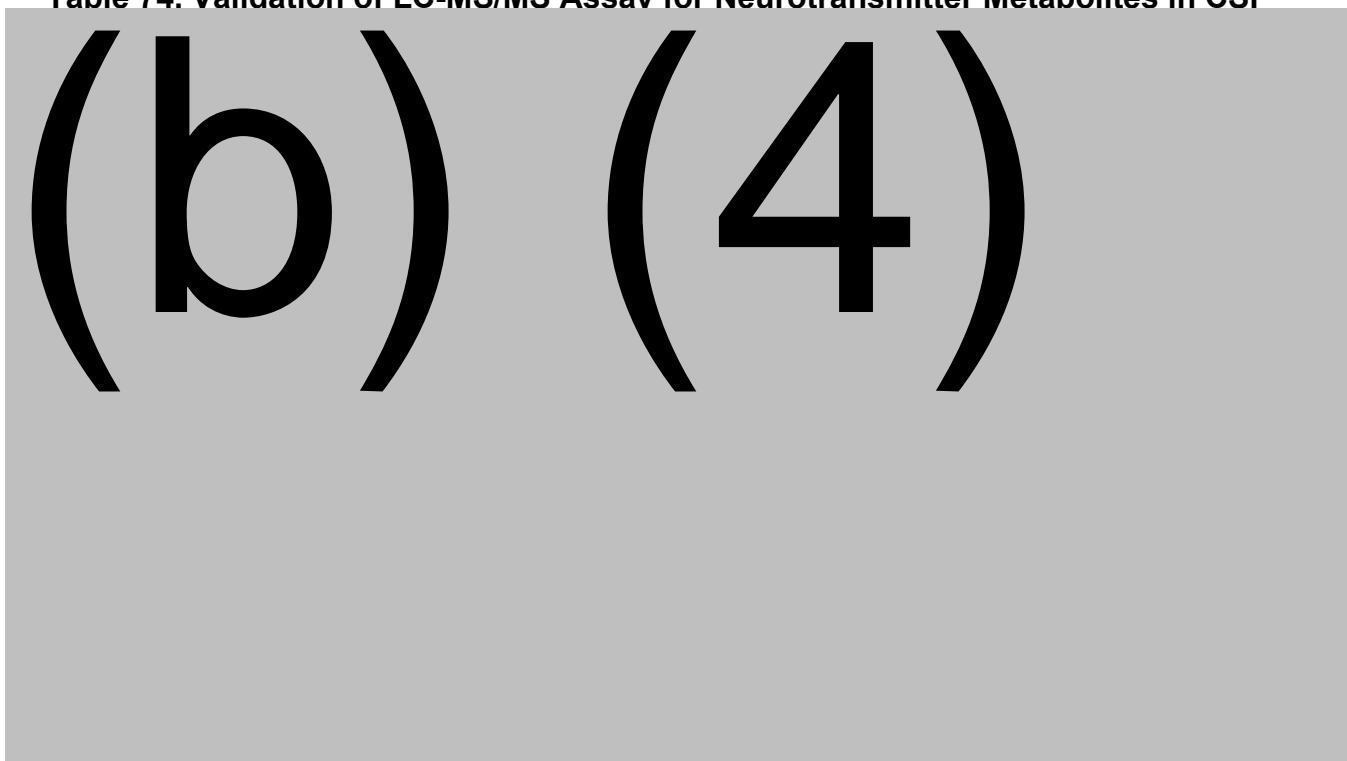
(b) (4)



Assay Validation: The assay validation was performed using the QC samples described above. The validation parameters and results are summarized in Table 74.

Table 74. Validation of LC-MS/MS Assay for Neurotransmitter Metabolites in CSF

(b) (4)



(b) (4)

(b) (4)

***Reviewer's Comments:** I have reviewed the method validation for the LC-MS/MS method as well as the interim bioanalytical report from study PTC-AADC-GT-002 and conclude that the methods were suitably validated for analysis of study/subject samples and was performed appropriately during the clinical trial.*

The original application did not include any information on bridging data between the (b) (4) LC-MS/MS methods. Because the applicant was proposing to use HVA as a biomarker to support efficacy, we requested information on the comparability between results from the two methods in the filing letter and IR 6. In amendments 6 and 8 (received 05/31/2024 and 06/14/2024), the applicant provided information showing that the sample preparation, the calibration ranges, and the validation with QC samples were similar between the two assays. In amendment 8, they noted that one difference between the two assays was the (b) (4) in the LC-MS/MS assay. However, the validation evaluated (b) (4) for HVA. Additionally, the use of an (b) (4)

In amendment 8, information was provided to show that the (b) (4)

. I agree with the applicant that the similarities between the two methods show that HVA results between the two assays can be compared without the need for a formal bridging study.


qPCR assay for detection of vector in patient samples

In the pivotal Study PTC-AADC-GT-02, the Applicant evaluated the virus load in human blood and cerebrospinal fluid (CSF) and shedding in human urine from subjects treated with eladocagene exuparvovec. The assay used for assessment of viral load in blood and CSF and virus shedding in urine is a qPCR assay targeting the gene of interest (GOI). The assay involves extraction of DNA from test samples, followed by qPCR analysis of the extracted DNA to detect and quantify the amount of the AAV vector in test samples. This assay was validated in (b) (4) studies, i.e., (b) (4) for samples of peripheral blood, urine, and CSF, respectively. (b) (4) validation studies were conducted following a similar validation strategy as described below.

Overall, the assay validation included assessment of the (b) (4)

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

(b) (4)



Overall Reviewer's Assessment of Relevant Sections of Module 4 and 5:

- ❑ In the filing letter and IR 6, we requested additional information to support comparability between the (b) (4) LC-MS/MS methods for analysis of HVA in human CSF. In Amendments 6 and 8, PTC provided the requested information.
- ❑ The validations provided for the (b) (4) LC-MS/MS methods were adequately performed to assure the methods are suitable for their intended purpose.
- ❑ The q-PCR -based virus shedding assay and the assays used to assess the immunogenicity of eladocagene exuparvovec in the pivotal clinical study including anti-AAV2 (b) (4) antibody assay, AAV2 neutralizing antibody assay, (b) (4) assay for anti-AAV2 and AADC cellular immune response, are adequately validated for their intended purpose.
- ❑ The PCR assay for virus shedding and the (b) (4) anti-AAV2 antibody assay used in supportive clinical studies are not adequately qualified.