Summary Basis for Regulatory Action

Date:	November 13, 2024
From:	Bo Liang, PhD Review Committee Chair Division of Gene Therapy 1 (DGT1) Office of Gene Therapy (OGT) Office of Therapeutic Products (OTP)
BLA STN:	125722/0
Applicant:	PTC Therapeutics, Inc.
Submission Receipt Date:	March 15, 2024
PDUFA Action Due Date:	November 13, 2024
Proper Name:	eladocagene exuparvovec-tneq
Proprietary Name:	KEBILIDI
Indication:	Treatment of adult and pediatric patients with aromatic L-amino acid decarboxylase (AADC) deficiency

* PDUFA=Prescription Drug User Fee Act

Recommended Action: The Review Committee recommends approval of this product.

_____

Director, Office of Clinical Evaluation

_____

Director, Office of Compliance and Biologics Quality

Discipline Reviews	Reviewer / Consultant - Office/Division
CMC • CMC Product (OTP/OGT, OCBQ/DMPQ and OCBQ/DBSQC) • Facilities review (OCBQ/DMPQ) • Pre-License Inspection and Establishment Inspection Report (OCBQ/DMPQ and OTP/OGT/DGT1) • QC, Test Methods, Product Quality (OCBQ/DBSQC)	Bo Liang, OTP/OGT/DGT1 Jacob Bitterman, OTP/OGT/DGT1 Susan Butler, OTP/OGT/DGT1 Prajakta A Varadkar, OCBQ/DMPQ Kinjal Patel, OCBQ/DMPQ Yen Phan, OCBQ/DBSQC Hsiaoling Wang, OCBQ/DBSQC Wei Tu, OCBQ/DBSQC Noel Baichoo, OCBQ/DBSQC
Clinical • Clinical (Product Office) • Postmarketing safety Pharmacovigilance review (OBPV/DE) • BIMO	Avanti Golikeri, OTP/OCE/DCEGM Shaokui Wei, OBPV/DPV Peter Lenahan, OCBQ/DIS
Statistical • Clinical data (OBPV/DB) • Non-clinical data	Jingyi Zhai, OBPV/DB
Non-clinical/Pharmacology/Toxicology • Toxicology (Product Office) • Developmental toxicology (Product Office) • Animal pharmacology	Mondona McCann, OPT/DPT1
Clinical Pharmacology	Sojeong Yi, OTP/OCE/DCEGM
Labeling • Promotional (OCBQ/APLB) • USPI Review • Proprietary Name Review • Package and Container	Benjamin Cyge, OCBQ/DCM/APLB Afsah Amin,CBER/OTP/OCE Oluchi Elekwachi OCBQ/DCM/APLB Tolani Ishola OTP/ORMRR
Other Review(s) not captured above categories, for example: • Consults • Devices • Software • Human Factors • FONSI	Consults: Andrey Sarafanov, OPPT/DH Device: Johnny Lam, OCTHT/DCT1 Gregg Kittlesen, CDRH/OHT5 Kyran Gibson, CDRH/OHT3
Advisory Committee Summary	N/A

Table of Contents

1. Introduction

PTC Therapeutics, Inc. submitted a Biologics License Application (BLA), STN 125722, for licensure of eladocagene exuparvovec-tneq, with the proprietary name of KEBILIDI. KEBILIDI is an adeno-associated virus (AAV) vector-based gene therapy indicated for the treatment of adult and pediatric patients with aromatic L-amino acid decarboxylase (AADC) deficiency.

KEBILIDI is designed to express functional AADC in transduced cells to increase dopamine synthesis. The total recommended dose of $1.8x10^{11}$ vector genomes (vg) is administered during a single neurosurgical procedure via 4 infusions into the putamen of the brain (2 into the anterior putamen, 2 into the posterior putamen). KEBILIDI is administered using a SmartFlow Neuro cannula that is authorized by FDA for intraparenchymal infusion.

This document summarizes the basis for an accelerated approval of KEBILIDI. Consistent with 21 USC 355, substantial evidence of effectiveness of KEBILIDI for patients with AADC deficiency is based on a single adequate and well-controlled investigation with confirmatory evidence. Specifically, a single-arm pivotal clinical study (n=13) and an external control natural history cohort comprised the adequate and well controlled investigation. KEBILIDI safety and efficacy is based on an analysis of a population consisting of 12 children with the severe phenotype of AADC deficiency enrolled in the clinical trial (1 child dropped out of the study). In this study, KEBILIDI was administered using the SmartFlow Neuro cannula. The primary efficacy outcome was motor milestone achievement at 48 weeks post-treatment assessed using the Peabody Developmental Motor Scale, Second Edition (PDMS-2).

The review team recommends accelerated approval of KEBILIDI based on an intermediate clinical endpoint of motor milestone achievement at Week 48 compared to an untreated natural history cohort. This intermediate endpoint is considered reasonably likely to predict clinical benefit. Effectiveness of KEBILIDI was demonstrated in achievement of new motor milestones after treatment, which was unexpected when compared to the untreated natural history cohort. Additional evidence included mechanism of action and pharmacodynamic data demonstrating post-treatment increases in cerebrospinal fluid (CSF) homovanillic acid (HVA) as a downstream metabolite of dopamine and putamen specific ^{18}F-DOPA uptake, reflecting increases in AADC activity. The major risks of KEBILIDI include procedural-related complications and dyskinesia and can be mitigated by post-procedural monitoring and use of dopamine antagonists, respectively. The risks of KEBILIDI are acceptable in the context of the serious manifestations of AADC deficiency, which has no FDA-approved therapies.

Overall, the benefit-risk assessment is favorable in the indicted population, and the approval will address an unmet medical need. Continued approval for this indication is contingent upon verification of the long-term clinical benefit in a confirmatory study. The review team recommends accelerated approval of the BLA with an accelerated approval Postmarketing Requirement (PMR) and CMC Postmarketing Commitments (PMCs) listed in Section 11.c of this document.

2. \Background

Aromatic L-amino acid decarboxylase (AADC) deficiency is a rare autosomal recessive neurodevelopmental disorder caused by biallelic mutations in the *DDC* gene, resulting in deficiency of AADC and decreased synthesis of dopamine, serotonin, norepinephrine, and epinephrine. Prevalence of AADC deficiency globally and within the United States is unknown, Wassenberg et al (2017) has identified 117 case reports in the literature, and estimated prevalence is roughly 1-2 in 1,000,000 newborns per the National Organization for Rare Disorders. However, due to the rarity of AADC deficiency, it is likely underdiagnosed.

Clinical presentation of AADC deficiency is heterogenous and is broadly classified into three main phenotypes: “mild”, “moderate”, and “severe”. The “severe” phenotype describes children who are unable to achieve any motor milestones (with gross motor function limited to poor or no head control) and have severe hypotonia, feeding difficulties, oculogyric crises (dystonic movements of the eye, face, neck that can last for several hours and occur several times per week), and autonomic dysfunction. Patients with the “severe” phenotype are completely dependent on caregivers and experience early mortality in childhood due to sequelae from hypotonia and autonomic dysfunction. The “mild” phenotype describes patients who have less gross motor impairment and can achieve the ability to ambulate independently. These patients, who can live into adulthood, may not experience motor impairments and experience primarily autonomic dysfunction as well as sleep and behavioral disturbances. The “moderate” phenotype describes patients who fall in between the “severe” and “mild” phenotypes, achieving some motor milestones (i.e., head control, sitting, standing) but are unable to ambulate independently.

There are no FDA-approved treatment options for AADC deficiency. Off-label use of oral medications such as dopamine agonists, monoamine oxidase inhibitors (MAOIs), and pyridoxine (B6) are considered standard of care (SoC). Patients with the severe phenotype of AADC deficiency do not demonstrate any improvements in motor function in response to these SoC therapies. Initiation of dopamine agonists in patients with the mild and moderate phenotype can result in rapid improvements in gross motor function and achievement of new motor milestones (including improvements in head control, sitting, standing and walking) that would be unexpected in these phenotypes. Improvements in hypotonia, oculogyric crises, and autonomic dysfunction have also been reported (Wen et al 2020). Due to the rarity of the disease and the limited case reports published in the literature, both responder rate and durability of standard of care medications is not characterized. Despite availability of SoC therapies, there remains unmet medical need for an FDA-approved treatment to address AADC deficiency, regardless of phenotype.

KEBILIDI is an AAV gene therapy product that delivers a functional copy of the *DDC* gene into the putamen of the brain and aims to increase levels of functional AADC in patients with AADC deficiency. This product was approved for use as UPSTAZA by the European Medicines Agency (EMA) and United Kingdom’s Medicinal Health Products Regulatory Agency (MHRA) in 2022 and by the Israel Ministry of Health in 2023 for children 18 months and older with the severe phenotype of AADC deficiency. At the time of BLA submission, a total of 4 patients had received the product in international commercial use.

Table 1. Regulatory History

Regulatory Events / Milestones	Date
1. IND submission	February 28, 2020
2. Orphan Drug designation granted	June 8, 2016
3. Pre-BLA meeting	December 12, 2023
4. Rare Pediatric Disease designation granted	November 7, 2016
5. BLA 125722/0 submission	March 15, 2024
6. BLA filed	May 13, 2024
7. Mid-Cycle communication	July 8, 2024
8. Late-Cycle meeting	August 29, 2024
9. Action Due Date	November 13, 2024

3. Chemistry Manufacturing and Controls (CMC)

The CMC review team concludes that the KEBILIDI manufacturing process is capable of yielding a product with consistent quality characteristics. The CMC review team recommends approval. KEBILIDI 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 KEBILIDI 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 ≤ -65 °C. After product thaw, each vial contains an extractable volume of 0.5 mL, for a single dose only.

a. Product Quality

Manufacturing summary

KEBILIDI is produced by (b) (4) adherent human embryonic kidney (b) (4) cells (b) (4) cells) (b) (4)

To manufacture the drug product, (b) (4) 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 x 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, packaged individually into cartons, and stored frozen at ≤ -65 °C.

Manufacturing control strategy

Consistency of 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 (Table 2). 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.

Process validation

(b) (4) drug product manufacturing process validation included 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 were also performed, including aseptic processing simulation and shipping validation studies. Process consistency will continue to be monitored and assessed post-approval according to the continued process verification (CPV) plan.

Impurity profile

Product-related and process-related impurities are monitored as in-process tests or release tests with acceptable limits. Product-related impurities including (b) (4) are monitored. The process-related impurities that are monitored include (b) (4) Most process-related impurities are removed during purification. (b) (4) Clearance of (b) (4) is monitored using in-process tests. Other impurities are measured as lot release tests. The acceptance limits for all impurities will be reassessed and revised after 10 commercial lots are manufactured as post-marketing commitments.

Stability

The drug substance is stable for (b) (4) when stored (b) (4) The drug product is stable for 48 months when stored frozen (≤-65 °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 drug product lots used in supportive clinical trials were not analytically comparable to drug product lots produced by the current manufacturing process. However, the current manufacturing process was utilized to produce the drug product used in the pivotal clinical study and is the commercial process.

Manufacturing risks
The risk of product contamination with microbial and viral adventitious agents is minimized by i) ensuring adequate control of raw materials, especially those of biological origin that are used in the generation of cell banks, virus banks, and product manufacturing; ii) testing of cell banks, virus banks, (b) (4) for microbials and adventitious viral agents; and iii) demonstrating robust viral clearance by the (b) (4) process. The risk of extractables and leachables that could originate from the product manufacturing process and the container closure system was analyzed, and the analytical studies and toxicological assessments were sufficient to mitigate this risk.

Compatible Delivery Devices
KEBILIDI is approved to be used with the SmartFlow Neuro Cannula. 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. Specific models of SmartFlow Neuro 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.

PMC
Two PMCs are needed to address thevalidation of two of the analytical methods. One PMC is needed to assess the suitability of the sterility test method to detect , an environmental isolate, to provide additional sterility assurance. Three PMCs are agreed upon to re-assess the acceptance limits for in-process tests (two) and lot release tests (all) after 10 commercial lots are manufactured.

b. Testing Specifications

Table 2. 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)		
Endotoxin	(b) (4)	
Sterility	(b) (4)	No growth

Abbreviation: (b) (4).

The analytical methods and their validations and/or qualifications reviewed for the (b) (4) (b) (4) drug product were found to be adequate for their intended use, except for the outstanding issues for (b) (4) testing of (b) (4) drug product. PTC Therapeutics provided a written commitment in amendment 50 (dated Oct. 8, 2024) to resolve the issue as a Postmarketing Study Commitment by May 31, 2025. An additional PMC is committed in amendment 55 to assess the suitability of the drug product sterility method to detect (b) (4) an environmental isolate, to provide additional sterility assurance in Annual Report on January 31, 2026.

c. CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of KEBILIDI along with activities performed and inspectional histories are listed in Table 3.

Table 3. Facilities Involved in the Manufacture and Testing of KEBILIDI

Name/Address	FEI Number	DUNS Number	Inspection / Waiver	Justification/ Results
(b) (4) *Drug substance (DS) and drug product (DP) manufacturing, and storage*	(b) (4)		Pre-License Inspection	No prior FDA inspection history
(b) (4) *DP release testing*	(b) (4)		Waived	ORA (OPQO) inspection (b) (4): VAI

(b) (4) *DP release testing*	(b) (4)		Waived	(b) (3) (A) ORA (OPQO MRA inspection review (b) (3) (A): VAI
(b) (4) *Primary labeling of final DP filled vials*	(b) (4)		Waived	ORA (OPQO) inspection (b) (4): NAI

ORA- Office of Regulatory Affairs (ORA has since been reorganized and renamed the Office of Inspections and Investigations);
OPQO- Office of Pharmaceutical Quality Operations; NAI – No Action Indicated; VAI – Voluntary Action Indicated; MRA- Mutual Recognition Agreement

The Division of Manufacturing and Product Quality (DMPQ) in CBER conducted a pre-license inspection (PLI) of the DS and DP manufacturer, (b) (4) , and a Form FDA 483 was issued at the end of the inspection. The firm's response to the observations and the corrective actions were reviewed and found to be adequate. The inspection was classified as Voluntary Action Indicated (VAI).

The Office of Regulatory Affairs (ORA)/Office of Pharmaceutical Quality Operations (OPQO) conducted a surveillance inspection of (b) (4) . Form FDA 483 was issued, and the inspection was classified as VAI.

(b) (3) (A) performed an inspection of (b) (4) A GMP Certificate was issued. ORA/OPQO reviewed the (b) (3) (A) inspection report under the Mutual Recognition Agreement in (b) (3) (A) and classified the inspection as VAI.

ORA/OPQO performed a surveillance inspection of (b) (4)
No Form FDA 483 was issued, and the inspection was classified as NAI.

e. Container/Closure System

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

(b) (4) . The container closure integrity (CCIT) was performed at (b) (4) facility using the (b) (4) . All acceptance criteria were met.

f. Environmental Assessment

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 clinical 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 made.

4. Nonclinical Pharmacology/Toxicology

In vitro pharmacology studies demonstrated that (b) (4) cells with rAAV2-AADC resulted in a dose-dependent increase in dopamine production.

Single-dose toxicology studies were conducted in (b) (4) rats and non-human primates (NHPs) using direct bilateral intraputaminal infusion. There were no significant adverse findings noted in a 6-month toxicology study in (b) (4) rats administered dose levels ranging from $7.5x10^8$ – $7.5x10^9$ vg/animal.

Biodistribution findings in this rat study support dose and time-dependent reductions in vector DNA levels in the putamen from Day (D) 7 to D180. Persistence of vector DNA was most notable in the putamen, cerebrum, cerebellum, and spinal cord at all time points, with the highest levels in the putamen. AADC RNA expression peaked at D30 and declined slightly or remained steady throughout subsequent timepoints. Anatomical distribution of AADC RNA was consistent with vector DNA results.

A 30-day toxicology study in NHPs to evaluate the safety of 0.001% poloxamer 188 did not identify any findings related to test article formulated with or without poloxamer 188 at dose levels of $7.02x10^9$ – $7.02x10^{10}$ vg/animal.

Studies to evaluate the safety pharmacology, developmental and reproductive toxicity, genotoxicity, and carcinogenicity/tumorigenicity of KEBLIDI were not conducted. These studies were not warranted based on the product characteristics and target patient population.

5. Clinical Pharmacology

The clinical pharmacology data is acceptable to support the accelerated approval of KEBILIDI. The pharmacodynamic data in this BLA provide mechanistic and pharmacodynamic evidence that serves as confirmatory evidence of effectiveness that supports the data from the single adequate and well controlled Study AADC-002. Together this data support substantial evidence of effectiveness in patients with AADC deficiency.

The clinical pharmacology review focused on the results from Study AADC-002 where the to-be-marketed product was infused at a total dose of 1.8×10^{11} vg into the putamen, as the supportive studies (studies AADC-010 and AADC-011) differed from Study AADC-002 in the drug product used, study design, and assays.

Pharmacodynamics
Pharmacodynamic data from Study AADC-002 included CSF HVA as a downstream metabolite of dopamine and putamen specific ^{18}F-DOPA uptake via PET scan reflecting AADC enzyme activity in the putamen. These were assessed at baseline, Week 8, and Week 48 post-treatment. All patients showed increases in both CSF HVA and putamen specific ^{18}F-DOPA PET uptake in the putamen starting as early as Week 8, maintained elevated through Week 48. At Week 8, CSF HVA increased from baseline by a median of 27 nmol/L (range: 12 to 57), which was maintained at Week 48 by a median of 25 nmol/L (range: 13 to 58). Putamen-specific ^{18}F-DOPA PET uptake increased from baseline by a median of 259% (range: 65% to 620%) at Week 8 and 271% (range: 25% to 760%) at Week 48. Of note, the post-treatment increases in CSF HVA and putamen specific ^{18}F-DOPA uptake were also observed in the supportive, ex-U.S. studies (AADC-010 and AADC-011) where a different manufactured version of the product was used.

The pharmacodynamic data including the increases in CSF HVA and putamen specific ^{18}F-DOPA PET uptake support the mechanism of action of KEBILIDI (i.e., the transgene expression of the AADC in the putamen leads to increased HVA and L-DOPA production). Given that AADC deficiency is caused by mutations in the *DDC* gene encoding the AADC enzyme in the brain, these pharmacodynamic data provide mechanistic and pharmacodynamic evidence that serves as confirmatory evidence of effectiveness in this BLA (supplementing the single adequate and well-controlled study AADC-002).

Pharmacokinetics
Biodistribution and viral shedding assessment in Study AADC-002 indicated that the risk for transmission to untreated individuals is low. Vector DNA was detected in the blood of 5 of 13 patients (38%) on Day 3, which fell below the limit of detection by Week 3. No viral vector was detected in any urine or CSF samples.

Immunogenicity
Patients with pre-existing anti-AAV2 neutralizing antibody titers >1:1200 at screening were not eligible for Study AADC-002. All patients who received KEBILIDI showed substantial increases in titers of anti-AAV2 antibodies (both total binding antibodies and neutralizing antibodies) starting from Week 3 post-treatment, which remained increased from baseline through Week 48. The highest titers of anti-AAV2 neutralizing antibody in each patient ranged from 1:80 to 1:10,240. Potential cellular immune response to KEBILIDI could not be assessed due to the limited number of samples. The currently available data is insufficient to determine the effect of anti-AAV2 antibodies on clinical efficacy, safety, pharmacokinetics, or pharmacodynamic profiles of KEBILIDI due to the small sample size and limited follow-up duration of Study AADC-002.

6. Clinical/Statistical

a. Clinical Program

To support the efficacy and safety of KEBILIDI, the Applicant submitted data from a single phase 2 study, Study AADC-002. The is an ongoing single arm, multicenter, open-label, 5-year study evaluating the safety and efficacy of a single KEBILIDI dose of 1.8 x 10^{11} vg in 13 children with genetically confirmed, severe AADC deficiency. The product was administered directly into the CNS in a single stereotactic neurosurgical procedure as 4 infusions into the putamen (2 in the anterior putamen, 2 in the posterior putamen). All 13 patients had the severe phenotype of AADC deficiency defined as having achieved no gross motor milestones at baseline and having had no historical clinical response to SoC therapies (e.g., dopamine agonists, MAOIs, and pyridoxine). Patients were determined to have skull maturity by imaging for neurosurgical device placement required for product administration. The key pre-specified efficacy endpoints included the change from baseline to week 48 in gross motor milestone achievement (assessed by the Peabody Developmental Motor Scale, second edition; PDMS-2), putaminal specific ^{18}F-DOPA PET uptake, and changes in neurotransmitter metabolites in CSF (HVA, 5-hydroxyindolaectic acid, and 3-OMD), at weeks 8 and 48 post-administration. Additional exploratory assessments were conducted on developmental domains/cognition, neurologic symptoms, and feeding/weight.

The 13 patients in Study AADC-002 had the following baseline characteristics: median age at treatment was 2.8 years (range 1.3-10.8 years); 7 patients (54%) were homozygous or compound heterozygous for the c.714+4A>T “founder” *DDC* variant (found in Asians); 7 patients (54%) were female; 10 patients (77%) were Asian, 2 patients (15%) were White, and 1 (8%) patient was of “other” race. All patients had achieved no gross motor milestone (score 0 or 1 on PDMS-2). The efficacy population includes 12 patients (one patient discontinued study participation prior to week 48 assessments). Of the 12 patients, 8 patients (67%) achieved a new gross motor milestone at week 48 (score 2 on PDMS-2 in at least “full head control”) post-product administration. The Applicant submitted cross-sectional data from an external cohort of 44 untreated patients with severe AADCD as a comparator group. Untreated patients in this cohort had severe gross motor developmental delay with no gross motor milestone achievement at a median age of 7.3 years (range 1.6 to 21 years).In the 8 treated patients with a clinical response, the highest motor milestone achieved included: 3 patients achieved “full head control”, 2 patients achieved “sitting with or without assistance”, 2 patients achieved “walking backwards”, and one patient was able to “sit unassisted.” In comparison, none of the 44 untreated patients had documented motor milestone achievement at last assessment. All 13 treated patients demonstrated consistent and sustained increases in HVA and L-DOPA, assessed via quantitative assessment in CSF and putaminal specific ^{18}F-DOPA PET uptake respectively. These pharmacodynamic effects on AADC disease-specific biomarkers reflect a direct treatment effect of the product on the molecular pathway of the disease and provide strong confirmatory evidence of effectiveness.

Substantial evidence of effectiveness for eladocagene exuparvovec in AADC deficiency is established based on data from a single adequate and well-controlled trial, Study AADC-002, and additional evidence of effectiveness was based on pharmacodynamic data from the same trial. The change from baseline to week 48 in gross motor milestone achievement (based on the PDSM-2 scale) was accepted as an intermediate clinical

endpoint that is reasonably likely to predict clinical (neurologic) benefit in this population. Additional follow-up of patients is needed to confirm clinical benefit in the post market setting. As such, the review team recommends accelerated approval based on gross motor milestone achievement at Week 48 with a post-marketing requirement to provide longer-term efficacy data to verify and describe the clinical benefit as well as demonstrate durability of the efficacy of KEBILIDI in patients with AADCD.

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

Bioresearch Monitoring (BIMO) inspections were issued for one domestic and one foreign clinical study site that participated in the conduct of Clinical Study PTC-AADC-GT-002. A third BIMO inspection was issued for an additional foreign site that participated in the conduct of a supportive study. The inspections did not reveal any issues that impact the data submitted in this original Biologics License Application (BLA).

c. Pediatrics

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the biological product for this indication has an orphan drug designation, this application is exempt from this requirement.

The clinical study for KEBILIDI was conducted in children between 1.3 to 10.8 years of age. The clinical data support the safety and effectiveness of KEBILIDI in children with AADC deficiency.

d. Other Special Populations

KEBILIDI has not been studied in any special populations.

7. Safety and Pharmacovigilance

The safety population was identical to the efficacy population, comprised of the 13 children who received treatment with KEBILIDI in Study AADC-002. Duration of follow-up ranged from 23 to 101 weeks (median 63 weeks). No safety data is available in one child after 23 weeks due to dropout from the study.

Serous adverse events included 2 cases of acute cardiac/respiratory failure occurring within 24 hours of the neurosurgical procedure for KEBILIDI administration, both recovered and both associated with post-operative/recovery related issues. An additional serious risk of cerebrospinal fluid leaks was identified in the 2 ex-U.S studies but none in Study AADC-002. Dyskinesia was the most commonly reported adverse event, occurring in 10 (77%) children within the first 3 months of KEBILIDI administration with two events requiring hospitalization. Remaining adverse events included: pyrexia (38%), hypotension (38%), anemia (31%), salivary hypersecretion (23%), hypokalemia (23%), hypophosphatemia (23%), insomnia (23%), and hypomagnesemia (15%). Post licensure safety surveillance activities will include routine pharmacovigilance with adverse event reporting in accordance with 21CFR 600.80. The data available currently do not suggest

any safety signals that warrant a Risk Evaluation and Mitigation Strategy (REMS) for this product. The identified risks can be mitigated through product labeling and routine pharmacovigilance.

8. Labeling

The proposed proprietary name, KEBILIDI, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on September 25, 2024, and was found acceptable. CBER communicated the acceptability of the proprietary name to the Applicant on October 7, 2024. PTC's proposed proper name suffix, -tneq, was reviewed and found acceptable on August 26, 2024. CBER communicated the acceptability of the proper name, eladocagene exuparvovec-tneq, to the Applicant on September 26, 2024.

Along with the review committee, APLB has performed iterative reviews of the proposed and revised prescribing information, container, and package labeling. As of October 31, 2024, the labeling is acceptable from a comprehension, readability, and promotional perspective.

9. Advisory Committee Meeting

This BLA was not referred to the Cellular, Tissue, and Gene Therapies Advisory Committee because the information submitted, including the clinical study design and trial results, did not raise concerns or controversial issues that would have benefitted from an advisory committee discussion.

10. Other Relevant Regulatory Issues

This application received Orphan Drug and Priority Review designations, and a Rare Pediatric Disease Priority Review Voucher.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

The Applicant provided substantial evidence of effectiveness and reasonable assurance of safety based on an adequate and well-controlled investigation. The review team recommends accelerated approval of KEBILIDI for the treatment of adult and pediatric patients with AADC deficiency based on an intermediate clinical endpoint of motor milestone achievement at Week 48.

b. Benefit/Risk Assessment

KEBILIDI administration demonstrates clinically meaningful improvements in motor milestone achievement in patients with the severe phenotype of AADC deficiency. This benefit outweighs the serious risks of KEBILIDI- procedural-related complications and dyskinesia. Given the lack of FDA-approved therapies for AADC deficiency regardless of phenotype and the mechanism of action of this gene therapy product aiming to restore the deficient AADC enzyme, the benefit-risk profile of KEBILIDI is considered favorable for all patients with AADC deficiency, regardless of phenotype and severity of presentation.

c. Recommendation for Postmarketing Activities

Accelerated approval regulations require that the Applicant conduct adequate and well-controlled trials to verify and describe the clinical benefit of KEBILIDI. The Applicant agreed to conduct the following studies:

1. Submit the clinical reports and datasets of clinical studies conducted in patients with AADC deficiency in the United States treated with KEBILIDI to verify and describe its clinical benefit. Such studies should, at minimum, evaluate the product's effects on the serious manifestations of AADC deficiency in adult and pediatric patients, including but not limited to motor function.

Final study report submission: September 30, 2029

The review team determined that KEBILIDI does not require a PMR safety study under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) or a REMS. The Applicant will conduct routine pharmacovigilance activities in accordance with 21 CFR 600.80

The Applicant agreed to the following CMC PMCs:

2. PTC commits to reassessing the acceptance criteria for release testing of KEBILIDI 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

3. 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

4. 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

5. PTC commits to perform additional robustness assessments for the (b) (4) (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

6. 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.

7. PTC commits to re-assessing the accuracy, precision, and linearity of the (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

12. References

Wassenberg, T, M Molero-Luis, K Jeltsch, GF Hoffmann, B Assmann, N Blau, A Garcia-Cazorla, R Artuch, R Pons, TS Pearson, V Leuzzi, M Mastrangelo, PL Pearl, WT Lee, MA Kurian, S Heales, L Flint, M Verbeek, M Willemsen, and T Opladen, 2017, Consensus guideline for the diagnosis and treatment of aromatic l-amino acid decarboxylase (AADC) deficiency, Orphanet J Rare Dis, 12(1):12.

Wen, Y, J Wang, Q Zhang, Y Chen, and X Bao, 2020, The genetic and clinical characteristics of aromatic L-amino acid decarboxylase deficiency in mainland China, Journal of Human Genetics, 65(9):759-769.