

**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Pharmacovigilance
Division of Pharmacovigilance**

Pharmacovigilance Review Memorandum

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Subject: Pharmacovigilance Plan Review

Sponsor: PTC Therapeutics

Product: Eladocagene exuparvovec

Proposed Indication: Treatment of patients with aromatic L-amino acid decarboxylase (AADC) deficiency

Submission Type/Number: BLA 125722/0

Submission Date: March 15, 2024

Action Due Date: November 14, 2024

1. OBJECTIVE

The purpose of this review is to assess the adequacy of the sponsor's pharmacovigilance plan (PVP) submitted under the original BLA 125722/0 based on the safety profile of Eladocagene exuparvovec. Our review will determine whether any safety-related studies such as Postmarketing Requirements (PMRs) are warranted and/or if there will be agreed-upon studies as Postmarketing Commitments (PMCs), or if Risk Evaluation and Mitigation Strategies (REMS) are required for Eladocagene exuparvovec, should this product be approved.

2. BACKGROUND

Aromatic L-amino acid decarboxylase (AADC) deficiency is an ultra-rare autosomal recessive disorder of dopaminergic and serotonergic pathways. It is caused by mutations in the DOPA decarboxylase (DDC) gene that encodes for AADC, the enzyme responsible for the decarboxylation of L-3,4-dihydroxyphenylalanine (L-DOPA) and 5-hydroxytryptophan (5-HTP) to form the neurotransmitters dopamine and serotonin, respectively. AADC deficiency causes a marked or complete loss of dopamine production in the brain that manifests in young children and most commonly results in failure to produce dopamine, profound motor development defect (e.g., full head control and the ability to sit, stand, and walk), cognitive dysfunction, and often death within the first decade of life.

Drug therapies currently prescribed for AADC deficiency are primarily intended to treat symptoms. Available pharmacological interventions include dopamine agonists, monoamine oxidase inhibitors, and pyridoxine therapies. Most patients do not respond to these available treatments because these therapies cannot replace or increase dopamine production in the brain, and therefore inadequately improve motor function and achieve developmental milestones.

3. PRODUCT INFORMATION

3.1 Product Description

Eladocagene exuparvovec is a gene therapy medicinal product that expresses human aromatic L-amino acid decarboxylase enzyme (hAADC). It is a nonreplicating recombinant adeno-associated virus serotype 2 (AAV2)-based vector containing the complementary deoxyribonucleic acid (cDNA) of the human DDC gene under the control of the cytomegalovirus immediate-early promoter. Eladocagene exuparvovec is produced in human embryonic kidney cells by recombinant DNA technology.

Eladocagene exuparvovec is provided in a single-dose 2 mL vial containing 2.8×10^{11} vector genomes (vg) of eladocagene exuparvovec in 0.5 extractable mL of solution. Each mL of solution contains 5.6×10^{11} vg of eladocagene exuparvovec. Eladocagene exuparvovec is administered by bilateral intraputamen infusion in one surgical session at two sites (anterior and posterior) per putamen. Patients will receive a total dose of 1.8×10^{11} vg delivered as four 0.08 mL (0.45×10^{11} vg) infusions (two per putamen).

After infusion into the putamen, the product results in the expression of hAADC enzyme and subsequent production of dopamine, which is required for functional, cognitive, and emotional development.

3.2 Proposed Indication

Eladocagene exuparvovec is indicated for the treatment of patients aged (b) (4) and older with (b) (4) aromatic L-amino acid decarboxylase (AADC) deficiency (b) (4)

OBPV defers to product office on the final language for the indication statement. Please see the final version of the package insert submitted by the sponsor for the final agreed-upon indication after FDA review.

4. PERTINENT REGULATORY HISTORY

Eladocagene exuparvovec received marketing authorization from the European Medicines Agency on 18 July 2022, from the United Kingdom Medicines and Healthcare Products Regulatory Agency on 17 November 2022, and from the Israel Ministry of Health on 18 February 2023. Eladocagene exuparvovec has been marketed under the trade name Upstaz™.

5. MATERIALS REVIEWED

Materials reviewed in support of this assessment include the following:

5.1 Pertinent Sections of the Licensing Application

- Section 1.14 Proposed Labeling, BLA 125722/0
- Section 1.16 Risk Management Plan (RMP), BLA 125722/0.44
- Section 2.7.4 Summary of Clinical Safety, BLA 125722/0
- Section 5.3.5 Reports of Efficacy and Safety Studies, BLA125722/0
- Section 5.3.6 Reports of Postmarketing Experience: Periodic Safety Update Report 03 - 17JUN2023 to 16DEC2023, BLA 125722/0
- Section 1.11.4 Response to FDA Information Request (IR)#11 dated June 25, 2024, BLA 125722/0.14
- Section 1.11.4 Response to FDA IR#25, AADC-MA-406 Registry Protocol, dated September 11, 2024, BLA 125722/0.35
- Section 1.11.4 Response to FDA IR#29 dated September 17, 2024, BLA 125722/0.44

5.2 Input from the Clinical Reviewer

In discussion with the clinical team, the clinical review team raised no new safety concerns that require additional safety-related studies as PMRs or agreed-upon studies as PMCs or required mitigation measures as a REMS for Eladocagene exuparvovec.

6. DESCRIPTION OF CLINICAL TRIAL SAFETY DATABASE

6.1 Clinical Studies

The clinical study safety data reviewed are from the Summary of Clinical Safety submitted to BLA125722/0. OBPV defers to the product office on final review of the clinical database, including safety and efficacy outcomes, which will inform the final language in the U.S. Package Insert (USPI). Below is our *focused* review of the sponsor data initially submitted to the BLA, to inform decisions pertaining to pharmacovigilance planning, should this BLA 125722/0 be approved. Please refer to the package insert for the final clinical safety data.

The safety data of Eladocagene exuparvovec was based on five prospective clinical studies (AADC-CU/1601, AADC-010, AADC-011, AADC-1602, and PTC-AADC-GT-002). A summary of each study and the pertinent safety issues is presented in Table 1. The safety data for Eladocagene exuparvovec were based primarily on results of Studies AADC-CU/1601, AADC-010, AADC-011 and Study PTC-AADC-GT-002. The long-term safety data were from observational long-term follow-up (LTFU) of patients treated in Study AADC-1602 and PTC-sponsored registry study (PTC-AADC-MA-406).

Table 1: Overview of Clinical Studies Contributing to the Safety Assessment of Eladocagene exuparvovec

Study ID Study Date	Study Design	Safety Endpoints	Route of Administration and Dose	Number of Patients	Study Status
AADC- CU/1601 27-Feb-2010 To 21-Aug-2017	Phase I, single arm, open label observational study	Collection of AEs, laboratory data, vital signs, electrocardiograms, physical examination, neurological findings, virus excretion	Bilateral intraputaminial infusion of a 1.8×10^{11} vg dose of eladocagene exuparvovec	8 patients (3M/5F)	Completed
AADC-010 22-Oct-2014 To 18-Dec-2020	Phase I/II, single arm, open label interventional study	Collection of AEs, laboratory data, vital signs, electrocardiograms, physical examination, neurological findings, virus excretion	Bilateral intraputaminial infusion of a 1.8×10^{11} vg dose of eladocagene exuparvovec	10 patients (5M/5F)	Completed
AADC-011 09-Nov-2016 To 24-Jan-2022	Phase IIb, single arm, open label interventional study	Collection of AEs, laboratory data, vital signs, electrocardiograms, physical examination, neurological findings, virus excretion	Bilateral intraputaminial infusion of a 1.8×10^{11} vg dose or 2.4×10^{11} vg dose of eladocagene exuparvovec	12 patients (8M/4F)	Completed
AADC-1602 23-Jun-2016 To 16-Jun-2023	Long-term follow-up study of subjects who received treatment in prior clinical studies	Collection of AEs	No additional product is given in this study	26 patients (13M/13F)	Ongoing, Interim study report

PTC-ADDC-GT-002 21-Jul-2021 To 27-Oct-2023	Phase II, open label interventional, device safety study	Assessment of AEs associated with the surgical administration of eladocagene exuparvovec to pediatric subjects using the SmartFlow MR-compatible ventricular cannula, other AEs, laboratory data, vital signs, physical examination, neurological findings, virus excretion	Bilateral intraputamenal infusion of a 1.8×10^{11} vg dose of eladocagene exuparvovec	13 patients (6M/7F)	Ongoing, Interim study report
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6.2 Adverse Events

The safety measures included treatment-emergent adverse events (TEAEs), serious AEs (SAEs), death, and adverse events of special interest.

6.2.1 Integrated Data (Studies AADC-CU/1601, AADC-010, and AADC-011)

6.2.1.1 Study design

Studies AADC-CU/1601, AADC-010, and AADC-011 were open-label, single center, single arm study clinical trials for AADC-deficient patients. Thirty subjects (16 males and 14 females) were included in three clinical studies (8 subjects in AADC-CU/1601, 10 subjects in AADC-010, and 12 subjects in AADC-011). The median age at treatment was 33 months and ranged from 19 months to 102 months. All subjects received intraputamenal infusions of eladocogene exuparvovec during a single operative procedure. Twenty-one subjects received a total dose of 1.8×10^{11} vg and nine subjects received a total dose of 2.4×10^{11} vg. The median duration of follow-up of subjects in the integrated analysis was 59.3 months with range of 11.8 to 68.3 months.

6.2.1.2 Study results

TEAEs and SAEs

All subjects experienced at least one TEAE within 13 months after gene therapy. Pyrexia and dyskinesia were the most frequently reported TEAEs within the first 13 months after treatment. Pneumonia, gingivitis, scoliosis, gastroenteritis, and upper respiratory tract infection were the most commonly reported AEs that occurred >13 months after treatment (Table A in Appendix).

All TEAEs considered by the investigator to be related to treatment occurred within the first 13 months following therapy. Dyskinesia was the most commonly occurring TEAE that was considered to be related to treatment and was experienced by almost all subjects (26 subjects, 86.7%) within the first 13 months after gene therapy. Pneumonia was the most frequently reported SAE, both within and >13 months after treatment. No SAE was considered by the investigator to be related to study treatment.

Twelve subjects (40.0%) had TEAEs that were identified as potentially related to the surgical procedure. Anemia was reported in 8 subjects and was considered to be a result of blood loss during surgery. Three subjects experienced four events of cerebrospinal fluid (CSF) leak. Two events in one subject were reported as SAE, and all other events were nonserious.

6.2.2 Study PTC-AADC-GT-002

6.2.2.1 Study design

Study PTC-AADC-GT-002 is an ongoing, open-label, phase 2 study to evaluate the safety of the SmartFlow magnetic resonance-compatible ventricular cannula in the administration of eladocogene exuparvovec to subjects with AADC deficiency. Thirteen patients have been treated with the 1.8×10^{11} vg dose of eladocogene exuparvovec in this study. At the data cutoff date (27-Oct-2023), 13 subjects had received gene therapy, and 10 subjects were ongoing in this study (three subjects withdrawn from study). The median age at treatment in Study PTC-AADC-GT-002 was 33 months and

ranged from 16 to 129 months. The median duration of follow-up was 14 months with range from 5 to 23 months.

6.2.2.2 Study results

TEAEs and SAEs

All subjects experienced at least one TEAE within 14 months after gene therapy (Table B in Appendix). The most frequently reported TEAEs were pyrexia (10 subjects, 76.9%) and dyskinesia (10 subjects, 76.9%). Nine subjects were reported with SAEs; pneumonia was the only SAE reported in more than 1 subject. Dyskinesia was the only SAE considered by the investigator to be related to gene therapy (2 events in 1 subject).

Ten subjects experienced a TEAE considered related to gene therapy, the most frequent of which was dyskinesia in 10 subjects. One subject experienced a TEAE (pyrexia) considered related to ¹⁸F-DOPA.

Eight subjects (61.5%) experienced TEAEs considered related to the surgical procedure. Pyrexia was the most frequently reported TEAE considered related to surgery. Anemia was reported in one subject. None of the events considered related to the surgical procedure were SAEs. No CSF leaks were reported in the study.

None of the TEAEs reported during the study was considered to be related to the surgical device.

6.2.3 Study AADC-1602

6.2.3.1 Study design

Study AADC-1602 is an ongoing long-term systematic follow-up study of patients with AADC deficiency to understand their prognosis and evaluate the effects of various treatments. Twenty-six subjects from the 3 clinical studies (AADC/CU-1601, AADC-010, and AADC-011) were enrolled in Study AADC-1602. The median duration of follow-up from the time of gene therapy was 79 months (6.6 years) and ranged from 27.2 to 126.5 months (approximately 2 to 10.5 years).

6.2.3.2 Study result

Twenty-three (88.5%) subjects experienced at least one TEAE during the long-term follow-up period (Table C in Appendix). The most frequently reported TEAEs were gingivitis (12 subjects, 46.2%) and scoliosis (9 subjects, 34.6%). Thirteen (57.7%) subjects were reported with SAEs; pneumonia was the most frequently reported SAE (7 subjects, 26.9%). None of the TEAEs reported during the study was considered to be related to eladocogene exuparvovec. No dyskinesia was reported in Study AADC-1602.

6.2.4 PTC-sponsored Registry Study (PTC-AADC-MA-406)

PTC-AADC-MA-406 is a two-part, international, real-world, observational registry of participants diagnosed with AADC deficiency with or without treatment with eladocogene exuparvovec. This registry is ongoing in the EU, Brazil, the United Kingdom (UK), Israel, the Kingdom of Saudi Arabia (KSA), Turkey, and the United States (US) for Part A of the registry, and in France, Germany, Italy, Spain, Brazil, and

the UK for Part B of the registry to monitor the safety and effectiveness of eladocagene exuparvovec.

As of 16 December 2023, 60 participants had been included in Study PTC-AADC-MA-406 at 17 sites in 4 European member states (France, Germany, Italy, and Spain), Brazil, the UK, Israel, the KSA, Turkey, and the US. Adverse events are not collected in the natural history Part A of protocol PTC-AADC-MA-406; however, they are collected in Part B. Eight participants have been treated and enrolled in Part B, and a total of 18 TEAEs have been reported cumulatively. These events were bradycardia, bronchitis, dyskinesia (5 reports), hyperphagia, fever (3 reports), gastrointestinal bleed, hyperphagia, motor dysfunction, nasopharyngitis, oral fungal infection, respiratory tract viral infection, and sleep disorder. Based on the IR response #29 dated September 17, 2024, most of these events were recovered/resolved, and three events (dyskinesia) were ongoing on the date of data cut of 16 June 2024.

As of 16 December 2023, four participants in Part A (natural history) have died during the study, and 25 participants have discontinued. Based on the IR response #29 dated September 17, 2024, these four patients died due to complications related to their underlying disease (AADC deficiency). Since they were not treated with eladocagene exuparvovec, they were not included in the six deaths reported in Study AADC-1602. Of 25 participants discontinued, 15 received eladocagene exuparvovec treatment, four received other AADC-d gene therapy, four died, one withdrawal, and one other (planned to receive gene therapy).

6.2.5 Deaths

In total, 6 subjects have died since receiving gene therapy in the eladocagene exuparvovec clinical studies (AADC/CU-1601, AADC-010, and AADC-011, and AADC-1602). A summary of each death report is presented in Table 2. All deaths except one (death occurred at 1 year) occurred five years after gene therapy administration. None of the deaths was considered related to gene therapy or the surgical procedure, and most were considered related to the underlying AADC deficiency by the sponsor. No deaths were reported in Study PTC-AADC-GT-002.

Table 2. Overview of Death Reports in Studies AADC/CU-1601, AADC-010, AADC-011, and AADC-1602

Case ID	Age at treatment (month)	Sex	Adverse Event	Time from treatment to Death	Death Cause
Subject (b) (6)	32	Male	Influenza B	1 year (12 months)	Encephalitis due to influenza B
Subject (b) (6)	99	Female	Death	7 years (84 months)	Aspiration
Subject (b) (6)	93	Male	Cyanotic and unresponsive	5 years (67 months)	Brain death

Case ID	Age at treatment (month)	Sex	Adverse Event	Time from treatment to Death	Death Cause
Subject (b) (6)	33	Female	Decreased saturation	10 years (120 months)	Organ failure
Subject (b) (6)	53	Male	Respiratory problem	5 years (65 months)	AADC deficiency
Subject (b) (6)	35	Female	Dehydration	6 years (74 months)	Cardiopulmonary arrest

Reviewer comment: Additional information on these six deaths is provided in a response to a clinical IR submitted to STN125722/0.15. Most cases had limited information regarding death. The sponsor stated that eladocogene exuparvovec treated patients may continue to have some autonomic dysfunction that can contribute to risk of aspiration and difficulties in thermoregulation, which likely contributed to death in these patients.

6.2.6 Adverse events of special interest

Dyskinesia

In Studies AADC-CU/1601, AADC-010, and AADC-011, twenty-six subjects (86.7%) experienced 37 events of dyskinesia. Dyskinesia was one of the most frequently reported TEAEs. Most events of dyskinesia resolved within 7 months of clinical onset. Most events were mild to moderate in severity; only 2 events were severe. Onset of dyskinesia generally occurred approximately a month after gene therapy. One event of dyskinesia occurred more than 12 months after eladocogene exuparvovec administration. The median time to first onset was 25 days and the median duration was 48 days. Events decreased over time, with a marked decline approximately 4 months after eladocogene Exuparvovec.

In Study PTC-AADC-GT-002, ten subjects (76.9%) experienced 16 events of dyskinesia, and the majority were mild or moderate; one event was an SAE that was considered severe. The median time to onset of first post-gene therapy dyskinesia was 27.5 days and median duration was 104.5 days.

Surgical-Related Adverse Events, Including CSF Leaks

In Studies AADC-CU/1601, AADC-010, AADC-011, twelve subjects (40.0%) had TEAEs that were identified as potentially related to the surgical procedure. Eight subjects (26.7%) experienced anemia that was considered to be a result of blood loss during surgery. Three subjects experienced four events of CSF leak. The events occurred approximately one month and five months after eladocogene exuparvovec infusion (These events occurred in the early study AADC-UC-1601 due to improper closure of burr holes. The problem has been resolved in the later studies AADC-011 and AADC-002). The majority of events were mild, two event of CSF leak in one subject were reported as SAEs. All events were resolved without intervention except one event of anemia.

In Study PTC-AADC-GT-002, eight subjects (61.5%) had TEAEs that were identified as related to the surgical procedure. Pyrexia was the most frequently reported TEAE considered related to surgery (four subjects). Anemia was reported in one subject. The majority of events were mild. None of the events considered related to the surgical procedure were SAEs. All events resolved with the exception of two events that were ongoing at the time of reporting (one event of skin pressure mark, one event of anemia). No CSF leaks were reported in Study PTC-AADC-GT-002.

Immunogenicity

In Studies AADC-CU/1601, AADC-010, AADC-011, all subjects showed minimal or no anti-AAV2 capsid antibody titers at baseline. An increase in anti-AAV2 capsid antibodies was detected from Month 2 post-surgery, and the titers tended to stabilize or decrease over time.

In Study PTC-AADC-GT-002, all subjects had serum total (IgG) and NAb anti-AAV2 antibody titers that were low (<1:200) or below the MRD at baseline. From Week 8 through 48 post treatment, all subjects had an increase in anti-AAV2 antibody titers. This increase in titers did not appear to affect safety or the production of dopamine.

Viral Shedding

No viral shedding was detected in Studies AADC-CU/1601 (blood samples) or AADC-010 (blood or urine samples). In Study AADC-011, virus excretion was detected in the urine of 1 subject at Month 6. The subject was unable to return to the site due to Coronavirus disease 2019 (COVID-19) travel restrictions, so no additional samples for this subject were collected at further timepoints.

In Study PTC-AADC-GT-002, no viral shedding was detected in pre- or post-surgery CSF or urine samples.

Reviewer comment: Data from these studies indicated that eladocogene exuparvovec had an acceptable safety profile and no long-term safety concerns were identified in the indicated patient population. All treatment-related AEs were well-known events following the gene therapy and are labeled in the proposed package insert.

When interpreting these findings, it should be noted that the sample size was small (43 subjects in Studies AADC-CU/1601, AADC-010, AADC-011, and PTC-AADC-GT-002; 26 subjects in Study AADC-1602), which is insufficient to detect the rare adverse events.

7. SUMMARY OF POSTMARKETING EXPERIENCE

There were nine patients exposed to eladocogene exuparvovec in postmarketing experience between 18 July 2022 (International birth date) and 16 December 2023. Out of those nine patients, six patients have been enrolled the registry Part B (details in section 6.2.4). There were no new safety concerns identified in post-market adverse event analyses.

8. SPONSOR'S PHARMACOVIGILANCE PLAN

The sponsor Risk Management Plan (RMP, Version 1.0) includes the Pharmacovigilance Plan (PVP). The summary of identified risks, potential risks, and the important missing information is presented in Table 3:

Table 3: Summary of Safety Concerns as Proposed by the Sponsor

Identified risk(s)	<ul style="list-style-type: none">• Dyskinesia• Procedural complications, including CSF leaks
Potential risk(s)	<ul style="list-style-type: none">• Tumorigenicity• Third party transmission
Missing information	<ul style="list-style-type: none">• Use in children ≤ 18 months old• Long-term safety (up to 5 years)

8.1 Analysis of Sponsor's PVP

8.1.1 Identified risks

Dyskinesia

Due to the chronic severe deficiency of dopamine, the sensitivity of the dopaminergic receptors in patients with AADC deficiency may be elevated. After treatment with eladocagene exuparvovec, over-sensitivity of the receptors may manifest as dyskinesia. This is a pharmacodynamic effect related to the restoration of dopamine to the sensitized dopamine-deficient brain. The sensitivity of the receptors decreases gradually after treatment, but it may take months to return to resolve.

In Studies AADC-CU/1601, AADC-010, and AADC-011, twenty-six subjects (86.7%) experienced 37 events of dyskinesia. Dyskinesia was the second most frequently reported adverse event (AE) in Studies AADC-CU/1601, AADC 010, and AADC-011. Onset of dyskinesia generally occurred approximately 25 days after gene therapy with a mean duration of approximately 2 months. Most events of dyskinesia resolved within 7 months of clinical onset. The majority of events were mild to moderate in severity; only 2 events were severe. Most dyskinesias were considered possibly/probably related to eladocagene exuparvovec. One event of dyskinesia occurred more than 12 months after eladocagene exuparvovec administration.

In Study PTC-AADC-GT-002, ten subjects (76.9%) experienced 16 events of dyskinesia. Dyskinesia was the second most frequently reported adverse event (AE) in Study PTC-AADC- GT-002. The majority were mild or moderate; one event was a serious adverse event (SAE) that was considered severe. Median time to onset of first post-gene therapy dyskinesia was 27.5 days and median duration was 104.5 days.

Procedural Complications, Including CSF Leaks

Eladocagene exuparvovec is administered by bilateral intracerebral infusion into the putamen in one surgical session at 2 sites per putamen, which is a minimally invasive neurosurgery with general anesthesia. The common risks including hemorrhage, stroke, infection (around the surgery site) and CSF leaks which occur when there is a tear or hole in the membranes surrounding the brain or spinal cord, allowing the clear fluid that surrounds and cushions those organs to escape.

In Studies AADC-CU/1601, AADC-010, and AADC-011, 12 subjects (40.0%) had treatment-emergent adverse events (TEAEs) that were identified as potentially related to the surgical procedure. Anemia was reported in 8 subjects and was considered to be a result of blood loss during surgery. Two events in one subject were reported as SAEs; all other events were nonserious. The majority of events were mild, and none was considered related to gene therapy. All events resolved, with the exception of one event of anemia. Three subjects experienced four events of cerebrospinal fluid leak. The events occurred approximately one month and five months after eladocagene exuparvovec infusion. Three events were mild, and one was moderate in severity, and all events were resolved without intervention.

In Study PTC-AADC-GT-002, eight subjects (61.5%) had TEAEs that were identified as related to the surgical procedure. Pyrexia was the most frequently reported TEAE considered related to surgery (4 subjects). Anemia was reported in one subject. None of the events considered related to the surgical procedure were SAEs. The majority of events were mild. All events resolved with the exception of 2 events that were ongoing at the time of reporting (one event of skin pressure mark, one event of anemia). No AEs of CSF leakage have been reported, and no evidence of leaks were found in brain imaging assessments.

8.1.2 Potential risks

Tumorigenicity

As a virus (adeno-associated virus [AAV]) is used for delivery of hAADC cDNA, the potential for tumorigenicity due to insertional mutagenesis needs to be considered. This is a gene therapy specific risk consideration. Potentially life-threatening, but minimal likelihood of occurrence based on studies to date. No evidence from studies with the product. The potential for eladocagene exuparvovec to cause tumorigenicity is being evaluated in the long-term follow-up study (Study AADC-1602), which will follow treated subjects for 10 years after receiving eladocagene exuparvovec therapy.

Third Party Transmission

Third-party transmission occurs via exposure from handling, preparing, or administering the product and waste materials, or from shedding of the product after administration. AEs would be similar to those observed in patients who administered the product but excluding those attributable to the administration procedure. AEs secondary to chronic severe deficiency of dopamine (e.g., dyskinesia) will probably not occur in a healthy third party. AEs are expected to be mild and transient.

8.1.3 Important missing information

Use in children ≤18 months old

Majority of the AADC population that are treated in the clinical studies are ≥18 months old. One child aged 16 months has been included in Study PTC-AADC-GT-002. Thus, treatment of further patients aged 18 months and below are required to determine the safety profile in this population.

Long-term safety (up to 5 years)

This is a gene therapy specific risk consideration. Although not anticipated, long-term safety issues may occur. Patients exposed to eladocogene exuparvovec should be followed for up to 5 years to further characterize this risk.

8.2 Analysis of Sponsor's PVP Activities

8.2.1 Routine Pharmacovigilance

The sponsor proposed to use routine pharmacovigilance to monitor postmarketing safety of Eladocogene exuparvovec. Routine pharmacovigilance activities include adverse reactions reporting, signal detection, cumulative review, and periodic safety update report production.

8.2.2 Additional Pharmacovigilance Activities

Additional pharmacovigilance activities are further intended to evaluate the long-term safety of eladocogene exuparvovec. Studies PTC-AADC-GT-002 and PTC-AADC-MA-406 (Part A and Part B) will further evaluate long-term safety.

PTC-AADC-MA-406: A Two-Part, International, Real-World, Observational Registry of Participants Diagnosed with Aromatic L-Amino Acid Decarboxylase Deficiency (AADC-d) With or Without Treatment with Eladocogene Exuparvovec

Part A: United States, Italy, Germany, France, United Kingdom, Brazil, Spain, Turkey, and Saudi Arabia.

Part B: France, Italy, and the United Kingdom. Additional countries may be added based on the commercial availability of eladocogene exuparvovec. (PTC agreed to include US sites in Part B of the PTC-AADC-MA-406 registry in IR response dated September 17, 2024, submitted to STN125722/0.44).

Objectives

Part A: To describe the natural history of AADC-d in participants on standard of care (SoC).

Part B: To assess the long-term effectiveness and safety of treatment in motor function over time with eladocogene exuparvovec in participants with AADC-d for a minimum of 10 years.

Design

This is an international, multicenter, longitudinal, real-world, observational registry of untreated participants diagnosed with AADC-d (Part A) and participants who

have been treated with eladocogene exuparvovec (Part B). Part A of the registry is to observe the natural history of AADC-d, with the intention of gathering data about the AADC-d diagnosis, disease progression, SoC, and healthcare resources utilization, among other aspects. For Part B, participants will be followed for long-term clinical efficacy outcomes and safety for a minimum of 10 years following eladocogene exuparvovec administration.

Endpoints

Parts A and B:

- Acquisition of motor milestones as measured by the Peabody Developmental Motor Scale, second edition (PDMS-2).
- Changes in motor function over time as measured by the Gross Motor Function Measure-88 (GMFM-88).
- Changes in cognitive and language development over time as measured by the Bayley Scales of Infant and Toddler Development, third edition (Bayley-III).
- Changes in OGC episodes over time.
- Changes in symptoms of interest (e.g., respiratory tract infections, feeding tube dependence, and body weight) over time.
- Changes in PRO (quality of life as measured by the Pediatric Quality of Life Inventory [PedsQL], Euro-QoL-5-Dimension [EQ-5D], and Health Utilities Index Mark 3 [HUI3]) over time.

Part B Only:

- Number and frequency of adverse events (AEs) and serious adverse events (SAEs).

Number of participants

Part A, the enrollment target is approximately 50 participants with a diagnosis of AADC-d.

Participants who subsequently receive eladocogene exuparvovec will move into Part B of the registry. Additionally, individuals who receive or previously received eladocogene exuparvovec as part of a clinical study or early access program and are not otherwise included in a clinical study for long-term follow-up are eligible to enroll directly into Part B.

The enrollment target for Part B is a minimum of 50 participants or, if not achievable, at least 50% of all patients who receive eladocogene exuparvovec treatment during the 5-year enrollment period.

Duration

Part A: Approximately 7 years (2-year enrollment period + minimum 5-year follow-up for each participant).

Part B: Approximately 15 years (5-year enrollment period + minimum 10-year

follow-up for each participant post-treatment).

Participants in Part A who receive eladocogene exuparvovec treatment will progress into Part B and be followed up for a minimum of 10 years post-treatment.

Reviewer comment: *In response to FDA feedback, the Sponsor submitted an updated PVP (version 1.0, STN 125722/0.44) in which the Sponsor revised the PVP activities by including Studies PTC-AADC-GT-002 and PTC-AADC-MA-406 (Part A and Part B) to further evaluate long-term safety. The registry study PTC-AADC-MA-406 is considered a voluntary postmarketing sponsor study.*

Reviewer's assessment: *The sponsor's proposed post-marketing pharmacovigilance plan is adequate for all safety concerns noted in Table 3. No new safety signals have been identified that would justify further assessment with a PMR or require mitigation under a REMS. There is no agreed-upon study as a PMC.*

9. DPV ASSESSMENT

Based on the review of safety data in five clinical studies (AADC-CU/1601, AADC-010, AADC-011, AADC-1602, and PTC-AADC-GT-002), we conclude that Eladocogene exuparvovec has an acceptable safety profile and no new safety concerns were identified in the indicated patient population that would require additional characterization in postmarketing studies or additional mitigation. DPV concurs with the sponsor's proposed pharmacovigilance activities in the proposed RMP.

10. DPV RECOMMENDATIONS

Should Eladocogene exuparvovec be approved, DPV agrees with routine pharmacovigilance for safety monitoring, as proposed by the sponsor in the RMP, with adverse event reporting as required under 21 CFR 600.80. The reviewed available safety data do not indicate a need for safety-related studies as PMRs, or a REMS. There are no safety-related studies as PMCs for this product. The sponsor will conduct a long-term follow-up safety study (PTC-AADC-MA-406) as a voluntary study. Please see the final version of the Package Insert submitted by the sponsor for the final agreed-upon language describing Eladocogene exuparvovec.

Appendix

Table A: Treatment-Emergent Adverse Events Reported in ≥10% of Subjects in Studies AADC-CU/1601, AADC-010, and AADC-011)

Adverse Event Category ^a	1.8×10 ¹¹ vg Dose (%) (N=21)	2.4×10 ¹¹ vg Dose (%) (N=9)	Overall (%) (N=30)
Total Number of TEAEs	467	149	616
Subjects With ≥1 TEAE	21 (100.0)	9 (100.0)	30 (100.0)
Pyrexia	21 (100.0)	9 (100.0)	30 (100.0)
Dyskinesia	21 (100.0)	5 (55.6)	26 (86.7)
Upper respiratory tract infection	14 (66.7)	7 (77.8)	21 (70.0)
Pneumonia	15 (71.4)	4 (44.4)	19 (63.3)
Gastroenteritis	14 (66.7)	4 (44.4)	18 (60.0)
Upper gastrointestinal haemorrhage	13 (61.9)	3 (33.3)	16 (53.3)
Diarrhoea	11 (52.4)	2 (22.2)	13 (43.3)
Hypotension	5 (23.8)	6 (66.7)	11 (36.7)
Breath sounds abnormal	3 (14.3)	7 (77.8)	10 (33.3)
Gingivitis	7 (33.3)	3 (33.3)	10 (33.3)
Anaemia	4 (19.0)	4 (44.4)	8 (26.7)
Cyanosis	7 (33.3)	1 (11.1)	8 (26.7)
Dehydration	4 (19.0)	2 (22.2)	6 (20.0)
Developmental hip dysplasia	5 (23.8)	1 (11.1)	6 (20.0)
Hypokalaemia	5 (23.8)	1 (11.1)	6 (20.0)
Mouth ulceration	4 (19.0)	2 (22.2)	6 (20.0)
Scoliosis	6 (28.6)	0	6 (20.0)
Dermatitis diaper	3 (14.3)	2 (22.2)	5 (16.7)
Eczema	3 (14.3)	2 (22.2)	5 (16.7)
Tooth extraction	4 (19.0)	1 (11.1)	5 (16.7)
Bronchitis	4 (19.0)	0	4 (13.3)
Decubitus ulcer	2 (9.5)	2 (22.2)	4 (13.3)
Dental caries	3 (14.3)	1 (11.1)	4 (13.3)
Gastrooesophageal reflux disease	4 (19.0)	0	4 (13.3)
Hypovolaemic shock	4 (19.0)	0	4 (13.3)
Initial insomnia	4 (19.0)	0	4 (13.3)
Acute sinusitis	3 (14.3)	0	3 (10.0)
Bradycardia	2 (9.5)	1 (11.1)	3 (10.0)
Bronchiolitis	2 (9.5)	1 (11.1)	3 (10.0)
Cerebrospinal fluid leakage	3 (14.3)	0	3 (10.0)
Choking	1 (4.8)	2 (22.2)	3 (10.0)
Feeding disorder	3 (14.3)	0	3 (10.0)
Influenza	3 (14.3)	0	3 (10.0)
Irritability	0	3 (33.3)	3 (10.0)
Joint dislocation	2 (9.5)	1 (11.1)	3 (10.0)
Nasopharyngitis	3 (14.3)	0	3 (10.0)
Ocular hyperaemia	2 (9.5)	1 (11.1)	3 (10.0)
Otitis media acute	3 (14.3)	0	3 (10.0)
Rash	1 (4.8)	2 (22.2)	3 (10.0)
Respiratory failure	2 (9.5)	1 (11.1)	3 (10.0)
Stress ulcer	2 (9.5)	1 (11.1)	3 (10.0)

Table B: Summary of Treatment-Emergent Adverse Events by PT Reported in ≥2 Subjects in Study PTC-AADC-GT-002

Adverse Event Category	Number of Subjects (%) (N=13)
Total number of TEAEs	241
Subjects with ≥1 TEAE	13 (100.0)
Dyskinesia	10 (76.9)
Pyrexia	10 (76.9)
Diarrhoea	8 (61.5)
Cough	5 (38.5)
Dermatitis diaper	5 (38.5)
Anaemia	4 (30.8)
Hypotension	4 (30.8)
Nasopharyngitis	4 (30.8)
Pneumonia	4 (30.8)
Vomiting	4 (30.8)
COVID-19	3 (23.1)
Hypokalaemia	3 (23.1)
Hypophosphataemia	3 (23.1)
Influenza	3 (23.1)
Insomnia	3 (23.1)
Nasal congestion	3 (23.1)
Rhinorrhoea	3 (23.1)
Salivary hypersecretion	3 (23.1)
Upper respiratory tract infection	3 (23.1)
Contusion	2 (15.4)
Eye swelling	2 (15.4)
Hypoglycaemia	2 (15.4)
Hypomagnesaemia	2 (15.4)
Hypoxia	2 (15.4)
Oculogyric crisis	2 (15.4)
SARS-CoV-2 test positive	2 (15.4)
Scratch	2 (15.4)
Viral test positive	2 (15.4)

Table C. Treatment-Emergent Adverse Events Reported in ≥3 Subjects in Study AADC-1602

Adverse Event Category	Number of Subjects (%) (N=26)
Total Number of TEAEs	213
Subjects with ≥1 TEAE	23 (88.5)
Pyrexia	2 (7.7)
Dyskinesia	0
Upper respiratory tract infection	6 (23.1)
Pneumonia	7 (26.9)
Gastroenteritis	6 (23.1)
Upper gastrointestinal haemorrhage	3 (11.5)
Diarrhoea	5 (19.2)
Hypotension	3 (11.5)
Breath sounds abnormal	0
Gingivitis	12 (46.2)
Anaemia	2 (7.7)
Cyanosis	0
Dehydration	2 (7.7)
Developmental hip dysplasia	6 (23.1)
Hypokalaemia	2 (7.7)
Mouth ulceration	1 (3.8)
Scoliosis	9 (34.6)
Dermatitis diaper	2 (7.7)
Eczema	1 (3.8)
Tooth extraction	0
Bronchitis	1 (3.8)
Decubitus ulcer	1 (3.8)
Dental caries	2 (7.7)
Hypovolaemic shock	2 (7.7)
Initial insomnia	0
Bronchiolitis	1 (3.8)
Cerebrospinal fluid leakage	0
Feeding disorder	0
Influenza	3 (11.5)
Irritability	0
Joint dislocation	4 (15.4)
Rash	1 (3.8)
Respiratory failure	2 (7.7)
Cough	3 (11.5)
Nasopharyngitis	3 (11.5)
COVID-19	6 (23.1)