BLA CLINICAL & CLINICAL PHARMACOLOGY REVIEW MEMORANDUM

Application Type	351(a) original BLA
STN	125722
CBER Received Date	03/15/2024
PDUFA Goal Date	11/13/2024
Division / Office	Division of Clinical Evaluation-General Medicine/Office of Clinical Evaluation/OTP/CBER
Priority Review (Yes/No)	Yes
Reviewer Name(s)	Avanti Golikeri, MD (Clinical) Sojeong Yi, PhD (Clinical Pharmacology)
Review Completion Date	
Supervisory Concurrence Team Lead Branch Chief Division Director	 Shelby Elenburg, MD Elizabeth Hart, MD Patroula Smpokou, MD
Applicant	PTC Therapeutics, Inc.
Established Name	Eladocagene exuparvovec
(Proposed) Trade Name	KEBILIDI
Pharmacologic Class	Adeno-associated virus (AAV) vector-based gene therapy
Formulation(s), including Adjuvants, etc.	Adeno-associated virus vector type 2 (rAAV-hAADC) expressing (b) (4)-AADC
Dosage Form(s) and Route(s) of Administration	Suspension for intraparenchymal CNS administration
Dosing Regimen	Single dose $1.8x10^{11}$ vg delivered as four $0.45x10^{11}$ vg intra-parenchymal (putaminal) infusions during single neurosurgical stereotactic surgery
Approved Indication	Treatment of adult and pediatric patients with aromatic L-amino acid decarboxylase (AADC) deficiency
Orphan Designated (Yes/No)	Yes

TABLE OF CONTENTS

GLOSSARY

3-OMD	3-O-methyl-L-3,4-dihydroxyphenylalanine
5-HIAA	5-hydroxyindoleacetic acid
^{18}F-DOPA	L-6-[18F] fluoro-3, 4-dihydroxyphenylalanine
AADC	aromatic L-amino acid decarboxylase enzyme
AADCD	aromatic L-amino acid decarboxylase deficiency
AAV	adeno-associated virus
anti-AAV2	anti-adeno-associated virus serotype 2
BLA	biologics license application
BSITD-III	Bayley Scales of Infant and Toddler Development, third edition
CMC	chemistry, manufacturing, and controls
CSF	cerebrospinal fluid
CT	computed tomography
FDA	U.S. Food and Drug Administration
hAADC	human aromatic L-amino acid decarboxylase enzyme
HPLC-MS/MS	high-performance liquid chromatography with tandem mass spectrometry
HVA	homovanillic acid
IND	investigational new drug application
IR	information request
L-DOPA	L-3,4-dihydroxyphenylalanine
MAOI	monoamine oxidase inhibitors
MR/MRI	magnetic resonance/magnetic resonance imaging
NAb	neutralizing antibodies
NHDB	Natural History Database
NORD	National Organization for Rare Disorders
PDMS-2	Peabody Developmental Motor Scale, second edition
PET	positron emission tomography
SAE	serious adverse event
TAb	total binding antibody
vg	vector genome

1. EXECUTIVE SUMMARY

On March 15, 2024, PTC Therapeutics submitted an original Biologics Licensing Application (BLA), STN BL 125722, for accelerated approval of eladocagene exuparvovec. The Applicant proposed the indication "for treatment of aromatic L-amino acid decarboxylase deficiency."

Aromatic L-amino acid decarboxylase deficiency (AADCD) is a rare, autosomal, recessive disorder that results from biallelic mutations in the *DDC* gene, leading to a deficiency in the aromatic L-amino acid decarboxylase (AADC) enzyme. The AADC enzyme is responsible for several decarboxylation reactions required for the synthesis of neurotransmitters. A deficiency in the AADC enzyme results in deficiencies in dopamine, epinephrine, norepinephrine, and serotonin. Clinical manifestations of AADCD include global developmental delay (including delay or lack of motor milestone achievement), hypotonia, autonomic dysfunction, sleep abnormalities and irritability.

Clinical presentation of AADCD is heterogenous and 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), 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 for activities of daily living and experience early mortality in childhood due to these impairments. The "mild" phenotype includes patients who have less gross motor impairment and can achieve the ability to ambulate independently. Some of these patients with mild disease, who can live into adulthood, may not have any 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 master independent ambulation.

There are no FDA-approved therapies for AADCD. Off-label use of oral medications such as dopamine agonists, monoamine oxidase inhibitors (MAOIs), and pyridoxine (B6) are considered current standard of care therapies. Symptomatic management with anticholinergic drugs and benzodiazepines is also considered on a case-by-case basis. Patients with severe AADCD have not been observed to respond to these therapies, while patients with mild and moderate disease generally have rapid and robust improvements in motor function after initiation of these standard of care therapies. Regardless of phenotype, there is unmet medical need for an FDA-approved therapy to target the underlying cause of AADCD.

Eladocagene exuparvovec is a recombinant adeno-associated virus serotype 2 (AAV2)-based gene therapy product that contains a copy of the human *DDC* gene. A single dose

of 1.8 x 10^{11} vg is administered over four intraputaminal infusions utilizing SmartFlow® Cannula (manufactured by ClearPoint Neuro) during a single stereotactic neurosurgical procedure. Of note, a de novo submission for SmartFlow Cannula is being reviewed in parallel with this BLA review by the Center for Devices and Radiological Health.

Consistent with 21 USC 355(d), the Applicant proposes to support substantial evidence of effectiveness of eladocagene exuparvovec for AADCD with a single adequate and well controlled trial and confirmatory evidence from mechanistic and pharmacodynamic data. Specifically, the single trial consists of data from Study AADC-002, a single-arm, multicenter, open-label trial in children with severe AADCD treated with the product compared to data from an external natural history cohort of untreated children with severe AADCD. Study AADC-002 enrolled 13 children with the severe phenotype of AADCD, defined by the Applicant as having achieved no gross motor milestone at baseline and having previously demonstrated no clinical response to standard of care medications. Efficacy data was available in 12 of the 13 enrolled children, with one dropout at week 23 prior to completion of any efficacy assessments.

The Applicant requested accelerated approval based on improvement in cerebrospinal fluid (CSF) homovanillic acid (HVA) levels, a byproduct of dopamine breakdown. The Applicant proposed that ≥20% increase from baseline to Week 8 after treatment in CSF HVA is reasonably likely to predict clinical benefit, defined as long-term improvements in gross motor milestone achievement. For this analysis, the Applicant proposed to use each patient as their own control (baseline-controlled comparison). To characterize the relationship between CSF HVA and clinical outcomes, data from 22 children treated with eladocagene exuparvovec in two open-label, single arm studies conducted in Taiwan were submitted. Of note, these 2 studies utilized a product that was deemed to have (b) (4) compared to the intended United States commercial product used in pivotal study AADC-002 and, thus, they two products are not considered comparable. As such, data on safety and efficacy of the product used in the 2 Taiwan studies are not considered in the safety and efficacy assessments of this application or as supportive evidence for using CSF HVA for accelerated approval.

The review team identified several limitations to the Applicant's proposed justification and evidence to support that a ≥20% increase from baseline to week 8 after treatment in CSF HVA is a surrogate endpoint reasonably likely to predict clinical benefit. This included the following observations: post-treatment CSF HVA levels remained substantially below normal and within the range of levels measured in untreated patients; there was no observed correlation between post-treatment parameters of CSF HVA (absolute post-treatment levels, absolute change from baseline, and percent change from baseline) and gross motor outcomes in the treated patients; uncertainty and lack of evidence to support the Week 8 timepoint for assessment of HVA changes; lack of longitudinal data in healthy children and in untreated children with AADCD to characterize the levels and degree of interpatient and intrapatient variability in CSF HVA.

Overall, the submitted justification and evidence did not support the use of CSF HVA as a surrogate endpoint reasonably likely to predict clinical benefit on motor manifestations in treated patients with AADCD.

Despite the uncertainty in the proposed primary endpoint, substantial evidence of effectiveness was observed in the proposed secondary endpoint of motor milestone achievement assessed using the Peabody Developmental Motor Scale, Second Edition (PDMS-2). Motor milestone achievement in the treated children at Week 48 was compared to data on an external cohort of untreated children submitted by the Applicant in a "Natural History Database" (NHDB). The NHDB collated motor outcome data from published case reports of untreated children with AADCD. 11 of 12 evaluable patients treated in study AADC-002 had no motor milestone achievement at baseline and were categorized as having "severe" disease. Seven of the 11 treated patients (64%) gained new motor milestones after 48 weeks of eladocagene exuparvovec treatment; specifically, 3 patients achieved full head control, 2 patients achieved sitting with or without assistance, and 2 patients achieved walking backwards. These are unexpected outcomes compared to the natural history cohort, where 40 (91%) children had no documented motor milestone achievement and 4 (9%) had at least one motor function assessment limited to incomplete head control at a median age of 7.3 years (1.6-19 years). The one remaining patient out of the 12 in Study AADC-002 was identified as having a "variant" of the severe phenotype, with no head control but the ability to sit with assistance at baseline. After treatment, this patient achieved the ability to sit without assistance but remained without full head control. While there were no children in the natural history cohort with a similar clinical presentation, the observed improvement in motor function can be attributed to the gene therapy. Despite early evidence of clinical benefit of eladocagene exuparvovec in these 8 children, there is uncertainty regarding the durability of the treatment effect on gross motor achievement as patient follow-up was limited to less than 2 years from product administration. In addition, two treated patients showed signs of potential waning of the treatment effect over longer term follow up. At last follow-up, both patients no longer had full mastery of their highest achieved motor milestone (sitting unassisted and sitting with assistance), assessed as having only partial ("emerging" per PDMS-2 scale) achievement of these milestones,

Clinical Reviewer and Clinical Pharmacology Reviewer Conclusions

Given the uncertainties in the proposed CSF HVA surrogate biomarker and the unknown durability of the motor outcome improvements seen in the treated children, the clinical and clinical pharmacology review teams recommend accelerated approval based on an intermediate clinical endpoint of gross motor milestone achievement at Week 48, where early improvements in motor outcomes are thought to be reasonably likely to predict long-term clinical benefit on motor function. The confirmatory study, which will follow motor milestone achievement in the study patients until 60 months post treatment, will be used to verify and describe the clinical benefit of the product and to characterize the

durability of the motor benefits. No efficacy data were submitted on adults or patients with other AADCD phenotypes (mild and moderate). Additionally, there is uncertainty in the efficacy of eladocagene exuparvovec on the non-motor manifestations of AADCD.

Confirmatory evidence of effectiveness includes pharmacodynamic data demonstrating post-treatment increases in CSF HVA (a downstream metabolite of dopamine) and ^{18}F-DOPA uptake into the putamen, reflecting increases in AADC enzyme activity and mechanistic evidence of the product's mechanism of action as supplying the missing enzyme and, thus, directly target the underlying cause of the disease.

The most significant observed risks from eladocagene exuparvovec in children treated in Study AADC-002 include events of cardiac and respiratory failure and dyskinesia. The events of cardiac and respiratory failure occurred in two children within 24 hours of the neurosurgical procedure for product administration. While the provided patient narratives suggest that these events may be related to autonomic instability secondary to underlying disease, these events appear to have been precipitated by study procedures required to receive the gene therapy. Therefore, the clinical reviewer assessed these events to meet the following criteria of the 2007 Food and Drug Administration Amendments Act to require a post-marketing safety study: "Assess signals of serious risk related to use of the drug." However, the decision was made at the office and division level that a post-marketing safety study would not be issued. These risks were instead captured in the product labeling, where events of cardiac and respiratory failure were included under "Procedural-Related Complications" in section 5. Dyskinesia, reported in 77% of children treated in Study AADC-002, was the most common adverse reaction. Other adverse reactions in ≥15% of children included pyrexia, hypotension, anemia, salivary hypersecretion, hypokalemia, hypophosphatemia, insomnia, and hypomagnesemia.

AADCD is a rare, autosomal, recessive, neurodevelopmental disorder with high unmet medical need, particularly in children with the severe phenotype. Despite uncertainties regarding the proposed surrogate endpoint of CSF HVA, early improvements in motor outcomes that were unexpected based on the disease natural history of gross motor progression were observed. While risks such as post-procedural complications (including events of cardiac and respiratory failure) were identified, these risks were not thought to outweigh the observed benefits for children with the severe phenotype of AADCD. Patients with the severe phenotype experience significant motor and cognitive impairment, complete dependence on caregivers, substantial morbidity, and early mortality, and have significant unmet medical need with no response to available treatment options. There was no evidence submitted to demonstrate favorable benefit-risk in the mild and moderate disease phenotypes. Patients with the mild and moderate phenotype have been observed to respond well to oral standard of care therapies, which have less risk than eladocagene exuparvovec. Additionally, patients with the mild disease may not experience abnormalities in motor function. No data were submitted to

characterize the benefit of eladocagene exuparvovec on nonmotor manifestations of the disease. There were also no data submitted to assess the benefit-risk in adults, including the uncertainty in the appropriateness of the intended dose in an adult population with the disease. Therefore, the clinical review team recommends accelerated approval based on intermediate clinical endpoint for children with the severe phenotype of AADCD.

Team Leader and Branch Chief Conclusions and Regulatory Recommendations

As described by the primary reviewer, exercising maximum regulatory flexibility, we agree with granting eladocagene exuparvovec accelerated approval based on an intermediate clinical endpoint, motor milestone achievement (assessed on PMDS-2) 48 weeks after treatment. However, we believe the indication should be further refined to specify the population for which there is data to support benefit and to provide more detail on the anticipated benefit. Specifically, we propose an indication of (b) (4)

Our rationale for limiting the indication to specifically (b) (4) is that this was the only benefit demonstrated in the clinical trial. Based on location of administration and mechanism of action of the gene therapy, eladocagene exuparvovec is anticipated to impact motor manifestations. However, as the product is administered into the putamen, there is uncertainty regarding distribution to other areas of the brain, and the ability of the gene therapy to impact non-motor disease manifestations, including autonomic instability. Although limited clinical data beyond gross motor milestones was collected in the pivotal study, the available interpretable data within the BLA suggest eladocagene exuparvovec may not offer benefit for other disease manifestations. For instance, with respect to oculogyric crises (OGCs), one patient experienced worsening of OGCs following product administration and no child had resolution of OGCs. Therefore, in our opinion there is insufficient evidence to support extrapolation to a broader indication beyond (b) (4) of AADCD.

We recommend limiting the population to children (b) (4) years as the oldest child treated with the to- be- marketed product was (b) (4) years of age. While the pivotal study sample size is too small to conduct sub-group analyses by age, the children who had the greatest improvement in motor milestones, including the ability to walk, were treated at the youngest ages. In the supportive studies conducted with a similar gene therapy that has greater potency, a similar trend was seen, where younger age at treatment was highly correlated with greater improvement in motor score at 1 and 2 years after treatment ($p<0.001$) (Tai et al. 2022). This clinical observation is consistent with the biomarker data from the pivotal study showing change in CSF HVA and 18F dopa uptake were greater in children treated at younger ages. From a physiology perspective,

there is increased neuroplasticity in younger children, which we believe explains these age-based findings. As a result, there is substantial uncertainty as to whether adolescents and adults retain enough neuroplasticity to benefit from the product. There is also uncertainty as to appropriate dosing in older/larger patients. We are not recommending a younger age limit as this is addressed in contraindications; given the need for stereotactic neurosurgery to administer the gene therapy product, it is not feasible to administer the product to very young children who have not achieved skull maturity.

When considering the uncertainties of benefit on disease manifestations beyond gross-motor function and uncertainties of durability of effect on motor milestones, known risks of gene therapy and neurosurgical procedure, uncertainty of safety profile of eladocagene exuparvovec based on the small safety population, and alternative oral standard of care therapies that are generally recommended for mild and moderate phenotypes of AADCD, we recommend that this be further limited to patients with genetically confirmed, severe AADCD. Pre-market studies in a broader population with regard to other AADCD disease manifestations, severity phenotypes and older ages can occur in parallel with the confirmatory trial.

Division Director Conclusions and Regulatory Recommendations

In this BLA, the Applicant submitted safety and efficacy data from 13 patients with the severe, early-onset form of AADCD treated with eladocagene exuparvovec in Study AADC-002. Study AADC-002 is a single-arm, open-label clinical trial designed to evaluate the safety of the neurosurgical device, the pharmacodynamic and clinical effects of the product, and the safety of the product at various timepoints post-product administration (8 weeks, 48 weeks, 5 years). The trial's key pre-specified endpoints for efficacy include: achievement of gross motor milestones (assessed with 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. The population consists of 13 children with severe AADCD aged 1.3-10.8 years at product administration (median 2.8 years old), predominantly of Asian descent, and predominantly carrying at least one copy of the founder variant in the DDC gene (c.714+4A>T) seen in the Asian population. One of the 13 patients discontinued trial participation prior to the week 48 efficacy assessments and was not included in the efficacy analysis as week 48 efficacy data was not available. The efficacy population includes 12 of the 13 treated patients. The safety population includes all patients treated in Study AADC-002; the safety assessment was supplemented by safety data in children with similar disease at baseline treated in two single-arm, open-label studies conducted in Taiwan with a product manufactured through a different process (and determined to not be comparable to the to-be-marketed product).

With respect to efficacy, the submitted data from the single study AADC-002 demonstrate that 8 of 12 treated patients who at baseline had achieved no gross motor milestone (score 0 or 1 on PDMS-2 scale), achieved a new gross motor milestone at week 48 (score 2 in at least "full head control") post-product administration with a responder rate of 67%. The Applicant submitted data from an external cohort of 44 untreated patients with similar disease severity as a comparator group. Untreated patients in this cohort had severe gross motor developmental delay with no gross motor milestone achievement after a median duration of follow up of 7.3 years (range 1.6 to 21 years). Treated patients in Study ADC-002 demonstrate a 67% response rate in achievement of a new motor milestone compared to no patient in the external untreated cohort who had a gross motor milestone achievement after similar follow up duration. In Study AADC-002, treated patients consistently demonstrated increases in the disease-specific biomarkers in the CNS, HVA and L-DOPA, assessed via quantitative assessment in CSF and putaminal specific ^{18}F-DOPA uptake via PET scan respectively. With respect to safety, serious adverse events reported across all studies include dyskinesia and post-surgical complications. Other, non-serious, commonly reported adverse events include pyrexia, hypotension, anemia, and insomnia.

In summary, the submitted data establish substantial evidence of effectiveness for eladocagene exuparvovec based on a single adequate and well-controlled trial (AADC-002) plus confirmatory evidence. In Study AADC-002, 67% of patients showed a clinical response (achieved a new gross motor milestone after 48 weeks of follow up post-product administration) compared to no patients in the external comparator group of untreated patients achieving any gross motor milestone after comparable follow up duration. Confirmatory evidence of effectiveness is based on demonstration of consistent treatment effects on pharmacodynamic biomarkers of neurotransmission, HVA and L-DOPA, in all treated patients in Study AADC-002, indicative of a direct positive pharmacologic effect on the canonical pathway of the disease. The demonstrated achievement of new gross motor milestones in treated patients is of unclear long-term clinical meaningfulness as this is a chronic disease but appears to represent a clinical endpoint (intermediate) that is reasonably likely to predict a clinical (neurologic) benefit in the studied population. The safety of the product appears to be adequately characterized given the disease rarity. The observed toxicities related largely to the neurosurgical procedure can be adequately mitigated through product labeling and routine pharmacovigilance.

In conclusion, the demonstrated benefit of eladocagene exuparvovec on gross motor function in conjunction with the consistent and favorable treatment effects on disease-specific neurotransmitter levels in the CNS outweigh the observed safety risks which can be adequately mitigated in the post-marketing setting. Given the uncertainty surrounding the clinical meaningfulness of a favorable effect on gross motor milestone achievement over a relatively short duration of follow up (48 weeks), accelerated approval is reasonable given that this efficacy finding is reasonably likely to predict a positive effect

on general motor functioning and improvement in quality of life in addition to the fact that AADCD is a serious disease with high unmet needs (with no pharmacologic agents approved and labeled for the disease).

I recommend accelerated approval with a post-marketing requirement to verify the clinical benefit and the durability of that benefit over a longer follow up duration (at least 5 years). I recommend that the product be indicated for “the treatment of pediatric patients with AADCD” given the clear demonstrated treatment effects on both the motor functional deficits and on the fundamental neurotransmitter synthesis defects associated with the disease pathology as a whole. As AADCD is a monogenic disease with a clearly established single molecular pathway, I believe that the efficacy can be extrapolated to pediatric patients outside the age range of the treated patients and to those with mild/moderate disease severity as AADCD exists along a wide spectrum of severity, which is typical of monogenic inborn errors of metabolism. The efficacy and safety of the product have not been evaluated in adults with AADCD and more data is needed to inform a benefit-risk determination and an appropriate dosage regimen in this population.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Thirteen children with the severe phenotype of AADCD were treated with eladocagene exuparvovec in a single, phase 2, single-arm, open label clinical study (AADC-002). Data from two studies conducted in Taiwan (using a different manufactured product than the intended to-be-marketed product), AADC-010 and AADC-011, were also submitted as supportive data. The data from these studies are used to evaluate the proposed use of CSF HVA as a surrogate endpoint reasonably likely to predict clinical benefit. However, clinical data from these studies are not used in the evaluation of efficacy given that patients were treated with a formulation of eladocagene exuparvovec that was deemed not comparable to the commercial product used in study AADC-002 supporting the BLA (Section 4.1). Table 1 below provides the baseline demographic characteristics and genotype of the patients enrolled in each study.

Table 1: Baseline Patient Characteristics in Study AADC-002 (N=13)

Characteristic	**n (%)**
Sex	
Female	7 (54%)
Male	6 (46%)
Race	-
Asian	10 (77%)
White	2 (15%)
Other	1 (8%)[1]
Ethnicity	-
Hispanic or Latino	2 (15%)
Not Hispanic or Latino	10 (77%)
Not Reported / Unknown	1 (8%)
Age at Treatment (months)	-
Median	33
Min – max	16-129
Genotype	
c.714 + 4A>T homozygous	2 (15%)
c.714 + 4A>T/c.1297dup	2 (15%)
c.260C>T/c.286G>A	1 (8%)
c.714+4A>T/c.1297_1298INSA	1 (8%)
c.242C>T/p.PRO81LEU	1 (8%)
c.367G>A/c.1234C:T	1 (8%)
c.714+4A>T/4P.75	1 (8%)
c.568_569INSCGATC/c.863T>C	1 (8%)
c.714+4A>T/c.304G>A	1 (8%)
c.EX11-12/c.557A>G	1 (8%)
c.304G>A/c.304 G>A	1 (8%)

Source: Reviewer analysis of AADC-002 ADSL Dataset, 2.7.3 Summary of Clinical Efficacy

Reviewer Comment:

- *There is generally an even distribution between male and female patients enrolled in the single pivotal study. While the study was conducted internationally (sites in United States, Israel and Taiwan), the study primarily enrolled patients of Asian descent, the majority of whom carried at least one founder variant. AADCD has been identified to be more prevalent in certain Asian populations (Taiwanese, Chinese, and Japanese) due to a founder variant (c.714+4A>T) seen in these populations. One publication (Wassenberg et al. 2017) reports that 67 out of 117 (57%) patients compiled from the authors' literature search were of non-Asian descent. The demographic distribution of AADCD in the United States is unknown. In response to an information request, the Applicant reports that AADCD patients of White, African American, and Alaskan Native race have identified for potential commercial treatment if eladocagene exuparvovec is approved.*
- *Given the rarity of AADCD and the unknown demographic distribution in the United States, there is limited information on differences in clinical course based on country of origin, ethnicity, or sex. It is not feasible to do any subgroup analyses of safety or efficacy based on these demographic factors due to the small study population. Therefore, there remains uncertainty as to whether the patients enrolled in the clinical study may be representative of the patients who would be treated with eladocagene exuparvovec in U.S. commercial use.*

1.2 Patient Experience Data

Patient experience data was incorporated into the review of the clinical data submitted in this BLA. This includes a qualitative patient experience report entitled "AADC Deficiency Digital Ethnography" conducted and submitted by the Applicant and several publications on the quality of life of patients and caregivers.

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☐	Patient-reported outcome	
☒	Observer-reported outcome	Section 7

☒	Clinician-reported outcome	Section 7
☒	Performance outcome	Section 7
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☒	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	Section 7
☐	Observational survey studies	
☒	Natural history studies	Section 7
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted**	
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting	
☐	FDA Patient Listening Session	
☒	Other stakeholder meeting summary report	Section 7
☐	Observational survey studies	

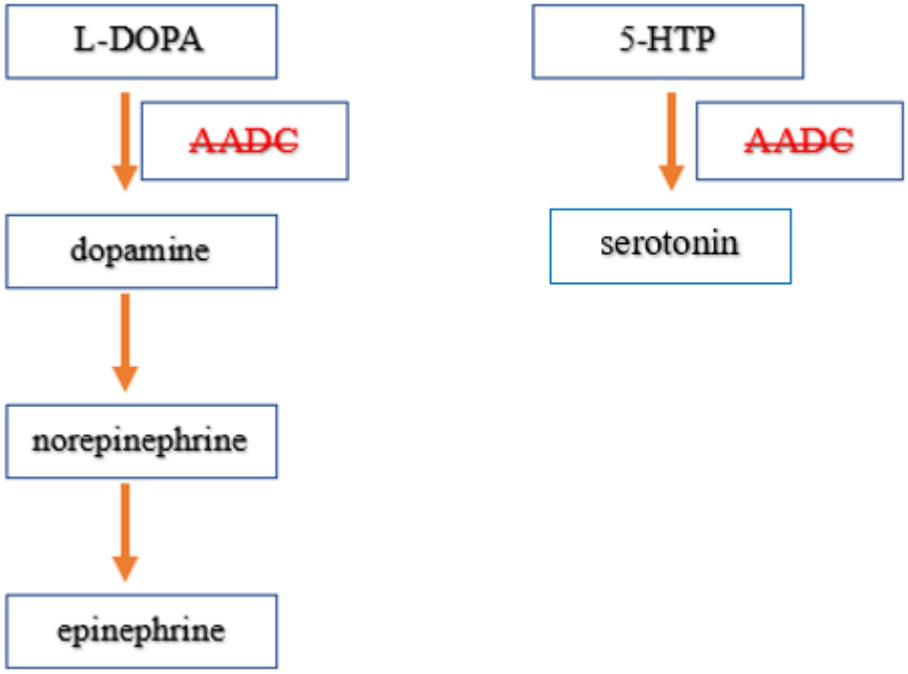
☐	Other: (please specify)	

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Aromatic L-amino acid decarboxylase deficiency is a rare, autosomal recessive disorder of neurotransmitter synthesis resulting from biallelic pathogenic mutations in the *DDC* gene, which encodes for the aromatic L-amino acid decarboxylase (AADC) enzyme. The AADC enzyme is responsible for several decarboxylation reactions in the synthetic pathways of neurotransmitters, which are shown in Figure 1. Patients with AADCD have deficiencies in dopamine, serotonin, norepinephrine, and epinephrine.

Figure 1: Neurotransmitter Synthesis in Aromatic L-Amino Acid Decarboxylase Deficiency



Source: Reviewer generated graphic
Abbreviations: 5-HTP, 5-hydroxytryptophan;AADC, aromatic L-amino acid decarboxylase; L-DOPA, levodopa

Per the National Organization for Rare Disorders (NORD), the estimated incidence at birth of AADCD is roughly 1 to 2 in 1,000,000 newborns in the United States. The global incidence and prevalence are unknown. There is no newborn screening program for AADCD in the U.S., and it is frequently misdiagnosed. The number of patients worldwide with AADCD is uncertain—(Wassenberg et al. 2017) report 117 cases have been

identified in the literature, while (Himmelreich et al. 2019) report that 350 patients with AADC deficiency have been reported. Regardless, the number of affected patients is likely underestimated given frequent misdiagnosis. While there is a high prevalence of AADCD in Asian populations (particularly patients of Chinese, Taiwanese, and Japanese descent) due to a founder variant (c.714+4A>T), AADCD does affect patients of diverse ethnic origins, with 50 of the 117 patients identified as being of Asian descent in a literature search conducted by one publication (Wassenberg et al. 2017). Reported ethnic origins of other patients include Caucasian, Arabic, and Iranian descent.

Clinical manifestations that can occur in patients with AADCD include delayed or lack of achievement of motor milestones, hypotonia/dystonia, autonomic dysfunction, cognitive impairment, gastrointestinal problems (constipation, diarrhea, gastroesophageal reflux), sleep and behavioral disturbances, and oculogyric crises. Oculogyric crises are sustained dystonic episodes that can last up to 24 hours where patients experience deviation of the eyes, rhythmic orofacial movements, neck flexion, tongue protrusion, and jaw spasms.

AADCD is broadly classified into three main phenotypes: “mild,” “moderate,” and “severe.” It is important to note that while these classifications exist, all patients with AADCD (regardless of their phenotype) experience manifestations that can significantly impact their daily lives. The “severe phenotype” represents patients who have no development in motor milestones, have severe cognitive impairment, and are completely dependent on caregivers for all aspects of daily living. These patients have no improvements in motor functioning despite treatment with standard of care medications (discussed in Section 2.2 below).The “mild phenotype” represents patients who develop the ability to ambulate without assistance and have mild intellectual disability. These patients can present predominantly with autonomic symptoms without clear signs of a movement disorder, with either normal gross motor development or motor development that is slightly delayed. The “moderate” phenotype represents any patient who falls in between the “mild” and the “severe” phenotype. Patients with moderate AADCD develop motor milestones over time but have significant delays when compared to children with normal development and are generally unable to achieve the ability to ambulate. Patients with the mild and moderate phenotype do demonstrate responses to standard of care therapies. In a majority of cases, there is no evidence of a progressive clinical course with loss of previously acquired skills. However, regression in language skills and a decline in motor function due to secondary factors (such as joint contractures) has been reported in some cases (Wassenberg et al. 2017). Given the rarity of the condition, it often is misdiagnosed, especially in the mild and moderate phenotypes.

Most reported cases in the literature have the severe phenotype, while there are limited case reports on the mild and moderate phenotypes. There is no clear genotype-phenotype correlation, except for two exceptions. First, patients homozygous for the c.714+4A>T splice site founder variant (seen in Asian population) have been shown to

have the severe phenotype in all reported cases to date. Second, patients with variants in the L-DOPA binding site are known to be responsive to treatment with L-DOPA (see Section 2.2). CSF neurotransmitter levels and residual plasma AADC enzyme activity have not been observed to correlate with disease severity (Wassenberg et al. 2017).

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

While there are no approved therapies for treatment of AADCD, off-label use of certain medications including dopamine agonists, MAO inhibitors, and pyridoxine used in combination have been reported to help improve motor function in some patients with moderate and mild disease with variable success, though such use has been generally observed to have limited benefit in patients with severe disease (Wen et al. 2020). Some patients with the moderate and mild phenotypes were reported to have rapid and robust improvements in motor function after initiation of these therapies. (Wen et al. 2020) reports four patients with the moderate phenotype who demonstrated improvements in motor development after initiation of these medications, with three patients developing the ability to sit and one patient developing the ability to walk independently. (Bergkvist et al. 2022) reports one patient who developed improvements in head control, rolling over, vocalization, and muscle tone within 4 weeks of initiation of standard of care therapies. Based on a comprehensive review of the literature, it appears to remain uncertain as to whether patients with the mild and moderate phenotype have sustained long-term improvements in motor functioning in response to these medications. Positive responses to dopamine agonists on other disease manifestations such as hypotonia, oculogyric crises, voluntary movements and autonomic symptoms have been reported (Wassenberg et al. 2017).

Dopamine Agonists

The first-line treatment for AADCD is dopamine agonists. Consensus guidelines (Wassenberg et al. 2017) recommend the use of non-ergot-derived dopamine agonists (pramipexole, ropinirole, and transdermal patches of rotigotine) as first-line therapies. Ergot-derived dopamine agonists with strong serotonergic (5HT2b) agonist effect (pergolide and cabergoline) have been associated with cardiac valvulopathies and other fibrous complications and are not recommended for use in AADCD (Antonini and Poewe 2007). While ergot-derived dopamine agonists without 5HT2b agonist action (bromocriptine) also have risks of pulmonary and pericardial fibrosis (Andersohn and Garbe 2009), these medications have been routinely used with appropriate cardiac screening before and during treatment (Wassenberg et al. 2017).

Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors prevent the breakdown of dopamine and serotonin. MAOIs have been primarily used as co-treatment with dopamine agonists.

Pyridoxine

Pyridoxine (a form of vitamin B6) acts as a co-factor for the AADC enzyme and is also considered first-line therapy for AADCD as it may promote activity of the residual AADC enzyme. However, at high doses for prolonged periods of time, pyridoxine can cause reversible polyneuropathy. Pyridoxal phosphate, the active formulation of pyridoxine, can also be used but is often less readily available and more expensive than pyridoxine.

L-DOPA and Carbidopa

Patients with AADCD have elevated levels of L-3,4-dihydroxyphenylalanine (L-DOPA; see Figure 1). Therefore, L-DOPA is only recommended for patients with variants at the L-DOPA binding side (Wassenberg et al. 2017). Carbidopa is an AADC enzyme inhibitor and can be harmful in patients with AADCD and, thus, it is not recommended.

Additional Symptomatic Treatment

Additional therapies include anticholinergic drugs (for autonomic symptoms, dystonia, and oculogyric crises), benzodiazepines (sustained oculogyric or dystonic crises), folinic acid (in those with low CSF MTHF), and melatonin or clonidine for sleep problems.

Reviewer Comment:

- *As discussed in literature reports, some patients with mild or moderate disease may have improvements in symptoms with standard of care pharmacologic agents (used in combination) while others do not; patients with severe disease may have a more limited response to those therapies. Overall, data on patient clinical response to SoC pharmacologic agents is limited to draw definitive conclusions. Side effects such as dyskinesia, irritability, and insomnia are reported as reasons for using reduced doses or for drug discontinuation. However, one publication reports that the occurrence of side effects that lead to discontinuation of medications is low—approximately 12% for dopamine agonists and 6% for MAOIs. MAOIs have been associated with fewer side effects than dopamine agonists but have also been reported to be less beneficial (Pearson et al. 2020). Pyridoxine has generally been well-tolerated but not widely reported to be beneficial when administered alone.*
- *The availability and benefit of standard of care therapies should be considered within the benefit-risk evaluation of this high-risk gene therapy product, particularly in patients who do not have severe AADC and may have alternate therapeutic options.*
- *The long-term response and improvements in other disease manifestations in patients who respond to standard of care is not described in the literature.*

2.3 Safety and Efficacy of Pharmacologically Related Products

Currently, there are no other gene therapy-based products approved for AADCD. However, there have been numerous AAV gene therapy products approved by the Center for Biologics Evaluation and Research for other monogenic diseases. Generally, immune-mediated systemic toxicities have been associated with AAV gene therapy products including hepatotoxicity, thrombotic microangiopathy, neurotoxicity (including dorsal root ganglion toxicity), and oncogenicity (theoretical risk with limited confirmed case reports). However, the risks may vary based on the type of AAV vector used and the route of administration.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Eladocagene exuparvovec has received marketing authorization by the European Medicines Agency (July 18, 2022), the United Kingdom's Medicinal Health Products Regulatory Agency (November 2022), and Israel's Ministry of Health (February 2023) for the treatment of the severe phenotype of AADCD. At the time of BLA submission, eight children have received the product in commercial use in France, Germany, and Italy.

Reviewer Comment:

- *Marketing authorizations by international regulatory bodies were based on efficacy demonstrated through attainment of motor milestones in the two open-label studies conducted in Taiwan (AADC-010 and AADC-010); data from Study AADC-002 were not used in these approvals. Changes in CSF HVA were not used as the primary basis for these international approvals. Approval was based on the observation that 70% (14 out of 20) patients were able to achieve head control and 65% (12 out of 20) were able to achieve sitting unassisted two years after treatment, outcomes that were assessed as unexpected in the natural history.*

2.5 Summary of Pre- and Post-Submission Regulatory Activity Related to the Submission

Prior to submission of an Investigational New Drug Application (IND), the Agency had multiple interactions with the Applicant as a pre-submission under PS#003265. The Applicant intended to utilize the clinical and chemistry, manufacturing, and controls (CMC) programs ongoing at the time in Taiwan (studies AADC-010 and AADC-011) to support a U.S. BLA submission. However, the Agency noted that the device (the SmartFlow Canula) used for neurosurgical administration of the product, and the formulation of the product intended for U.S. commercial use, were not comparable to those used in the Taiwan studies. Therefore, the Applicant filed IND #19653 on February 28, 2020, to conduct a study in the U.S. to evaluate the safety and efficacy of the intended commercial eladocagene exuparvovec product and device in a new open-label, single-arm clinical study (AADC-002).

Eladocagene exuparvovec was granted orphan drug designation on June 8, 2016 (#DRU-16-5269), and rare pediatric disease designation on November 7, 2016 (#RPD-2016-63) for ”treatment of aromatic L-amino acid decarboxylase (AADC) deficiency”

After filing of the IND, the first formal meeting was held (October 6, 2022, Type C CRMTS#14126) between the Agency and the Applicant. The Agency provided feedback on the limitations of an NHDB compiled from literature publications as a historical external control, including that external comparator data can be vulnerable to bias (selection bias, lead time bias) and there can be substantial amounts of missing data that limit interpretability as a comparator.

On September 15, 2023, an informal teleconference was held between the Applicant and the Agency to discuss a proposal to use CSF HVA as the primary endpoint of the Applicant’s pivotal study and a surrogate endpoint to support accelerated approval. This differed from the Applicant’s original plan to assess efficacy based on motor milestone achievement at 5 years post-treatment. The Agency advised that the Applicant could move forward with a BLA submission based on a CSF HVA as a surrogate endpoint and provided advice on the information that would be needed to support their proposal. Agreement on whether the data would be sufficient to demonstrate CSF HVA as a surrogate endpoint reasonably likely to predict clinical benefit would be determined as a BLA review issue. Review of CSF HVA as a biomarker is discussed further in Section 7.

Final guidance for BLA content was issued in a pre-BLA meeting via written responses on December 12, 2023. The Applicant determined that the written responses were sufficient and cancelled the scheduled pre-BLA meeting.

Summary of regulatory history:

- July 7, 2017: Pre-submission End of Phase 2 Type B Meeting – CRMTS #10722
- November 9, 2017: Pre-submission Type C Meeting—CRMTS #10901
- April 18, 2019: Pre-submission Type C Meeting with FDA’s Division of Manufacturing and Product Quality—CRMTS #11810
- November 14, 2019: Pre-submission Type C Meeting—CRMTS#12032
- February 28, 2020: IND Filed
- March 27, 2020: IND placed on clinical hold due to reports of serious adverse events (SAEs) of delayed CSF leakage and CMC product characterization concerns
- July 17, 2020: Clinical hold lifted
- October 6, 2022: Type C CMC and Clinical Meeting—CRMTS #14126
- September 15, 2023: Informal teleconference to discuss biomarker
- December 12, 2023: pre-BLA written responses issued

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to enable the conduct of a complete clinical review.

3.2 Compliance With Good Clinical Practices And Submission Integrity

The two supportive studies AADC-010 and AADC-011, and the pivotal study AADC-002, were performed in compliance with good clinical practice.

Bioresearch Monitoring (BIMO) inspection assignments were issued for one domestic and two foreign clinical investigators (CI) who participated in the conduct of the following clinical studies: -AADC--002, AADC-010 and AADC-011. The inspections did not reveal substantive issues that impact the data submitted in this Biologics License Application (BLA).

3.3 Financial Disclosures

Covered clinical study (name and/or number): AADC-011, AADC-010, AADC-002
Was a list of clinical investigators provided? x Yes ☐ No (Request list from applicant)
Total number of investigators identified: 6 in AADC-002, 1 in AADC-010, 1 in AADC-011
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): N/A

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____

Significant payments of other sorts: _____

Proprietary interest in the product tested held by investigator: _____

Significant equity interest held by investigator in sponsor of covered study: _____

Is an attachment provided with details of the disclosable financial interests/arrangements? ☐ Yes ☐ No (Request details from applicant)

Is a description of the steps taken to minimize potential bias provided?

☐ Yes ☐ No (Request information from applicant)

Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0

Is an attachment provided with the reason? ☐ Yes ☐ No (Request explanation from applicant)

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

During the clinical development program, the Applicant used three different manufacturing processes to produce eladocagene exuparvovec: Process A, Process B, and Process C. Process C, the intended commercial process, was deemed not comparable to Process A and Process B. Process C contained a (b) (4) compared to the other two processes deemed by the CMC reviewer to have potential impacts on both safety and efficacy. This included potentially decreased efficacy (due to (b) (4)) and increased risks (due to (b) (4)) of the Process C commercial product in comparison to Process A and Process B products.

Therefore, the primary basis for the safety and efficacy evaluations was data from patients treated in Study AADC-002 who were treated with the Process C product (the intended commercial product).

4.2 Assay Validation

Assays important to safety and efficacy assessments included assays measuring CSF HVA and anti-adeno-associated virus serotype 2 (anti-AAV2) antibodies. No significant assay-specific issues were identified by the CMC review team that impact the clinical and clinical pharmacology review. Please see the CMC reviewer memo for additional discussion.

4.3 Nonclinical Pharmacology/Toxicology

The Applicant conducted in vitro proof-of-concept studies demonstrating a dose-dependent increase in dopamine production in (b) (4) with eladocagene exuparvovec. No proof-of-concept in vivo studies in the animal model of AADCD were conducted by the Applicant. No nonclinical data were submitted on CSF HVA with respect to its role in AADCD disease pathology and its potential use as a surrogate endpoint of clinical benefit (see discussion below).

Dose selection for the AADC-002 pivotal clinical trial was based on data published in the literature (using a different AAV gene therapy product) in non-human primate models of Parkinson's disease, where doses ranging from 1.1×10^{11} vector genomes (vg) to 1×10^{12} vg demonstrated increases in AADC protein expression, and doses greater than approximately 3×10^{11} vg were associated with behavioral improvement. Please see the pharmacology/toxicology reviewer's memo for additional discussion.

Single-dose toxicology studies in (b) (4) rats and non-human primates (NHPs) demonstrated no significant adverse findings at dose levels ranging from $7.5x10^{8}$ – $7.5x10^{9}$ vg/animal. Biodistribution findings in these studies showed both dose- and time-dependent reductions in vector DNA levels in the putamen from Day 7 to Day 180. 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. Anatomical distribution of AADC RNA was consistent with vector DNA results.

No nonclinical studies were conducted to evaluate the safety pharmacology, developmental and reproductive toxicity, genotoxicity, and carcinogenicity/tumorigenicity of eladocagene exuparvovec-tneq as such studies were not warranted based on the product characteristics and target patient population.

Reviewer Comment:

- *There were no preclinical studies to assess whether a higher dose would be needed for efficacy in older patients (due to higher brain and body weights). Please see Section 4.4.2 for clinical pharmacology discussion on dose selection.*

4.4 Clinical Pharmacology

In this BLA, pharmacodynamics (neurotransmitter metabolites in CSF and L-6-[^{18}F] fluoro-3, 4-dihydroxyphenylalanine [^{18}F-DOPA] uptake in the putamen), pharmacokinetics (biodistribution and viral shedding), and immunogenicity were evaluated in three clinical studies in patients with AADCD following the administration of eladocagene exuparvovec: Study AADC-002 (the pivotal study) and Studies AADC-010 and AADC-011 (the supportive studies).

This clinical pharmacology review is focused on the results from the pivotal study AADC-002 that used the to-be-marketed product (manufactured through Process C) because in addition to the difference in the products (see Section 4.1), assay methods and timepoints of clinical pharmacology assessments used in supportive studies were not comparable to those of the pivotal study, and no cross-study assay validations were performed.

For the supportive studies (AADC-010 and AADC-011), pharmacodynamics data were reviewed only 1) in support of the proposed mechanism of action of eladocagene exuparvovec (see Section 4.4.2), and 2) to understand the relationship between CSF HVA and motor milestone achievement with regard to the adequacy of CSF HVA as a surrogate endpoint as a basis of accelerated approval, which is discussed in Section 7.1.4. The summary of pharmacodynamics assessments and their relationship with motor milestone achievement in the supportive studies is in Appendix 2.

4.4.1 Mechanism of Action

Eladocagene exuparvovec is a recombinant adeno-associated virus serotype 2 (AAV2)-based vector containing the complementary DNA of the human *DDC* gene encoding the AADC enzyme under the control of the cytomegalovirus immediate-early promoter. Intraputaminal infusion of eladocagene exuparvovec results in AADC enzyme expression and subsequent production of dopamine in the putamen.

4.4.2 Human Pharmacodynamics

The increased CSF HVA and increased uptake of ^{18}F-DOPA in the putamen after eladocagene exuparvovec administration support the proposed mechanism of action of eladocagene exuparvovec in patients with AADCD, providing evidence of expression of the AADC enzyme from the *DDC* transgene, subsequently leading to increased production of dopamine in the putamen.

CSF HVA

As a major metabolite of dopamine, CSF HVA reflects dopamine production by the AADC enzyme in the brain.

In Study AADC-002, CSF HVA was measured using high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) at baseline, Week 8, and Week 48 after the gene therapy.

In all 13 patients who received the gene therapy, CSF HVA increased from baseline (Figure 2, Table 2). In 8 out of 13 patients whose CSF HVA levels were measured at both Week 8 and Week 48, an increase from baseline in CSF HVA was observed at Week 8, which remained higher than baseline at Week 48. Of the 8 patients, CSF HVA levels decreased from Week 8 to Week 48 in 4 patients while CSF HVA increased from Week 8 to Week 48 in the remaining 4 patients. Substantial intra-patient and inter-variability in CSF HVA levels was noted as shown in Table 2 and Figure 2: the difference between Week 8 and Week 48 within each patient ranged from -24.6 to 15.1 nmol/L, and the percent difference ranged from -44.9% to 38.9%.

Five of 13 patients were taking dopaminergic agents (dopamine agonists and MAOIs) at baseline, and 3 of them continued taking dopaminergic agents when Week 8 measurement was obtained, but none of patients were on dopaminergic agents at Week 48 measurement.

Clinical Pharmacology Reviewer Comment:

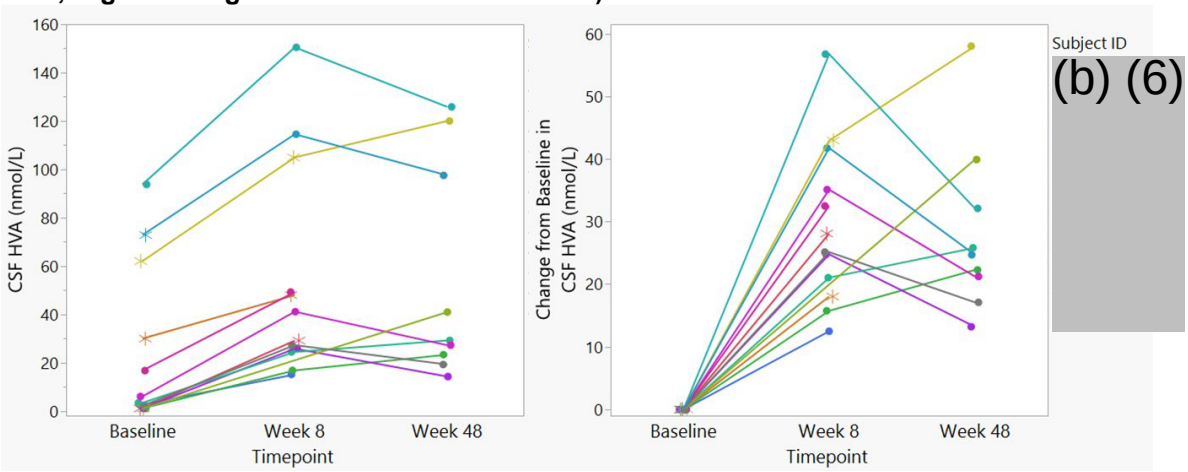
The CSF HVA observed in the presence of dopaminergic agents did not appear significantly different from those without dopaminergic agents (Figure 2).

Table 2: CSF HVA Levels by Timepoint in Study AADC-002*

Timepoints	Absolute HVA (nmol/L)	Change from Baseline (nmol/L)	Percent Change from Baseline (%)
Baseline	-	-	-
N	13	-	-
Mean (SD)	22.54 (32.34)	-	-
Median (Min, Max)	3.34 (1.00, 93.73)	-	-
Week 8	-	-	-
N[a]	12	12	12
Mean (SD)	53.87 (44.42)	29.53 (12.93)	851.1 (968.2)
Median (Min, Max)	35.09 (15.09, 150.48)	26.62 (12.49, 56.75)	534.7 (57.4, 2810.0)
Week 48[b]	-	-	-
N	9	9	9
Mean (SD)	55.25 (45.60)	28.27 (13.65)	1072.6 (1308.4)
Median (Min, Max)	29.16 (14.21, 125.84)	24.7 (13.21, 58.02)	773.1 (33.9, 3991.0)

Source: Study AADC-002, Table 14.2.2.6 and Applicant's Responses to Information Requests #4 dated May 20, 2024
Note: Lower limit of quantification (LLOQ) was 2 nmol/L, and values reported as <LLOQ was imputed as 0.5*LLOQ; Percent change from baseline = change from baseline/absolute value at baseline x 100; CSF HVA normal ranges was not reported.
[a] Patient (b) (6) did not complete the Week 8 visit assessments due to travel limitations.
[b] Reviewer calculated the results integrating the additional Week 48 data from 3 patients (ID (b) (6) which were submitted in responses to Information Requests #4 dated 5/20/2024.
Abbreviations: CSF, cerebrospinal fluid; HVA, homovanillic acid; N, number of patients; SD, standard deviation; Max, maximum; Min, minimum

Figure 2: CSF HVA Levels Over Time by Patient in Study AADC-002 (Left: Absolute CSF HVA; Right: Change from Baseline in CSF HVA)



Source: Reviewer's analysis based on FDAQ14.xpt, submitted in Applicant's Responses to Information Requests #12 dated July 1, 2024
Note: Lower limit of quantification (LLOQ) was 2 nmol/L, and values reported as <LLOQ was imputed as 0.5*LLOQ; Asterisk (*) presents results obtained in the presence of concomitant dopaminergic agents at the time of measurement.
Abbreviations: CSF, cerebrospinal fluid; HVA, homovanillic acid

Along with CSF HVA, 3-O-methyl-L-DOPA (3-OMD, a metabolite of L-DOPA) and 5-hydroxyindoleacetic acid (5-HIAA, a metabolite of serotonin) in CSF were also measured at baseline, Week 8, and Week 48. The trend of changes from baseline in 3-OMD was variable between patients for 3-OMD and the magnitude of changes in 5-HIAA was smaller than those of CSF HVA. See Figure 8 and Table 24 in Appendix 1.1.

Of note, in the supportive studies AADC-010 and AADC-011, CSF HVA, 3-OMD, and 5-HIAA were measured using a HPLC-electrochemical detection method at baseline and Month 12. In all patients with post-gene therapy assessments (N=19), CSF HVA increased at Month 12 except for one patient who also did not show any motor function improvement until Month 84. See Figure 14 and Table 25 in Appendix 2.1.

Putamen-Specific ^{18}F-DOPA Uptake

^{18}F-DOPA is L-6-[^{18}F] fluoro-3, 4-dihydroxyphenylalanine (i.e., a positron-emitting fluorine-labeled levodopa). Following intravenous administration, ^{18}F-DOPA is taken up by the pre-synaptic nigrostriatal dopaminergic neurons in the putamen and converted to dopamine by the AADC enzyme. ^{18}F-DOPA uptake into the putamen is assessed by positron emission tomography (PET) imaging, which reflects the AADC enzyme activity in the putamen.

In Study AADC-002, ^{18}F-DOPA uptake was measured at baseline, Week 8, and Week 48. The mean bilateral putamen specific uptake of ^{18}F-DOPA was calculated per PET imaging based on the ratio of mean intensity (in Becquerels/milliliter) in the bilateral putamen to those in the occipital cortex. After the gene therapy, all 13 patients showed

an increase in ^{18}F-DOPA uptake in the putamen from baseline (Figure 3, Table 3). In 9 of 13 patients for whom ^{18}F-DOPA uptake was assessed at both Week 8 and Week 48, the increase from baseline in ^{18}F-DOPA uptake was observed from Week 8 and remained increased from baseline until Week 48.

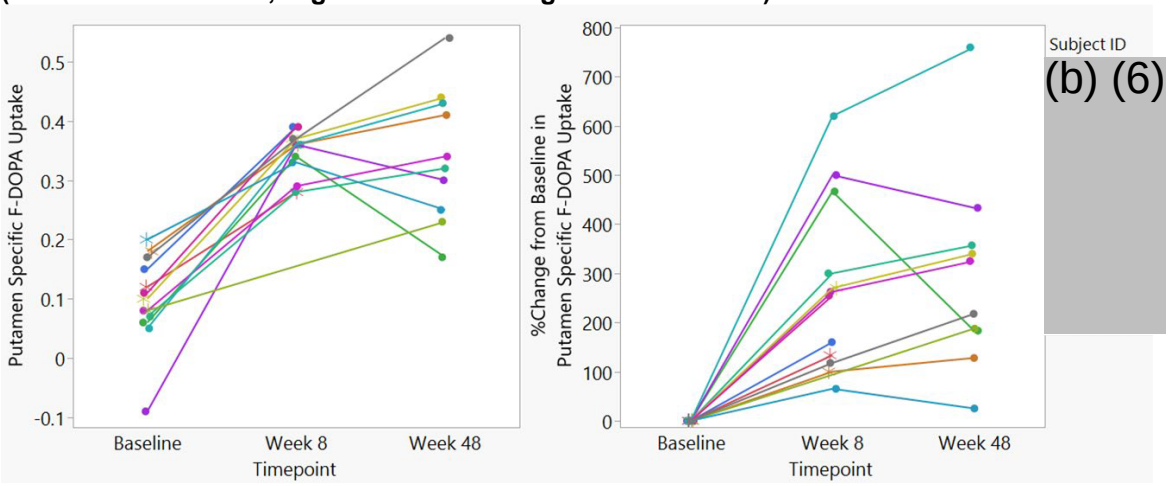
^{18}F-DOPA uptake results in the presence of dopaminergic agents did not appear different from the other results obtained in the absence of dopaminergic agents (Figure 3).

Table 3: Putamen Specific Uptake of ^{18}F-DOPA by Timepoint in Study AADC-002*

Timepoints	Absolute Value	Change from Baseline	Percent Change from Baseline (%)
Baseline	-	-	-
N	13	-	-
Mean (SD)	0.098 (0.074)	-	-
Median (Min, Max)	0.10 (-0.09, 0.20)	-	-
Week 8	-	-	-
N[a]	12	12	12
Mean (SD)	0.343 (0.040)	0.243 (0.084)	270.8 (175.9)
Median (Min, Max)	0.36 (0.28, 0.39)	0.225 (0.13, 0.45)	258.5 (65.0, 620.0)
Week 48[b]	-	-	-
N	10	10	10
Mean (SD)	0.343 (0.113)	0.253 (0.120)	295.7 (203.6)
Median (Min, Max)	0.33 (0.17, 0.54)	0.255 (0.05, 0.39)	271.3 (25.0, 760.0)

Source: Study AADC-002, Table 14.2.1.4 and Applicant's Responses to Information Requests #12 dated July 1, 2024.
Note: Percent change from baseline = change from baseline/absolute value at baseline x 100; Normal ranges for putamen specific uptake of ^{18}F-DOPA was not reported.
[a] Patient (b) (6) did not complete the Week 8 visit assessments due to travel limitations.
[b] Reviewer calculated the results integrating the additional Week 48 data from 3 patients (ID (b) (6) , which were submitted in Applicant's Responses to Information Requests #12 dated July 1, 2024.
Abbreviations: Max, maximum; Min, minimum; n, number of patients, SD, standard deviation

Figure 3: Putamen Specific Uptake of ^{18}F-DOPA Over Time by Patient in Study AADC-002 (Left: Absolute Value; Right: Percent Change From Baseline)



Source: Reviewer's analysis based on adnv.xpt of Study AADC-002 and Applicant's Responses to Information Requests #12 dated July 1, 2024.

Of note, in the supportive studies AADC-010 and AADC-011, putamen-specific ^{18}F-DOPA uptake was assessed at baseline and Months 12, 24, and 60 after the gene therapy, showing an increase from baseline in all patients (N=19). See Figure 15 and Table 26 in Appendix 2.2.

Please refer to reviewer's additional analyses on individual profiles over time of motor milestone achievement, CSF HVA, and putamen specific ^{18}F-DOPA uptake in arrays in Appendix 1.2 for the pivotal study and Appendix 2.3 for the supportive studies.

Clinical Pharmacology Reviewer Comment:

Large inter-patient variability in pharmacodynamic responses was observed in Study AADC-002, which may be due to a combination of several factors including the precision of intraputaminal drug infusion (which may affect the dose administered at the locations of infusion), the patient's age, DDC genotype, and other unknown factors. Out of 13 patients in Study AADC-002, 7 patients had founder variant (c.714+4A>T; 2 patients with homozygous variant and 5 patients with heterozygous) which confers a severe phenotype but due to the large variability and limited number of subjects with the same genotype, any specific trend was not found between different genotypes or within the same genotype group. Of note, in the supportive studies conducted in Taiwan, 10 out of 22 patients had the same c.714+4A>T homozygous genotype and among those patients, younger patients tended to show higher magnitude of changes in CSF HVA and ^{18}F-DOPA uptake and earlier improvement of motor function (see Figure 17).

4.4.3 Human Pharmacokinetics

Biodistribution and Viral Shedding

Biodistribution and viral shedding of AAV2-hAADC vector were evaluated in CSF, blood, and urine following intraputaminal infusion of eladocagene exuparvovec at a total dose of 1.8×10^{11} vg. Blood and urine were collected at baseline, Day 3, and Weeks 3, 8, 12, 24, 36 (blood only), and 48 after dosing. CSF was collected at baseline and Weeks 8 and 48. The vector DNA levels in those samples were measured using a quantitative polymerase chain reaction method.

Vector DNA was detected in the blood of 5 of 13 patients (38%) on Day 3, ranging from 4.0×10^{3} to 6.5×10^{3} copies/mL, which fell below the limit of detection ($<3.1\times10^{3}$ copies/mL) at later timepoints. Viral vector was not detected in any urine or CSF samples.

Clinical Pharmacology Reviewer Comment:

The viral shedding assessment indicates that the risk for transmission to untreated individuals is low.

4.4.4 Immunogenicity

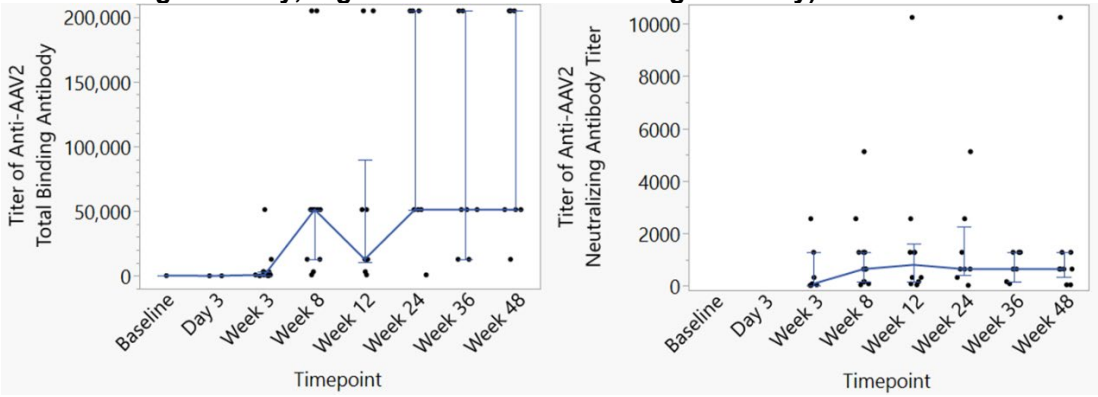
Humoral Immune Response (Anti-AAV2 Antibodies)

Anti-AAV2 total binding antibodies (TAb) and anti-AAV2 neutralizing antibodies (NAb) were assessed using an (b) (4) respectively. Serum samples were collected at screening, baseline, Day 3, and Weeks 3, 8, 12, 24, 36, and 48 after administration of eladocagene exuparvovec.

Patients with pre-existing anti-AAV2 NAb >1:1200 at screening were not eligible to enroll in the study. At baseline, anti-AAV2 TAb and NAb were negative in all patients except for one patient (Patient (b) (6)) with a low titer of TAb (1:200).

After the gene therapy, all 13 patients showed an increase in titers of anti-AAV2 TAb and NAb starting from Week 3. In nine patients who were followed up until Week 48, titers of both anti-AAV2 TAb and NAb remained high until Week 48 (Figure 4). Titers of anti-AAV2 TAb reached peak levels between Week 8 and Week 48, ranging from 1:800 to 1:204,800. Titers of anti-AAV2 NAb reached peak levels between Week 3 and Week 24, ranging from 1:80 to 1:10,240.

Figure 4: Titers of Anti-AAV2 Antibodies by Timepoint in Study AADC-002 (Left: Anti-AAV2 Total Binding Antibody, Right: Anti-AAV2 Neutralizing Antibody)



Source: Reviewer's analysis based on adis.xpt of Study AADC-002
Note: Black dots represent observations in each patient. Blue lines represent the median, and error bars represent the interquartile ranges.

Clinical Pharmacology Reviewer Comment:

Due to the small sample size and relatively short duration of follow-up up to Week 48, the available data are limited to determine whether there is an impact of anti-AAV2 antibodies on safety and efficacy.

Cellular Immune Response

T-cell mediated, antigen-specific responses to peptides derived from transgenic AADC protein or AAV2 capsid antigens were assessed by an (b) (4) assay. Peripheral blood mononuclear cell samples were planned to be collected at screening and at Day 1, Day 3, and Weeks 3, 8, 12, 24, and 48 after dosing. However, 46.9% of sample collection (46/98) was not done, and 69.2% of collected samples (36/52) were not suitable for the assay. The remaining 16 samples suitable for the assay were all negative.

Clinical Pharmacology Reviewer Comment:

- *The available data are limited to adequately characterize the cellular immune responses to eladocagene exuparvovec.*

4.4.5 Dose Rationale

In the pivotal study, a total dose of 1.8×10^{11} vg of eladocagene exuparvovec was administered to 13 patients who were 1 to 10 years of age, which is consistent with the proposed commercial dose.

The dose for the pivotal study (i.e., 1.8×10^{11} vg) was selected based on the previous clinical studies AADC-010 and AADC 011 in pediatric patients who were 1 to 8 years of age at a total dose of 1.8×10^{11} vg and 2.4×10^{11} vg (with Process B product). No apparent dose-dependent trend was observed between 1.8×10^{11} vg (n=13) and

2.4×10^{11} vg (n=9) in terms of motor milestone achievement, changes in CSF HVA, and percent changes in putamen specific F-DOPA uptake among pediatric patients (see Appendix 2.4). The first-in-human dose selection for AADC-010 in pediatric patients with AADCD was chosen based on nonclinical data in NHP models of Parkinson's disease and clinical data in adult patients with Parkinson's disease following intra-putaminal delivery of other rAAV2-hAADC vectors and the relative average brain mass of children (1,000 g) compared to adults (1,350 g).

Clinical Pharmacology Reviewer Comment:

- *The Applicant proposed using the same dose for all age groups in the commercial setting, including adult patients with AADCD. Currently, there are no clinical data demonstrating the efficacy of eladocagene exuparvovec in adult patients. Considering the relative brain mass, an adult dose might be estimated as approximately 30% higher than that of pediatrics (e.g., 2.4×10^{11} vg). A significant difference in transgene expression between the proposed dose and the 30% higher dose is not expected for the following reasons: 1) Eladocagene exuparvovec is administered locally into the putamen, and brain size does not vary significantly between children and adults (i.e., approximately 30% difference), and 2) The dose-response relationships of AAV-based gene therapies are not as steep as those of small molecule drugs, as also shown in the supportive studies AADC-010 and AADC-011 showing no apparent dose-response within a 1.3-fold dose range.*

4.5 Statistical

No formal statistical hypothesis testing was conducted for Study AADC-002. Descriptive statistics were used to analyze all endpoints. The sample size was based on feasibility of enrollment in this rare disease, rather than statistical power considerations. The intermediate clinical endpoint used for the basis of this accelerated approval decision (gross motor milestone achievement at Week 48), discussed further in Section 7, was not pre-specified in the protocol.

4.6 Pharmacovigilance

A Risk Evaluation and Mitigation Strategy was not deemed necessary given that risks were able to be mitigated through product labeling. Discussions on safety signals observed during the clinical studies, and the need for postmarketing requirements, can be found in Section 8 and Section 11 of this review.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

The Applicant conducted a single pivotal study AADC-002 in the U.S. utilizing the commercial product (manufactured through Process C) and the to-be-marketed device in

13 patients with AADCD. Patient-level analyses of efficacy were completed. The Applicant proposed using change from baseline in CSF HVA at Week 8 as a primary endpoint for the basis of accelerated approval. To support the understanding of CSF HVA as a reasonably likely surrogate endpoint, the Applicant submitted supportive data from two non-IND studies, AADC-010 and AADC-011, conducted in Taiwan. As discussed in Section 4.1, the Applicant was unable to establish comparability of the manufacturing processes used in Studies AADC-CU-1601 (Process A) and AADC-010 and AADC-011 (Process B), with Study AADC-002 (Process C, the to-be-marketed product). Therefore, the clinical efficacy data from studies using Process A and Process B products were only used to understand the relationship between CSF HVA and clinical outcomes. Given the small study population of Study AADC-002 and the small size of the safety database, analyses of the safety data from Studies AADC-CU-1601, AADC-010 and AADC-011 were pooled and conducted to understand whether there were any safety signals that could be extrapolated to use of eladocagene exuparvovec (regardless of the differences in manufacturing process).

Given the small sample size and limited duration of follow-up in the 13 patients enrolled in the pivotal study, the safety datasets from studies AADC-010 and AADC-011 were also analyzed. Safety analyses were conducted with primary focus on data from Study AADC-002. Supplemental safety analyses of AADC-010 and AADC-011 were conducted to understand whether there may be safety signals that could be extrapolated to use of eladocagene exuparvovec, regardless of drug product composition.

Given that data from studies AADC-010 and AADC-011 were used to facilitate interpretation of the CSF HVA biomarker and supplement safety analyses, all safety and efficacy data will be presented within the Integrated Summary of Efficacy (Section 7) and Integrated Summary of Safety (Section 8), rather than by individual study. Additionally, given that studies AADC-010 and AADC-011 were not used as the basis for both safety and efficacy assessments, details about these study protocols are not provided in Section 6.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

Source documents for this review include documents filed under original application for BLA 125722 and documents under IND #19653, which includes meeting minutes and correspondences between the FDA and the Applicant. Information requests (IRs) were sent to the Applicant to request clarification as needed during the BLA review.

5.3 Table of Studies/Clinical Trials

Table 4 below provides an overview of the clinical studies. Additional information on the clinical studies will be presented in Section 6. Please see Section 4.1 and the CMC review memo for discussion on the different manufacturing processes used by the Applicant.

Table 4: Table of Clinical Studies in the Eladocagene Exuparvovec Clinical Program

Study	Study Design	Study Objectives	Manufacturing Process[a]	Dose	Number of Patients	Study Status
AADC-CU-1601	Single arm, Phase 1 interventional and observational study with historical control	Retrospective and prospective evaluation of safety and efficacy in patients receiving "humanitarian assistance treatment" with eladocagene exuparvovec (compassionate use)	Process A	1.8×10^{11} vg	8	Completed
AADC-010	Phase 1/2, single-arm, prospective study with historical control	Safety and efficacy of eladocagene exuparvovec	Process B	1.8×10^{11} vg	10	Completed
AADC-011	Phase 2b, single-arm, non-randomized, prospective study	Safety and efficacy of eladocagene exuparvovec, including evaluation of a higher dose (2.4×10^{11} vg)	Process B	1.8×10^{11} vg (>3 years of age) 2.4×10^{11} vg (<3 years of age)	12: 3 patients >3 years of age receiving lower dose; 9 patients <3 years of age receiving higher dose	Completed
AADC-1602	Single-arm, long-term follow-up study	Long-term follow-up for 10 years post eladocagene exuparvovec therapy in patients treated in Studies AADC-CU/1601, AADC-010 and AADC-011	Process A and B	1.8×10^{11} vg or 2.4×10^{11} vg (<3 years of age)	24	Ongoing

Study	Study Design	Study Objectives	Manufacturing Process[a]	Dose	Number of Patients	Study Status
AADC-002*	Single-arm, Phase 2, open-label study	To assess the safety of the SmartFlow MR-compatible ventricular canula for administering eladocagene exuparvovec to pediatric patients and to assess pharmacodynamics by evaluating HVA levels	**Process C (proposed to-be-marketed product)**	1.8×10^{11} vg	13	Ongoing

Source: Adapted from BLA125722 5.2 Tabular Listing of All Clinical Studies
a-This refers to the different manufacturing processes for the eladocagene exuparvovec product, discussed in Section 4.1
*used to support this BLA

5.4 Consultations

5.4.1 Advisory Committee Meeting

An advisory committee was not held for this application 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.

5.4.2 External Consults/Collaborations

No external consults were obtained.

5.5 Literature Reviewed

Andersohn, F and E Garbe, 2009, Cardiac and noncardiac fibrotic reactions caused by ergot- and nonergot-derived dopamine agonists, Movement Disorders, 24(1):129-133.

Antonini, A and W Poewe, 2007, Fibrotic heart-valve reactions to dopamine-agonist treatment in Parkinson's disease, Lancet Neurol, 6(9):826-829.

Bergkvist, M, C Stephens, T Schilling, A Wang, X Yu, E Goodwin, L Golden, A Kristensen, and M Klein, 2022, Aromatic L-amino acid decarboxylase deficiency: a systematic review, Future Neurology, 17(4):FNL63.

BioPKU.org, c2024, JAKEdb: International Database of Patients with AADC Deficiency, accessed September 24, 2024, http://www.biopku.org/home/jake.asp.

Himmelreich, N, R Montioli, M Bertoldi, C Carducci, V Leuzzi, C Gemperle, T Berner, K Hyland, B Thöny, GF Hoffmann, CB Voltattorni, and N Blau, 2019, Aromatic amino acid decarboxylase deficiency: Molecular and metabolic basis and therapeutic outlook, Mol Genet Metab, 127(1):12-22.

Pearson, TS, L Gilbert, T Opladen, A Garcia-Cazorla, M Mastrangelo, V Leuzzi, SKH Tay, J Sykut-Cegielska, R Pons, S Mercimek-Andrews, M Kato, T Lücke, M Oppebøen, MA Kurian, D Steel, F Manti, KD Meeks, K Jeltsch, and L Flint, 2020, AADC deficiency from infancy to adulthood: Symptoms and developmental outcome in an international cohort of 63 patients, J Inherit Metab Dis, 43(5):1121-1130.

Tai, CH, NC Lee, YH Chien, BJ Byrne, SI Muramatsu, SH Tseng, and WL Hwu, 2022, Long-term efficacy and safety of eladocagene exuparvovec in patients with AADC deficiency, Mol Ther, 30(2):509-518.

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.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study AADC-002: "An Open-Label Trial to Address the Safety of the Smartflow MR-Compatible Ventricular Cannula for Administering Eladocagene Exuparvovec to Pediatric Subjects"

6.1.1 Objectives

Primary Objective

- To assess the safety of the SmartFlow magnetic resonance (MR)-compatible ventricular cannula for administering eladocagene exuparvovec to pediatric patients

Secondary Objective

- To assess the pharmacodynamics of eladocagene exuparvovec by evaluation of putaminal specific L-6-[^{18}F] fluoro-3,4-dihydroxyphenylalanine (^{18}F-DOPA) PET uptake at Weeks 8 and 48

Exploratory Objectives

- To assess the effect of eladocagene exuparvovec on:
    - Neurotransmitter CSF metabolites (HVA, 5-hydroxyindolaectic acid, and 3-OMD)
    - Motor development as assessed by the Peabody Developmental Motor Scale, second edition (PDMS-2).
    - Bayley Scales of Infant and Toddler Development, third edition (BSITD-III)
    - EQ-5D-Y
    - Body weight
    - AADC-specific symptoms (by neurological examination)
- To assess the safety of eladocagene exuparvovec treatment as assessed by treatment-emergent adverse events, neurological examinations, magnetic resonance imaging (MRI), and clinical laboratory tests.

6.1.2 Design Overview

This was a Phase 2, single-arm, open-label study. The study was divided into three phases: "Trial Phase," which followed patients for 8 weeks post treatment; the "Extension Phase," which followed patients from Week 9 until Week 48; and the "Long-Term Extension Phase," monitoring for long-term safety and efficacy from Week 49 until 5 years post treatment.

6.1.3 Population

The key eligibility criteria were as follows:

Inclusion Criteria

- Genetically confirmed AADCD with typical clinical characteristics and decreased AADC enzyme activity in plasma
- 1 year to <18 years of age
- Cranium sufficiently developed to allow placement of ClearPoint system for stereotactic surgery
- Persistent neurological defects secondary to AADCD despite standard medical therapy (dopamine agonists, monoamine oxidase inhibitor, pyridoxine, or other forms of B6) in the opinion of the investigator
- Unable to ambulate independently (with or without assistive devices)
- Stable dosage for 3 months prior to baseline for all medications related to treatment of AADCD, including dopamine agonists, monoamine oxidase inhibitors, anticholinergic drugs, and vitamin B6

Exclusion Criteria

- Anti-adeno-associated virus serotype 2 antibody titer higher than 1:1200, or >1 optical density value by enzyme-linked immunosorbent assay
- Pyridoxine 5'-phosphate oxidase or tetrahydrobiopterin deficiency

Reviewer Comment:

- *In order to allow for placement of the ClearPoint system for stereotactic surgery, children must have a fully mature skull, without open sutures, and sufficient skull thickness. While this typically occurs around age 2, patients between 1 and 2 years of age who were considered for the study were evaluated by the study investigator and skull imaging to ensure that there was sufficient skull thickness and maturity for the required neurosurgical procedure.*

6.1.4 Study Treatments or Agents Mandated by the Protocol

A total of 1.8×10^{11} vg of eladocagene exuparvovec was administered through 4 intraputaminal infusions during a single neurosurgical procedure.

6.1.5 Directions for Use

Eladocagene exuparvovec was administered using the SmartFlow MR-compatible ventricular canula to allow for infusion into the putamen of the brain.

Reviewer Comment:

- *The SmartFlow MR-Compatible ventricular canula was reviewed in parallel by the Center for Devices and Radiological Health (CDRH) in a de novo submission. There*

were no major issues in the review of the canula that impacted the review of eladocagene exuparvovec. Please refer to the CRDH de novo review.

6.1.6 Sites and Centers

Study AADC-002 was conducted at 6 clinical sites, 4 of which were in the U.S. The sites and the corresponding principal investigator are listed below:

a. Site 101: Texas Children's Hospital (Dr. Daniel Curry)
   Site 102: Boston Children's Hospital (Dr. Scellig Stone)
   Site 103: Cincinnati Children's Hospital (Dr. Sudhakar Vadivelu)
   Site 104: Duke University Hospital (Dr. Matthew Vestal)
   Site 201: Shebab Medical Center—Edmon and Lily Safra Children's Hospital, Israel (Prof. Bruria Ben-Zeev)
   Site 301: National Taiwan University Hospital (Dr. Yin-Hsiu Chien)

6.1.7 Surveillance/Monitoring

Patients were admitted for one night in the intensive care unit and hospitalized for up to three days. Discharge was determined at the treating physician's discretion, though patients were required to stay near the study site for a minimum of 7 days post-procedure.

Safety assessments included laboratory assessments (complete blood count, chemistry, coagulation), physical examinations including vital signs, height and weight. Viral shedding was assessed in blood, CSF, and urine. Anti-AAV2 antibody testing and T-cell sample collection were performed to assess for immune response to gene therapy. Table 5 shows the schedule of assessments for the Trial Phase (Day 0 through Week 8), Table 6 shows the schedule of assessments for the Extension Phase (Week 10 through Week 48), and Table 7 shows the schedule of assessments for the Long-Term Extension Phase (Week 60 through Month 60).

Table 5: Schedule of Assessments for Trial Phase of Study AADC-002 (Weeks 1-8)

Visit	1	2	3	4	5	6	7	8	9
Type of Visit (In-Person or Phone)	In-Person	In-Person	In-Person	In-Person	Phone	In-Person	Phone	Phone	In-Person
Visit Window	Screening Week -10 to -2	Baseline W-1	Dosing Day (Day 1)	Discharge (Day 3)	Week 2	Week 3	Week 4	Week 6	Week 8
Informed consent	X	-	-	-	-	-	-	-	-
Inclusion/exclusion criteria	X	X	-	-	-	-	-	-	-
Genetic testing[a]	X	-	-	-	-	-	-	-	-
Demography	X	-	-	-	-	-	-	-	-
Medical history	X	-	-	-	-	-	-	-	-
COVID-19 test	X	X	X	-	-	-	-	-	-
Pregnancy test[b]	X	X	X	-	-	X	-	-	X
AADC enzyme activity assessment (plasma)	X	-	-	-	-	-	-	-	-
Collect CSF history[c]	X	-	-	-	-	-	-	-	-
CSF neurotransmitter analysis[d]	-	-	X	-	-	-	-	-	X
Serum Anti-AAV2 antibody (IgG and neutralizing titers)	X	-	X	X	-	X	-	-	X
Viral shedding (blood and urine)	-	-	X	X	-	X	-	-	X
Viral shedding (CSF)	-	-	X	-	-	-	-	-	X
Physical examination[e]	X	X	X	X	-	X	-	-	X
Vital signs[f]	X	X	X	X	-	X	-	-	X
Height/weight	X	X	X	X	-	X	-	-	X
Brain MRI (T1-MPRAGE and T2-FLAIR sequences)	X	-	-	X	-	X	-	-	X
Real-time intrasurgical MRI	-	-	X	-	-	-	-	-	-
Postdose brain CT[g]	-	-	X	-	-	-	-	-	-
Brain 18F-DOPA PET	-	X	-	-	-	-	-	-	X

Visit	1	2	3	4	5	6	7	8	9
Chest x-ray	-	X	-	-	-	-	-	-	-
12 lead ECG	-	X	-	-	-	-	-	-	-
Oculogyric crisis eDiary instructions for use[h]	X	-	-	-	-	-	-	-	-
AADC-specific symptoms[i]	X	X	-	X	-	X	-	-	X
Laboratory tests[j]	X	X	-	X	-	X	-	-	X
T-cell sample collection	X	-	X	X	-	X	-	-	X
PDMS-2	-	X	-	-	-	-	-	-	-
Bayley-III	-	X	-	-	-	-	-	-	-
EQ-5D-Yk	-	X	-	-	-	-	-	-	-
Study drug injection (eladocagene exuparvovec)	-	-	X	-	-	-	-	-	-
AEs	-	X	X	X	X	X	X	X	X
Concomitant medications	-	X	X	X	X	X	X	X	X

Source: Adapted from AADC-002 Clinical Protocol

a-Genetic testing not repeated if there is prior documentation available; if drawn during screening, analyzed by a Central Laboratory

b-for females of child-bearing age only

c-Cerebrospinal fluid analysis history of homovanillic acid, 5-hydroxyindoleacetic acid, 3-O-methyldopa, pterins, 3-methoxy-4-hydroxphenylglycol, L-DOPA, 5-hydroxytryptophan if available

d- Cerebrospinal fluid homovanillic acid, 5-hydroxyindoleacetic acid, 3-O-methyldopa, appearance, red blood cells, white blood cells, protein, glucose

e-Complete physical examination on Screening, Baseline visit, dosing Day1; target physical exams for all other visits.

f-Vital signs include temperature, pulse, respiratory rate, and blood pressure.

g-brain CT performed for post-dose hemorrhage check should be performed within 6 hours after surgery.

h-Parent/caregiver must complete eDiary or paper diary for each OGC occurrence throughout the Trial Phase and Extension Phase. In the event that eDiary cannot be used, a paper version will be provided.

i-AADC specific symptoms include floppiness (hypotonia), limb and stimulus provoked dystonia, and muscle power. These were obtained as part of the neurological exam and no specific instrument(s) was used.

j-Laboratory tests include prothrombin time (PT), partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT), international normalized ratio (INR), complete blood count with differential, complete metabolic profile with bilirubin.

k-EQ-5D-Y will not be administered to patients under 4 years of age

Abbreviations: AE, adverse events; AADC, aromatic L-amino acid decarboxylase deficiency; Bayley III, Bayley Scale of Infant and Toddler Development-III, CSF, cerebrospinal fluid, CT, computed tomography; ECG, electrocardiogram; IgG, immunoglobulin G; MRI, magnetic resonance imaging; PET, positron emission tomography; PDMS-2, Peabody Developmental Motor Scale II

Table 6: Schedule of Assessments for Extension Phase of Study AADC-002 (Weeks 9-48)

Visit	10	11	12	13	14	15	16	17	18	19	20
Type of Visit	P	IP	P	P	IP	P	P	IP	P	P	IP
Visit Window	W10	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48
Pregnancy test[a]	-	X	-	-	X	-	-	X	-	-	X
CSF neurotransmitter analysis	-	-	-	-	-	-	-	-	-	-	X
Anti-AAV2 antibody (IgG and neutralizing titers)	-	X	-	-	X	-	-	X	-	-	X
Viral shedding (blood and urine)	-	X	-	-	X	-	-	X	-	-	X
Viral shedding (CSF)	-		-	-	-	-	-	-	-	-	X
Targeted physical examination	-	X	-	-	X	-	-	X	-	-	X
Vital signs[c]	-	X	-	-	X	-	-	X	-	-	X
Height/weight	-	X	-	-	X	-	-	X	-	-	X
Brain MRI (T1-MPRAGE and T2-FLAIR sequences)	-	-	-	-	-	-	-	-	-	-	X
Brain ^{18}F-DOPA PET	-	-	-	-	-	-	-	-	-	-	X
AADC-specific symptoms[d]	-	X	-	-	X	-	-	X	-	-	X
Laboratory tests[e]	-	X	-	-	X	-	-	X	-	-	X
T-cell sample collection	-	X	-	-	X	-	-	X	-	-	X
PDMS-2	-	-	-	-	X	-	-	-	-	-	X
Bayley-III	-	-	-	-	X	-	-	-	-	-	X
EQ-5D-Y[f]	-	-	-	-	X	-	-	-	-	-	X

Visit	10	11	12	13	14	15	16	17	18	19	20
AEs	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X

Source: Adapted from AADC-002 Clinical Protocol

a-for females of child-bearing age only; urine or serum per investigator's discretion, tested at a local laboratory

b-Cerebrospinal fluid homovanillic acid, 5-hydroxyindoleacetic acid, 3-O-methyldopa, pterins, 3-methoxy-4-hydroxphenylglycol, L-DOPA, 5-hydroxytryptophan if available

c-Vital signs include temperature, pulse, respiratory rate, and blood pressure.

d-AADC specific symptoms include floppiness (hypotonia), limb and stimulus provoked dystonia, and muscle power. Those were assessed as part of the neurological exam.

e-Laboratory tests include prothrombin time (PT), partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT), international normalized ratio (INR), complete blood count with differential, complete metabolic profile with bilirubin.

f-EQ-5D-Y will not be administered to patients under 4 years of age

Abbreviations: AE, adverse events; AADC, aromatic L-amino acid decarboxylase deficiency; Bayley III, Bayley Scale of Infant and Toddler Development-III; CSF, cerebrospinal fluid, IgG, immunoglobulin G; IP, in person visit; MRI, magnetic resonance imaging; P-Phone visit; PET, positron emission tomography; PDMS-2, Peabody Developmental Motor Scale II, W-week.

Table 7: Schedule of Assessments for Long-Term Extension Phase of Study AADC-002 (Weeks 49-260)

Visit	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**
Type of Visit	P	IP	P	IP	P	IP	P	IP	P	IP
Visit Window	W60	W72	W84	W96	W130/M30	W156/M36	W182/M42	W208/M48	W234/M54	W260/M60
Pregnancy test[a]	-	X	-	x	-	x	-	x	-	x
Physical examination[b]	-	X	-	x	-	x	-	x	-	x
Vital signs[c]	-	X	-	x	-	x	-	x	-	x
Height/weight	-	X	-	x	-	x	-	x	-	x
AADC-specific symptoms [d]	-	X	-	x	-	x	-	x	-	x
Laboratory tests[e]	-	-	-	x	-	x	-	x	-	x
PDMS-2	-	X	-	X	-	X	-	X	-	X
Bayley-III	-	X	-	X	-	X	-	X	-	X
EQ-5D-Y f	-	X	-	X	-	X	-	X	-	X
AEs	X	X	X	X	x	x	x	x	x	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x

Source: Adapted from AADC-002 Clinical Protocol

a-for females of child-bearing age only; urine or serum per investigator's discretion, tested at a local laboratory

b-Complete physical examination at week 96, 156, 208, 260; targeted physical exam at week 72.

c-Vital signs include temperature, pulse, respiratory rate, and blood pressure.

d-AADC specific symptoms include floppiness (hypotonia), limb and stimulus provoked dystonia, and muscle power. Assessed through neurological exam.

e-Laboratory tests include prothrombin time (PT), partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT), international normalized ratio (INR), complete blood count with differential, complete metabolic profile with bilirubin.

f-EQ-5D-Y will not be administered to patients under 4 years of age

Abbreviations: AE, adverse events; AADC, aromatic L-amino acid decarboxylase deficiency; Bayley III, Bayley Scale of Infant and Toddler Development-III; CSF, cerebrospinal fluid, IgG, immunoglobulin G; IP, in person visit; MRI, magnetic resonance imaging; P-Phone visit; PET, positron emission tomography; PDMS-2, Peabody Developmental Motor Scale II; W, week

6.1.8 Endpoints and Criteria for Study Success

The primary, secondary and exploratory endpoints for protocol for Study AADC-002 were as follows:

Primary Endpoints

- Change from baseline in HVA metabolite levels 8 weeks after administration.
- Assessment of adverse events (AEs) associated with the surgical administration of eladocagene exuparvovec to pediatric subjects using the SmartFlow MR-compatible ventricular canula 8 weeks after administration.

Secondary Endpoints

- Change from baseline in neurotransmitter CSF HVA levels 48 weeks after administration.
- Change in ^{18}F-DOPA uptake 8 and 48 weeks after administration.
- Change from baseline in neurotransmitter CSF metabolites 5-HIAA and 3-OMD at 8 and 48 weeks after administration.
- Attainment of motor milestones.
- Motor development as assessed by the PDMS-2.
- Cognitive and language development as assessed by Bayley-III.
- Change in EQ-5-DY.
- Change in body weight.
- Assessment of AADC-specific symptoms.
- Overall safety profile characterized by type, frequency, severity, timing, and relationship to study treatment of any TEAEs, neurological examination findings, brain imaging, or laboratory abnormalities.

Reviewer Comment:

- *As discussed in Section 2.5, the Sponsor initially designed study AADC-002 to demonstrate safety of the SmartFlow cannula, used to administer eladocagene exuparvovec, given that it was deemed not comparable to the device used in the Taiwan studies. Efficacy data was planned to come from the Taiwan studies (AADC-010 and AADC-011), where the primary endpoint was acquisition of motor milestones after treatment. However, when it was communicated to the Applicant that the drug product used in the Taiwan studies was also not comparable to the intended US commercial product (Type C meeting held on October 6, 2022, CRMTS #14126), the Sponsor amended their plan to use study AADC-002 as the single pivotal study to support registration. The Sponsor submitted a justification to use CSF HVA as a biomarker on November 21, 2022 (amendment 28), followed by a protocol amendment changing the primary endpoint to "change from baseline in HVA metabolite levels at the end of the Trial Phase (8 weeks after administration)" (received September 23, 2023 in amendment 45).*

6.1.9 Statistical Considerations & Statistical Analysis Plan

Due to the small study population, the statistical analysis plan included summaries and descriptive statistics of the safety and efficacy variables. Initially, the Applicant had planned to submit a BLA using efficacy data from the Taiwan studies. However, since the intended neurosurgical device for commercial administration of eladocagene exuparvovec was different than that used in the Taiwan studies, the Sponsor opened a U.S. IND and planned to enroll three patients in a study with the intent of primarily evaluating safety of the SmartFlow MR-compatible cannula (Study AADC-002). However, upon determination that the drug product used in the two Taiwan studies was not comparable to the intended U.S. commercial product and could not be used for the efficacy evaluation, the Sponsor increased the Study AADC-002 sample size to 13 patients to support assessments of efficacy and safety and used this as the pivotal study for this BLA.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Proposed Indication: "Treatment of Aromatic L-Amino Acid Decarboxylase Deficiency"

7.1.1 Methods of Efficacy Data Integration

Studies AADC-010 and AADC-011, conducted in Taiwan, were utilized to characterize CSF HVA as a biomarker reasonably likely to predict clinical benefit. CSF HVA and motor outcome data were integrated from these two studies as they treated patients with the same version of the eladocagene exuparvovec product. Data from these two studies are presented during the discussion of the primary endpoint in Section 7.1.4. However, given that the basis for efficacy is data from the 13 patients treated in pivotal study AADC-002, the focus of this section will be on analysis of data from this study. Pooled and patient-level analyses were conducted.

7.1.2 Demographics and Baseline Characteristics

Table 8: Baseline Characteristics of Patients Treated in Study AADC-002 (N=13)

Parameter	
Sex, n (%)	
Female	7 (54%)
Male	6 (46%)
Race, n (%)	-
Asian	10 (77%)
White	2 (15%)
Other	1 (8%)[1]
Ethnicity, n (%)	-
Hispanic or Latino	2 (15%)
Not Hispanic or Latino	10 (77%)
Not Reported / Unknown	1 (8%)
Age at Treatment (years)	-
Median	2
Min – max	1-10
Genotype	-
At least one c.714+4A>T variant (founder variant in Asian population)	7 (54%)
c.714+4A>T homozygous	2 (15%)
c.714+4A>T/c.1297dup	2 (15%)
c.714+4A>T / c.304G>A	1 (8%)
c.714+4A>T / c.1297-1298insA	1 (8%)
c.714+4A>T/4P.75	1 (8%)
c.242C>T homozygous	1 (8%)
c.367G>A/c.1234C>T	1 (8%)
c.568_569InsCGATC/ c.863T>C	1 (8%)
c.del ex 11-12/c.557A>G	1 (8%)
c.304G>A/c.304G>A	1 (8%)
c.260C>T / c.286G>A	1 (8%)
Taking concomitant medications at time of gene therapy treatment[1]	8 (62%)

Source: Reviewer analysis of AADC-002, 2.7.3 Summary of Clinical Efficacy
Abbreviations: Max, maximum; Min, minimum
1-excludes patients solely taking vitamin B6 (pyridoxine) therapy

Reviewer Comment:

- *Children ages 1 to 10 were treated in the clinical study, with 12 out of 13 treated patients under 5 years of age No adolescents or adults were treated in this clinical study.*
- *All treated patients had the severe phenotype of AADCD.*
- *It should be noted that 7 out of 13 (54%) of patients had the founder variant (c.714+4A>T) which usually confers the severe phenotype.*

- *The c.714+4A>T mutation is considered a founder variant with high prevalence in patients of southern Chinese descent (including Japan and Taiwan) (Himmelreich et al. 2019). The population enrolled in this study is primarily of Asian descent. The Applicant clarified that the country of descent for the 10 patients of Asian descent were as follows: Thailand (2 patients), China (2 patients), Malaysia (2 patients), India (1 patient), Singapore (1 patient), Taiwan (1 patient), and Nepal (1 patient). As discussed earlier in this review, the racial and ethnic distribution of patients in the United States with AADCD is not well characterized. The Applicant states they have identified AADCD patients of White, African American, and Alaskan Native races as well. Given the small study population, it was not feasible to conduct subgroup analysis to understood differences in safety or efficacy based on race or ethnicity.*

7.1.3 Patient Disposition

Disposition for patients treated with eladocagene exuparvovec in the pivotal study (AADC-002) at Week 48 are shown below in Table 9.

Table 9: Disposition of Patients in Pivotal Study AADC-002 at Week 48

Parameter	AADC-002 (n=13)
Completed Week 48 Assessment	12 (92%)
Early Withdrawal	1 (8%)

Source: Adapted from AADC-002 Interim Clinical Study Report, Response to Clinical Information Request
Abbreviations: Max, maximum; Min, minimum

One patient, (b) (6) , withdrew at study Week 23. The parent reported that they were unable to do any of the in-person assessments and withdrew consent to participate in the study. This patient had experienced an SAE of cardiorespiratory arrest with line placement after administration of the investigational product (see safety review section). As this patient dropped out prior to any collection of motor or CSF HVA assessments, this patient was not included in the efficacy analyses as no data were available for either assessments at week 48.

Reviewer Comment:

- *This reviewer notes that efficacy is demonstrated in a very small study population of 12 patients. Given this small sample size, this reviewer recommends that the post-marketing accelerated approval study to verify clinical benefit enroll additional patients to confirm the observations of efficacy in this population.*

7.1.4 Analysis of Proposed Primary Efficacy Endpoint for Approval: CSF HVA levels

As discussed in Section 6.1.8, the pre-specified clinical efficacy endpoint in Study AADC-002 (assessed as part of exploratory endpoints) was the change in motor development as assessed by the Peabody Developmental Motor Scale, second edition (PDMS-2). However, the Applicant proposed to support substantial evidence of effectiveness in this BLA based on the change from baseline in CSF HVA at Week 8

(exploratory endpoint in Study AADC-002), which the Applicant proposed was being reasonably likely to predict clinical benefit.

Data from the Taiwan studies (AADC-010 and AADC-011) were submitted to support use of CSF HVA as a reasonably likely surrogate endpoint. The Applicant observed post-treatment change in CSF HVA 12 months after administration (Table 10) that they assessed were correlated with highest motor milestone achievement at Month 60 (r-vlue = 0.72, p-value = 0.0034).

Table 10: CSF HVA by Timepoint in Studies AADC-010 and AADC-011

Parameter	Baseline	Month 12 Levels	Change From Baseline at Month 12
HVA	-	-	-
N	22	19	19
Mean (SD) (nmol/L)	11.50 (13.64)	33.45 (17.94)	24.21 (17.67)

Source: Adapted from Table 21, 2.7.3 Summary of Clinical Efficacy
Abbreviation: HVA-homovanillic acid

Based on this data, the Applicant proposed that a minimum of 20% increase from baseline in CSF HVA measured at Week 8 after treatment is reasonably likely to predict long-term improvements in motor outcomes in AADCD patients in Study AADC-002. This was based on the conclusion that all patients who subsequently developed motor milestones demonstrated a ≥20% increase in CSF HVA. Table 12 shows all CSF HVA data and motor milestone data in the patients enrolled in AADC-010 and AADC-011, which will be referenced throughout this subsection. Refer to Figure 16 and Figure 17 (by age of patients) in Appendix 2.3 for individual profiles in arrays of motor milestone achievement, CSF HVA, and putamen specific ^{18}F-DOPA uptake.

Clinical Pharmacology & Clinical Reviewer Comment

- *As noted, the pre-specified clinical efficacy endpoint and the primary pharmacodynamic endpoint proposed by the Applicant to support the BLA efficacy analyses were different. However, given that the clinical endpoint assessment was pre-specified prior to study start and used a standardized assessment tool (PDMS-2), this difference did not impact our conclusions on efficacy. Observations of improvements in motor milestones (discussed below) were not considered subject to bias given that patients with the severe phenotype of AADCD have been shown in the natural history to achieve no motor milestones in the absence of treatment.*

In reviewing the data, substantial limitations were identified by both the clinical and clinical pharmacology reviewers in the strength and appropriateness of using a threshold of >20% increase from baseline in CSF HVA as a surrogate endpoint reasonably likely to predict clinical benefit in the study AADC-002 population. The identified limitations are based on review of the submitted data from the 2 Taiwan studies, Studies AADC-010, AADC-011, and are as follows:

1. ***Uncertainty regarding the proposed threshold of >20% increase from baseline.*** *Based on the data submitted, there were uncertainties in the proposed threshold of a 20% increase from baseline to Week 8 as reasonably likely to predict clinical benefit.*

   The Applicant's proposed 20% threshold was based on the observation that a 20% increase from baseline in CSF HVA was the minimum percent increase in 18 out of 19 patients enrolled in the Taiwan studies who had CSF HVA measurements and demonstrated improvements in motor milestones. However, we note the following observations that introduce uncertainty in the significance of the proposed threshold:

   a. *The Applicant did not submit any data to characterize longitudinal changes and variability in CSF HVA levels over time in animal models, untreated children with AADCD, or healthy children. Therefore, without an understanding of the inter-patient variability in CSF HVA (including in relation to assay variability and concomitant medication use), it is difficult to interpret the changes in the treated patients and particularly to interpret whether a 20% change in CSF HVA may be within the range of variability due to patient factors or assay factors (independent of product specific effects). The clinical reviewer notes that there is additional uncertainty in how CSF HVA would be expected to change over time in children, who continue to undergo significant changes in synaptic formations (and potentially neurotransmitter levels).*

   b. *Two patients in the supportive studies had two pre-treatment CSF HVA levels (noted as "Baseline" and "Screening") drawn and run on the same assay. The remaining patients had the Baseline and Screening levels analyzed using different assays, which are not appropriate to compare. These are shown below in Table 11. As shown, one patient* (b) (6) *had a 40% increase between screening and baseline (where measurements were obtained 13 months apart).*

Table 11: Pre-Treatment CSF HVA Levels in Two Patients With Samples Run on the Same Assay

Patient ID	Screening CSF HVA (nmol/L)	Baseline CSF HVA (nmol/L)
(b) (6)	2.5	2.5
(b) (6)	10	14

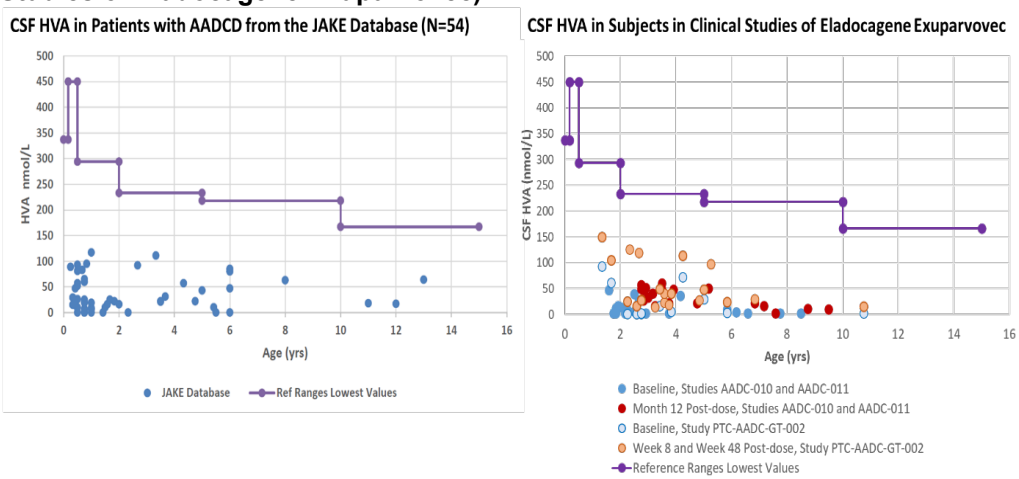
Source: Table 1, Applicant's Responses to Information Requests #12 dated July 1, 2024

   This child's measurements demonstrate the possibility that there can be variability in CSF HVA that exists in the absence of treatment that exceeds the 20% threshold. Therefore, the suitability of >20% changes in CSF HVA to represent a treatment response after administration of eladocagene exuparvovec is uncertain.

   c. *CSF HVA levels measured after treatment with eladocagene exuparvovec still remained substantially below the lower limit of the normal range and within the range of levels observed in untreated patients with AADCD. As*

shown in Table 12, no patients achieved normalization in CSF HVA levels after treatment. The highest post-treatment CSF HVA level was 60 nmol/L, still falling substantially below the assay lower limit of normal (294 nmol/L). The JAKE database, an international database of patients with AADCD (BioPKU.org c2024), has collected cross-sectional data on untreated patients with AADCD. Data comparing CSF HVA in patients in the JAKE database and patients treated in clinical studies of eladocagene exuparvovec (including Studies AADC-010, AADC-011, and pivotal study AADC-002) are shown below in Figure 5.

Figure 5: CSF HVA in Patients With AADCD by Age (Left: JAKE Database, Right: Clinical Studies of Eladocagene Exuparvovec)



Source: the left figure: Figure 2 in Applicant's Response to Information Requests #4 dated May 20, 2024; the right figure: Reviewer's analysis based on FDAQ14.xpt, submitted in Applicant's Responses to Information Requests #12 dated July 1, 2024
Note: Each circle represents CSF HVA value in each individual patient. The solid purple line represents the lowest values of the reference normal range for CSF HVA by age used in Studies AADC-010 and AADC-011 (see https://one-dh.testcatalog.org/show/7263317). No reference range was used in Study AADC-002 and reference ranges in multiple laboratories used in the JAKE Database were not provided. Reference ranges may vary by laboratory.
Lower limit of quantification (LLOQ) of CSF HVA was 5 nmol/L in Studies AADC-010 and AADC-011 and 2 nmol/L in Study AADC-002, and values reported as <LLOQ were imputed as 0.5*LLOQ
Abbreviations: CSF HVA, homovanillic acid in cerebrospinal fluid

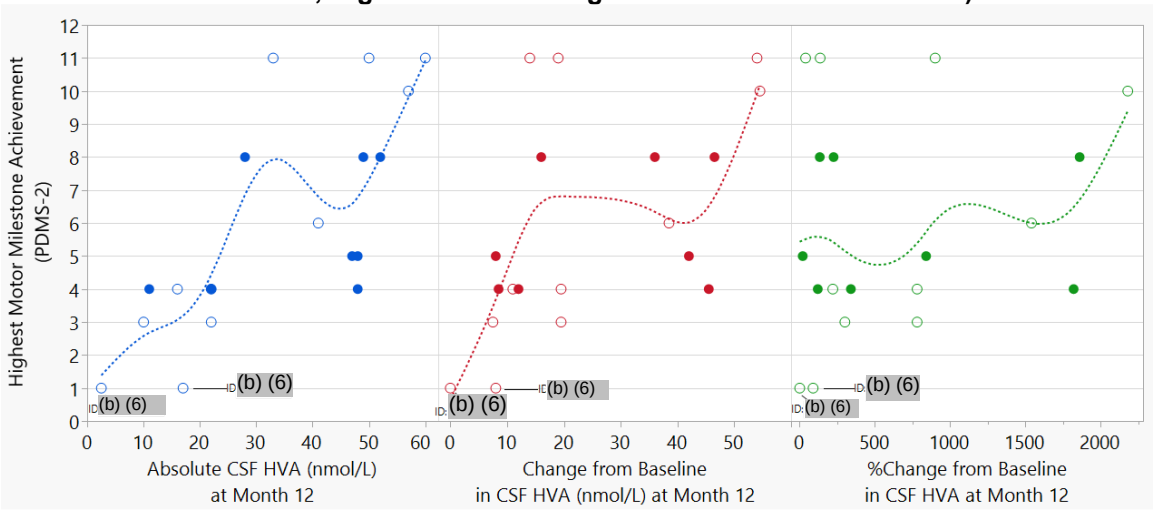
- *We note that the CSF HVA levels in the treated children appeared within the range of untreated children with AADCD enrolled in the JAKE database and did not normalize (compared to the normal reference ranges provided for the assays used in the two Taiwan studies). Therefore, it is unclear to what extent the changes in the CSF HVA levels were attributed to eladocagene exuparvovec or would be expected to due inter-patient variability. While it should be noted that the normal ranges of the assays used in the pivotal study and patients in the JAKE database may differ, the comparison is considered informative to contextualize the clinical trial CSF HVA data.*
- *As shown in Table 12, patient* (b) (6) *demonstrated an 89% increase from baseline in CSF HVA. Despite this increase in CSF HVA, this patient was*

observed to have only a transient partial head control that only lasted from Month 6 to Month 30 after treatment, with decline back to baseline (no motor milestones observed) occurring at Month 42 after treatment. Despite a robust increase in CSF HVA that was greater than 4x above the defined threshold of 20%, this patient did not have long-term clinical benefit.

2. ***There did not appear to be a close and consistent correlation between motor outcomes and parameters of CSF HVA, including absolute post-treatment value, absolute change from baseline, and percent change from baseline.***

Given the discussed uncertainty in the 20% threshold, both reviewers examined the overall relationship between CSF HVA and motor outcomes to further investigate the role of CSF HVA as a biomarker. Graphical representations are shown below in Figure 6, where close and consistent correlations in motor outcomes and parameters of CSF HVA levels are not evident. See Figure 10 and Figure 11 in Appendix 1.2 for the same analysis for Study AADC-002, indicating no clear correlations.

Figure 6: Relationship Between CSF HVA at Month 12 and Highest Motor Milestone in Studies AADC-010 and AADC-011 (Left: Absolute CSF HVA; Middle: Change From Baseline in CSF HVA; Right: Percent Change From Baseline in CSF HVA)



Source: Reviewer's analysis based on FDAQ14.xpt and FDAQ16.xpt submitted in Applicant's Responses to Information Requests #12 dated July 1, 2024.
Note: Motor milestones assessed on PDMS-2, 0=none, 1=partial head control, 2=full head control, 3=sitting with assistance, 4=sitting unassisted, 5=standing with support, 6=standing away from support, 7=walking with assistance, 8=free walking, 9=walking upstairs with support, 10=walking backward, 11=walking on taped line;
Open circles mean emerging skill and closed circles mean mastery of the skill for the motor milestone.
Dotted lines show smooth curves through the data with a spline method.
Lower limit of quantification (LLOQ) of CSF HVA was 5 nmol/L, and values reported as <LLOQ were imputed as 0.5*LLOQ
Abbreviations: CSF HVA, homovanillic acid in cerebrospinal fluid; PDMS-2, the Peabody Developmental Motor Scale-2

The uncertainty in the correlation between parameters of CSF HVA and motor outcomes in studies AADC-010 and AADC-011 can be further seen in the following observations:

a. *Patients* (b) (6) *were relatively similar in age at the time of treatment (7.8 and 8.5 years of age, respectively) and had the same baseline CSF HVA level (2.5 nmol/L). Both patients had similar percent changes from baseline in CSF HVA (340% and 300%, respectively) at Month 12. However, these patients had very different outcomes in motor function after treatment: Patient* (b) (6) *was able to achieve a highest motor milestone of "emerging sitting unassisted," and Patient* (b) (6) *was able to achieve the highest motor milestone of only "emerging full head control."*
b. *Patients* (b) (6) *were both 1.8 years of age at the time of treatment. Patient* (b) (6) *had a modest 39% increase from baseline in CSF HVA and achieved the milestone of "emerging walking on a taped line." Patient* (b) (6) *had a substantially larger, 1,860% increase from baseline in CSF HVA but had a relatively similar outcome to* (b) (6) *with achievement of the milestone of "free walking."*
c. *Patient* (b) (6) *had a Month 12 CSF HVA of 48 nmol/L with a highest motor milestone achievement of "sitting unassisted." In comparison, patient* (b) (6) *had a lower, Month 12 CSF HVA of 33 nmol/L but was able to achieve a higher motor milestone of "emerging walking on a taped line."*

Based on the data submitted from studies AADC-010 and AADC-011, both reviewers were unable to observe a clear correlation between the parameters of CSF HVA measured after treatment and motor outcomes.

3. ***There is uncertainty in the significance of the Week 8 timepoint.***

In both supportive studies, CSF HVA was measured at screening, baseline, and Month 12. Measurements at Week 8, as obtained in the pivotal study, were not obtained in the supportive studies. However, the pivotal study obtained Week 48 CSF HVA measurements in 8 out of 13 patients. For the purposes of data analyses, the Week 48 timepoint in the pivotal study was considered equivalent to the Month 12 timepoint in the supportive studies.

In the pivotal study, substantial intra-patient variability was found comparing levels at Week 8 and Week 48 after the gene therapy: the difference between Week 8 and Week 48 levels ranged from -24.64 to 15.07 nmol/L, and the percent difference ranged from -44.9% to 38.9% (Figure 2 in Section 4.4.2). Moreover, the correlation in CSF HVA between observations at Week 8 and Week 48 was unclear given the limited data in eight patients (See Figure 9 in Appendix 1.1).

This suggests that it is uncertain if change from baseline in CSF HVA at Week 8 can reliably represent that of Week 48 or later timepoints. This uncertainty, when considered with the discussed uncertainties in the correlation between clinical outcomes and CSF HVA, demonstrates that available data do not support the use of CSF HVA as a surrogate endpoint reasonably likely to predict clinical benefit.

Table 12: CSF HVA and Motor Milestones in Patients Enrolled in AADC-010 and AADC-011

Patient ID	Age at Treatment (years)	Baseline CSF HVA (nmol/L)	Month 12 CSF HVA (nmol/L)	% Change From Baseline in CSF HVA	Baseline Motor Milestone a	Last Motor Milestone (Time) a	Highest Motor Milestone (Time) a
(b) (6)	6.2	5[b]	16[b]	+220%	Emerging partial head control	Emerging sitting with assistance (M96)	Sitting unassisted (M60)
	7.8	2.5[b]	11[b]	+340%	None	Emerging sitting unassisted (M60)	Emerging sitting unassisted (M60)
	8.5	2.5[b]	10[b]	+300%	None	Emerging full head control (M60)	Emerging sitting with assistance (M30)
	2.5	6[d]	60[d]	+900%	None	Walking on taped line (M96)	Walking on a taped line (M84)
	2.8	2.5[c]	22[c]	+780%	Emerging partial head control	Sitting unassisted (M96)	Sitting unassisted (M84)
	6.6	2.5[d]	2.5[d]	0	Emerging partial head control	Partial head control (M84)	Partial head control (M30)
	2.7	28[c]	NA	NA	None	Emerging partial head control (M9)	Emerging partial head control (M9)e
	2.9	2.5[d]	48[c]	+1820%	None	Sitting unassisted (M24)	Sitting unassisted (M24)f
	2.2	2.5[c]	41[c]	+1540%	None	Standing with support (M84)	Standing with support (M48)
	1.8	2.5[d]	57[d]	+2180%	None	Walking backward normal stride (M84)	Walking backward normal stride (M84)

Patient ID	Age at Treatment (years)	Baseline CSF HVA (nmol/L)	Month 12 CSF HVA (nmol/L)	% Change From Baseline in CSF HVA	Baseline Motor Milestone a	Last Motor Milestone (Time) a	Highest Motor Milestone (Time) a
(b) (6)	5.8	10[b]	22[b]	+120%	None	Sitting unassisted (M36)	Sitting unassisted (M72)
	4.2	36[c]	50[c]	+39%	None	Emerging walking on taped line (M36)	Emerging walking on taped line (M36)
	1.8	12[d]	28[d]	+133%	None	Free Walking (M72)	Free walking (M72)
	3.8	<5[c]	22[c]	+780%	Emerging partial head control	Sitting with assistance (M72)	Sitting with assistance (M72)
	1.8	<5[d]	49[d]	+1860%	None	Free walking (M60)	Free walking (M60)
	2.5	40[c]	48[c]	+20%	None	Standing with support (M60)	Standing with support (M24)
	2	14[d]	33[c]	+136%	None	Emerging walking on taped line (M60)	Emerging walking backward using normal stride (M30)
	2.3	9[c]	17[c]	+89%	None	None (M54)	Partial head control (M18)
	1.8	5[d]	47[d]	+840%	Emerging partial head control	Standing with support (M36)	Standing with support (M24)

Patient ID	Age at Treatment (years)	Baseline CSF HVA (nmol/L)	Month 12 CSF HVA (nmol/L)	% Change From Baseline in CSF HVA	Baseline Motor Milestone a	Last Motor Milestone (Time) a	Highest Motor Milestone (Time) a
(b) (6)	1.6	47[d]	NA	NA	None	Emerging running speed (M36)	Emerging running speed (M36)
	1.9	16[d]	52[d]	+225%	None	Free walking (M24)	Free walking (M24)
	1.8	2.5[d]	NA	NA	None	NA	NA

Source: Reviewer analysis of ISS datasets.
a-motor milestones assessed on the Peabody Developmental Motor Scale-2 (PDMS2)
b-Reference range for assay 218-852 nmol/L
c-Reference range for assay 233-928 nmol/L
d-Reference range for assay 294-1115 nmol/
e-Patient died 11 months after gene therapy; last assessment was Month 9. Death discussed further in Section 8.4.1.
f-patient declined to enter long-term extension study.
g-Patient was reported to be unable to return to study site after Month 6 due to COVID-19 travel restrictions.
Lower limit of quantification (LLOQ) of CSF HVA was 5 nmol/L, and values reported as <LLOQ were imputed as 0.5*LLOQ;
Abbreviations: M, month; NA, not assessed

7.1.5 Analysis of Clinical Efficacy Endpoint: Motor Milestone Achievement (by PDMS-2)

The pre-specified endpoint for the efficacy analysis was motor milestone acquisition in pivotal study AADC-002. Motor milestone acquisition was assessed using the specific items on the PDMS-2 (Table 13, ordered by increasing difficulty), where a score of 0 represents no ability to do the skill, 1 represents "emerging" ability to do the skill, and 2 represents "mastery" of the skill. Differentiating between a score of 0, 1, 2 are specified in the PDMS-2 scoring manual.

Table 13: Motor Milestones as Assessed by PDMS-2 Items

Motor Milestone	PDMS-2 Item
Partial head control	Stationary 5
Full head control	Stationary 10
Sitting with assistance	Stationary 11
Sitting unassisted	Stationary 14
Standing with assistance	Locomotion 28
Standing without assistance	Locomotion 31
Walking with assistance	Locomotion 34
Walking without assistance	Locomotion 35
Walking backward using normal stride	Locomotion 44
Walking on a taped line	Locomotion 48

Source: BLA125722.0 Module 2.7 Summary of Clinical Efficacy, Table 6

Reviewer Comment:

- *For our analyses, achievement of a motor milestone was considered as having a score of "2" (mastery) at week 48 on any of the PDMS-2 items shown in the above Table 13.*
- *A treatment "responder" for purposes of the efficacy analysis is defined as any patient who achieved a score of 2 (mastery of) at least "full head control". As discussed below, improvements to "full head control" or higher were unexpected based on data in the untreated natural history cohort.*

All patients enrolled in the clinical study had the severe phenotype of the disease, defined by the Applicant as no motor milestone achievement by age 2 years and/or no response to standard of care medications.

Reviewer Comment:

- *Per (Wassenberg et al. 2017), the definition of the severe phenotype is patients with "no or very limited developmental milestones". Per (Pearson et al. 2020), the definition of the severe phenotype is "minimal or no attainment of motor milestones". The Applicant's definition of the severe phenotype includes the response to standard of care therapies. This is because most children can be assigned the severe phenotype if they do not have motor milestone achievement by age 2 (Bergkvist et al. 2022). However, given that the Applicant treated two children prior to age 2 years of age, a response to standard of care therapies*

was incorporated in the definition to verify the severe phenotype in these youngest children.

- *It should be noted that patient* (b) (6) *was noted to have an atypical presentation of the severe phenotype at baseline, with no head control but "emerging sitting with assistance". This is unusual given that motor milestones are generally acquired sequentially, with head control preceding all other motor milestones. It is certainly possible that this patient was assessed incorrectly (given subjective nature of assessment) and may not have fully met the criteria for "emerging sitting with assistance". However, all other aspects of the patient's clinical presentation were consistent with the severe phenotype, including a documented lack of response to standard of care medications.*
- *No patients with the mild or moderate phenotypes were enrolled in this study.*
- *As shown above in Table 8, 8 patients were taking concomitant medications at the time of gene therapy. These were not considered to affect interpretation of the motor milestone results. In order to be enrolled into the clinical trial, patients were required to have no motor milestone achievement and be stable on doses of concomitant medications for 3 months. Therefore, concomitant medications were not thought to confound motor milestone outcomes.*

Due to the variable duration of follow-up, motor milestone achievement at the Week 48 timepoint was used as the basis for the efficacy analyses. Week 48 assessments were available on 12 out of 13 patients enrolled in the study, with 1 patient dropping out at Week 23 prior to collection of efficacy assessments. Baseline motor milestones, highest post-treatment motor milestone and week 48 motor milestones are shown in Table 14.

Table 14: Motor Milestone Achievement in Patients Enrolled in Study AADC-002

Patient ID	Age at Treatment (Years)	Baseline Motor Milestone (PDMS-2 Score)	Highest Motor Milestone (Timepoint)	Week 48 Motor Milestone (PDMS-2 Score)	Treatment Response at Week 48*
(b) (6)	1.3	None (0)	Emerging walking backwards using normal stride (W48)	Walking backwards normal stride (2)	Responder
	1.7	Partial head control (0-1)	Walking backward with normal stride (W48)	Walking backwards normal stride (2)	Responder
	2.3	None (0)	Sitting unassisted (W48)	Sitting unassisted (2)	Responder

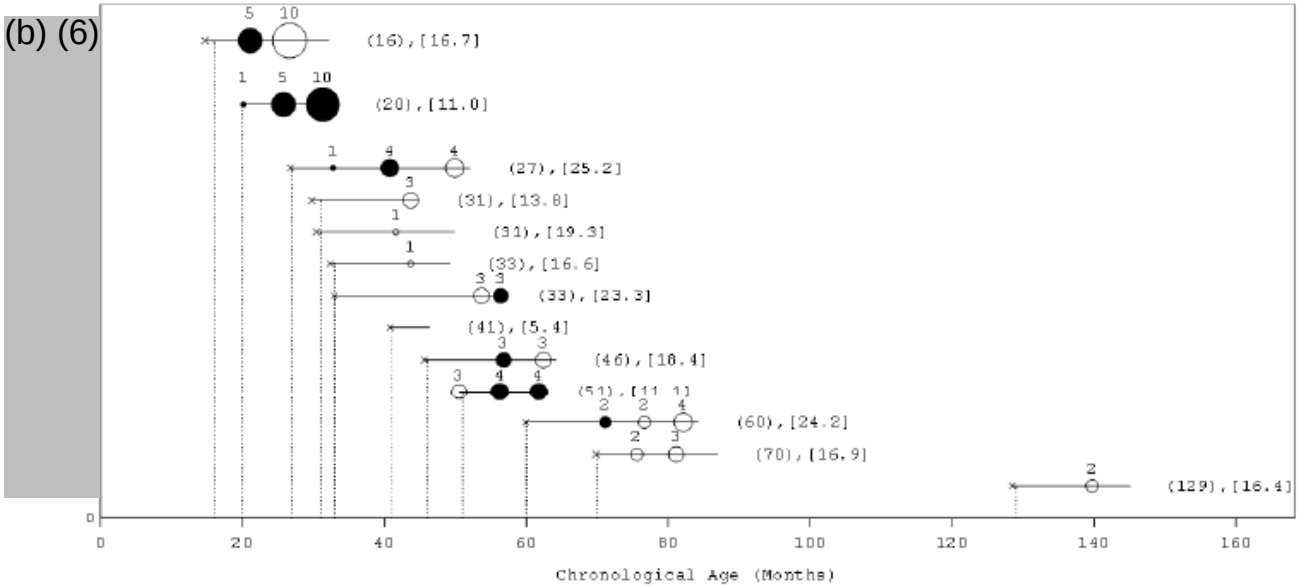
(b) (6)					
	2.6	None (0)	Emerging partial head control (W48)	Emerging partial head control (1)	Non-responder
	2.6	None (0)	Emerging sitting with assistance (W48)	Full head control (2), Emerging sitting with assistance (1)	Responder
	2.8	None (0)	Sitting with assistance (W96)	None (0)	Non-responder
	2.8	None (0)	Emerging partial head control (W48)	Emerging partial head control (1)	Non-responder
	3.4	None (0)	NA	NA	NA
	3.8	None (0)	Sitting with assistance (W48)	Sitting with assistance (2)	Responder
	4.3	No head control, emerging sitting with assistance (1)	Full head control, sitting unassisted (W48)	Full head control, sitting unassisted (2)	Responder
	5	None (0)	Emerging sitting unassisted (W96)	Full head control (2)	Responder
	5.8	None (0)	Emerging sitting with assistance (W48)	Full head control (2), Emerging sitting with assistance (1)	Responder
	10.8	None (0)	Emerging full head control (W48)	Emerging full head control (1)	Non-responder

Source: Reviewer analysis of AADC-002 CSR. This includes additional clinical data submitted in information requests.
a-Patient withdrew after Week 48
b-Patient declined to enter Long-Term Extension Phase of the study
c-Patient withdrew at Week 23
Abbreviations: NA, not assessed; W, week
*Treatment response defined as achieving score 2 (“mastery”) in at least “full head control”

In the 12 patients with clinical efficacy data (excludes the one dropout) at week 48, 11 patients had no gross motor milestones at baseline. One patient ((b) (6)) had the ability to sit with assistance, but as discussed above, was characterized as an “atypical” variant of the severe phenotype. At week 48, achievements in new gross motor milestones (where achievement is considered a score of “2” on the corresponding PDMS-2 item) were observed in 8 (67%) of the 12 patients: 3 (9%), achieved full head

control, 2 (36%) achieved sitting with or without assistance, 2 (18%) achieved walking backwards and the patient with the “atypical” variant of the severe phenotype achieved the ability to sit unassisted and full head control. Figure 7 shows all post-treatment motor milestone achievement versus chronological age.

Figure 7: Motor Milestone Achievement After Treatment With Eladocagene Exuparvovec in Study AADC-002



Source: Figure 1, Response to IR#35
Solid circle: Mastering (PDMS-2 score of 2); **Hollow circle**: Emerging (PDMS-2 score of 1).
The vertical dashed lines indicate age at the time of treatment (in months) for each subject.
The horizontal lines start from baseline PDMS-2 assessment up to last available follow-up time or data cutoff date (01 March 2024), whichever is earlier.
Age at treatment in months is shown in parentheses ( ); The duration of follow-up in months is shown in brackets [ ]
.**Motor milestones**: x =no motor milestone achieved; 1 =Partial head control (Sta Q5); 2 =Head control (Sta Q10); 3 =Sitting with assistance (Sta Q11);4 =Sitting unassisted (Sta Q14); 5 =Standing with support (Loc Q28); 6 =Standing away from Support (Loc Q31); 7 =Walking with assistance;); 8 =Walking to Toy (Loc Q35); 9 =Walking Up Stairs With Support (Loc Q40); 10 =Walking Backward using Normal Stride (LOC Q44).

To serve as a historical control to contextualize the motor outcome data, the Applicant submitted data on untreated patients with AADCD compiled from case reports in the literature that were referred to as a “Natural History Database” (NHDB). The Applicant identified case reports on 260 unique untreated patients AADCD. Of those 260 patients, 44 patients were identified as having a severe phenotype (similar to that of the patients treated with eladocagene exuparvovec in the clinical study) AND who had at least one motor milestone assessment after 2 years of age. This excluded 3 patients who were conservatively classified as having the severe phenotype, but were more consistent with the moderate phenotype due to robust response to standard of care medications. All 44 untreated patients from the external natural history cohort with the severe phenotype

had no documented motor milestone achievement at a median age of 7.3 years (range 1.6 to 21 years).

Reviewer Comment:

- *The motor outcomes in the 8 of 12 (67%) treated children are unexpected when compared to the motor outcomes in the untreated natural history cohort. While there were no untreated patients with a similar phenotype as patient* (b) (6) *to serve as a comparator in the NHDB, this reviewer assesses the observed improvements to "sitting without assistance" to be unexpected given the patient's documented lack of improvement on standard of care therapies.*
- *However, it should be noted that 3 children had motor milestone achievement at Week 48 limited to partial head control only. Given that these patients did not achieve full head control and no new motor milestone was gained, these outcomes were not assessed as a treatment effect.*
- *The clinical reviewer also notes that there may be relationship between age and response to treatment, where improvements in motor outcomes were more robust in the patients treated at a younger age. Patients* (b) (6) *were the youngest patients in the treated cohort (treated before 2 years of age) and had the most robust motor outcomes after treatment—"walking backwards." The oldest treated patient was treated at age 10 years and only demonstrated emerging full head control at week 48 (non-responder). However, it should be noted that given the small study population and short duration of follow-up, any definitive conclusions cannot be drawn.*
- *The clinical reviewer proposes that this may be due to a decrease in neuroplasticity that occurs with age, where young children are still undergoing significant changes in neurologic development that may be more amenable to treatment. However, with only 1 patient treated at over 6 years of age, this relationship between treatment effect and age is uncertain.*

An additional secondary endpoint was the change in dopamine production as assessed on ^{18}F-DOPA uptake in the putamen on PET scan (see Section 4.4.2 for additional discussion of the clinical pharmacology reviewer's analysis).

In Figure 12 and Figure 13 (by age of patients) in Appendix 1.2, individual profiles of motor milestone achievement over time along with those of CSF HVA and putamen specific ^{18}F-DOPA uptake are shown in arrays. Overall, CSF HVA and putamen ^{18}F-DOPA uptake increased from Week 8 after the gene therapy, followed by motor function improvement at later timepoints, as early as Week 24 in some patients.

Other secondary endpoints included:

- Motor development as assessed by the PDMS-2 total score.
- Cognition and language scores on the BSITD-III.

Reviewer Comment:

- *The PDMS-2 total score is derived from summation of scores obtained on the following subscales: stationary, locomotion, object manipulation, grasping, and visual-motor integration. Given that there are multiple subscales, it is possible to achieve substantial increase in PDMS-2 total scores without actual mastery of specific motor milestones. Additionally, patients cannot be used as their own baseline control to interpret PDMS-2 total score as (1) children are expected to have increases in their sub-domain scores with age and (2) the extent of improvement in these subdomains for children with AADCD without treatment is unclear given the lack of natural history comparator data. Therefore, PDMS-2 total scores not considered informative for the efficacy review.*
- Changes in cognition and language scores on the BSITD-III were not considered informative for the efficacy analyses for the following reasons:
    - *There is no cognition or language data on untreated patients provided in the NHDB. While patients with AADCD do have significant cognitive impairments, the severity and change in these impairments over time is not characterized in untreated children.*
    - *The language scores are also difficult to interpret in the 2 children who were enrolled at international study sites (Israel and Taiwan). There is uncertainty as to whether English (the language in which the BSITD-III is administered) was the primary language for those children.*

7.1.7 Subpopulations

Given the small study population, subpopulation analyses were not feasible.

7.1.8 Persistence of Efficacy

There is limited data to understand the persistence of efficacy beyond 48 weeks given the limited duration of follow-up in study patients. Motor data is available on twelve patients until Week 48, one patient until Week 72, and three patients until Week 96. There are two patients who are showing the potential for a waning treatment effect:

- Patient (b) (6) progressed from “sitting unassisted” at week 48 to “emerging sitting unassisted” at week 96.
- Patient (b) (6) progressed from “sitting with assistance” at week 48 to “emerging sitting with assistance” at week 96.

Reviewer Comment:

- *While this may suggest a potential for a waning treatment effect, additional factors much be considered including the subjective nature of the PDMS-2 assessment tool, uncertainty in whether the tool was administered by the same clinician and confounding factors that may impact the child’s ability to perform the assessment (including behavior, concurrent illness, time of day, etc.).*

- *While these patients have not demonstrated a significant regression in their milestones (have not completely lost some ability to sit and have not returned to their baseline), there is uncertainty whether the treatment effect may continue to wane in the future. Given this uncertainty, this reviewer recommends continued follow-up in the accelerated approval pathway to verify and describe the clinical benefit and durability of benefit.*

7.1.9 Product-Product Interactions

Although concomitant mediations were documented for all patients, no product-product interactions were expected or observed during the course of the clinical studies.

7.1.10 Additional Efficacy Issues/Analyses

The clinical reviewer also conducted analyses to understand the impact of eladocagene exuparvovec on the non-motor manifestations of AADCD.

The Applicant collected data on the feeding status of the treated patients, as shown in shown in Table 27.

The Applicant also collected data on episodes of oculogyric crises through utilization of an electronic diary filled out by caregivers. Oculogyric crises have been noted in the literature to be of significant burden to patients and caregivers, requiring hours of weekly symptom management (Pearson et al. 2020). In response to IR #17, the Applicant summarized both the total duration (hours) per month and the total number of episodes per month for each patient treated in Study AADC-002. This data was collected through an electronic diary that was filled out by parents/caregivers.

Reviewer Comment:

- *The clinical reviewer found it challenging to interpret the significance of the data submitted on feeding status and oculogyric crises.*
- *Surprisingly, only 4 of 13 treated children were utilizing a G-tube at baseline. This was unexpected given that patients without head control (and therefore, at increased risk for aspiration) would be expected to require G-tube nutrition. This may be due to patient and caregiver preference related to quality of life. After treatment with eladocagene exuparvovec, one patient* (b) (6) *was able to tolerate exclusive feeding by mouth without use of the G-tube after treatment with eladocagene exuparvovec and one patient was able to begin tolerating oral intake (though continued to require G-tube). Both patients were reported as achieving "emerging sitting with assistance at last follow-up".*
- *The data on oculogyric crises was recorded using caregiver report through an electronic diary. Review of the data did not demonstrate elimination of oculogyric crises in any patient. There was limited pre-treatment data on the frequency (including number of episodes and total duration) to use as a baseline for comparison and the post-treatment data demonstrated significant fluctuation in*

the frequency and duration of episodes that was challenging to interpret given the short duration of follow-up and lack of established baseline. Therefore, it was difficult to ascertain whether there was a treatment effect on oculogyric crises.

- *Therefore, evidence of effectiveness in this BLA submission comes solely from improvements in gross motor outcomes. The data are not sufficient to characterize impacts on other manifestations of AADCD.*

7.1.11 Efficacy Conclusions

In review of this BLA submission, the clinical and clinical pharmacology reviewers identified multiple uncertainties in the Applicant's proposal to utilize CSF HVA as a surrogate endpoint reasonably likely to predict clinical benefit as the basis for accelerated approval. This included uncertainty regarding the proposed threshold of >20% increase from baseline (including post-treatment CSF HVA levels in treated patients remaining substantially below the normal range and within the range of levels measured in untreated patients with AADCD in the JAKE database), a lack of clear and consistent correlation observed between parameters of post-treatment CSF HVA levels (absolute post-treatment levels, absolute change from baseline, and percent change from baseline) and clinical outcomes, and uncertainty regarding the proposed Week 8 timepoint. Therefore, we do not assess there to be sufficient data to support the Applicant's proposal to use CSF HVA as a surrogate endpoint reasonably likely to predict clinical benefit.

In analyses of the motor data, 8 out of 12 (67%) children (including the patient with the atypical variant of the severe phenotype) were assessed to have improvements in motor outcomes by achieving a new gross motor milestone after treatment with eladocagene exuparvovec that were unexpected when compared to the cohort of untreated children with similar disease severity submitted from the NHDB. Pharmacodynamic observations such as post-treatment changes in CSF HVA and ^{18}F-DOPA uptake support the proposed mechanism of action as discussed in Section 4.4. There was limited data to characterize the impacts of eladocagene exuparvovec treatment on the non-motor manifestations of AADCD (feeding, oculogyric crises). There remains uncertainty in the durability of effect, with less than two years of data on the treated patients and signs of potential waning of effect in two of the four (50%) treated patients who have been followed for more than one year (to Week 96).

There in additional uncertainty in the relationship between age and response to treatment; there was one child treated older than 5 years and no adolescents or adults were evaluated in the clinical study. In one study that published data from the clinical studies in Taiwan with the different version of the product, the authors state, "The increase in PDMS-2 total scores after eladocagene exuparvovec had a negative correlation with age, indicating that younger patients exhibited faster and greater improvements in PDMS-2 scores after gene therapy…This is likely related to a greater degree of neuronal plasticity in younger patients" (Tai et al. 2022). This clinical reviewer

proposes that it may be reasonable to extrapolate the efficacy data to adolescents given that brain and neuronal development continues in adolescence that may be responsive to treatment. Additionally, adolescents with the severe phenotype have significant unmet medical need with no alternative treatment options and early mortality. However, this reviewer does not believe there is sufficient evidence to extrapolate the efficacy to the adult population who are neurologically mature and may not respond to the therapy.

Additionally, no patients with the mild or moderate phenotypes of AADCD were evaluated in the clinical study. Patients with these phenotypes have been shown to have robust improvements on standard of care. Further, patients with the mild phenotype may also not experience any impairments in motor function. As discussed above, the effects of eladocagene exuparvovec on the non-motor manifestations of the disease were not characterized in the clinical study. Impacts on non-motor manifestations may not necessarily occur given the treatment is administered locally into the putamen of the brain, primarily responsible for motor function. Therefore, the clinical reviewer does not believe that the efficacy data can be extrapolated to the mild and moderate phenotypes of AADCD.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

The safety analysis includes all patients treated in the eladocagene exuparvovec development program, including those enrolled in studies AADC-010, AADC-011, AADC-CU/1601, and AADC-002. However, given the substantial differences in the gene therapy product used in each of these studies (as discussed in Section 4.1), data from Study AADC-002 (which treated patients with the intended commercial product) were used as the primary basis for determination of safety.

Data from the other studies (AADC-010, AADC-011, and AADC-CU/1601) were considered supplemental given the small size and limited duration of follow-up of the AADC-002 study population. The review team analyzed the data to understand whether there were any safety signals observed in these studies that may be applicable to use of any formulation of eladocagene exuparvovec and extrapolated to its commercial use. Study AADC-011 treated patients at two different doses—1.8×10^{11} vg (the intended commercial dose) and 2.4×10^{11} vg but with a product manufactured through a different process than the commercial product. Therefore, analyses were completed evaluating the safety of the two different doses to augment the safety database and assess for any dose-related toxicities that may be informative to the safety of the commercial use of eladocagene exuparvovec.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

As discussed above, Study AADC-GT-002 served as the primarily basis for the safety analysis. No patient has completed AADC-GT-002 and transitioned to long-term follow-up study AADC-1602. All data from studies AADC-CU/1601, AADC-010, AADC -011, and AADC-1602 were considered supplemental given the differences in the product.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Table 15 details the baseline demographics of the safety population.

Table 15: Demographics and Exposure of Safety Population

Parameter	**Studies AADC-101, AADC-011, AADC-CU1601 (n=30) N (%)**	**Study AADC-002 (n=13) N (%)**
Sex, n (%)	-	-
Female	16 (53%)	7 (54%)
Male	14 (47%)	6 (46%)
Race, n (%)	-	-
Asian	28 (93%)	10 (77%)
White	1 (3%)	2 (15%)
Other	1 (3%)	1 (8%)
Age at eladocagene exuparvovec treatment (years)	-	-
Median	33	33
Min – Max	19-102	16-129
Duration of follow-up after eladocagene exuparvovec treatment	-	-
Median	59 months*	72.0 weeks*
Min – Max	12-68 months*	23-109 weeks*

Source: Adapted from BLA 125722/0 Summary of Clinical Safety Table 2, Table 4, Table 5, 120 Day Safety Update
*Please note difference in time units.
Abbreviations: min-minimum, max-maximum

8.2.3 Categorization of Adverse Events

The Applicant used the Medical Dictionary for Regulatory Activities (MedDRA) version 26.0 to code System Organ Class and Preferred Terms.

8.3 Pooling of Data Across Studies/Clinical Trials

As discussed in other sections of this review, the Applicant treated patients with non-comparable versions of the product: Process A, Process B and Process C, the differences in which may impact safety. While data from studies AADC-CU1601, AADC-010, and AADC-011 are pooled given that they did not utilize the intended commercial product, it should be noted that patients in AADC-CU1601 were treated with Process A and patients in AADC-010 and AADC-011 were treated with Process B. Given no

availability of Process A material to test, comparability between Processes A and B is unknown.

8.4 Safety Results

8.4.1 Deaths

There were no deaths in the pivotal study AADC-002.

There were 6 deaths in the clinical development program, all in the ex-US studies, and all using a different product manufacturing than the intended commercial product: three patients in Study AADC-CU-1601, and three patients in Study AADC-010. One death was due to a viral infection and occurred 11 months after treatment. The remaining deaths occurred after completion of the 5-year study follow-up. Information on the deaths is summarized below, based on narratives submitted within the BLA and additional information provided in response to an IR. However, it should be noted that limited information was available on patients (b) (6) and all available information is described below.

- Patient (b) (6) received eladocagene exuparvovec at age 2 years 8 months. Approximately 11 months after study treatment, the patient developed fever, diarrhea, cough, and rhinorrhea thought to be attributed to influenza given a known outbreak in a family member and the patient's area of residence. One week after the development of initial symptoms, the patient was found unresponsive. Computed tomography (CT) scan revealed brain swelling with uncal herniation, and influenza B test was positive. Influenza B encephalitis was diagnosed. Despite receiving all supportive measures, the patient developed respiratory failure approximately 2 weeks later; the family decided to withdraw care, and the patient died. At the last assessment prior to the patient's death (Month 9 visit), improved motor function was noted with achievement of partial head control and emerging full head control.
- Patient (b) (6) received eladocagene exuparvovec at age 8 years 3 months. Approximately 7 years after treatment (and 2 years after completion of the primary study), the investigator was informed that the patient had died of aspiration. The patient had consented to enrollment in long-term study AADC-1602 but never actively participated in any study assessments in that study. At last assessment at Month 48 after treatment, this patient had not achieved any key motor milestones.
- Patient (b) (6) received eladocagene exuparvovec at age 7 years 9 months. The patient completed the 5-year follow-up in Study AADC-010 and had entered Study AADC-1602 for long-term follow-up. At the time of entry into long-term follow-up, the patient had been seizure-free for 3 years with sodium valproate treatment. Approximately 5.5 years after treatment, the patient appeared cyanotic and unresponsive, with no evidence of choking. Cardiopulmonary resuscitation initiated by emergency services resulted in return of spontaneous circulation.

Subsequent MRIs demonstrated widespread hypoxia and cytotoxic edema. During management of the hypoxic brain event, the patient developed oxacillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa* in the sputum. The patient then developed chest x-ray consistent with bronchopneumonia and respiratory distress. The patient died after a bradycardia event approximately 5.5 years after treatment. At the last visit at Month 60 after treatment, the patient had motor function improvements to sitting.

- Patient (b) (6) received eladocagene exuparvovec at age 2 years and 9 months. Approximately 10 years after gene therapy treatment, the patient developed severe organ failure, and the patient's mother reported that the patient had died due to cardiac arrest. Per report, the patient developed sustained hypoxia and bradycardia followed by unsuccessful resuscitation. At the Month 72 assessment, the patient was reported to have a highest motor milestone of standing with support.
- Patient (b) (6) received eladocagene exuparvovec at age 4 years and 5 months. Approximately 5.5 years after treatment, the study investigator received a report that the patient had died. The patient had a history of disease-related respiratory problems. However, additional details about the death were not available.
- Patient (b) (6) received eladocagene exuparvovec at age 2 years and 11 months. Approximately 6 years after treatment, the patient's mother reported that the patient had died to cardiopulmonary arrest. The patient had returned from a summer camp where she had a lot of activity and intermittent diarrhea. Upon arrival home, the patient was found unconscious in the bathtub, and emergency services observed that she was experiencing cardiorespiratory arrest. She was hospitalized for 2 weeks with generalized seizures and subsequently died. At Month 24, the patient had reached a motor milestone of sitting unassisted; after Month 24, the patient was unable to follow up for any other visits due to COVID-19 travel restrictions.

Reviewer Comment:

- *This reviewer does not assess any of these events to be potentially related to eladocagene exuparvovec. Aside from patient (b) (6) who died due to viral encephalitis, the remaining patients appear to have died secondary to underlying disease manifestations.*

8.4.2 Nonfatal Serious Adverse Events

Table 16 shows a summary of the SAEs in patients treated in pivotal study AADC-002.

Table 16: Nonfatal Serious Adverse Events in Patients Treated in Pivotal Study AADC-002

System Organ Class / Adverse Event	Number of Patients (%) (N=13)
Cardiac Disorders	-
Bradycardia	1 (8%)
Gastrointestinal disorders	-
Vomiting	1 (8%)
General Disorders and Administration Site Conditions	-
Pyrexia	1 (8%)
Infections and Infestations	-
Bacterial infection	1 (8%)
COVID-19 infection	1 (8%)
Pneumonia[1]	4 (31%)
Urinary tract infection	1 (8%)
Nervous system disorders	-
Dyskinesia	1 (8%)
Seizure	1 (8%)
Respiratory, thoracic, and mediastinal disorders	-
Bronchospasm	1 (8%)
Respiratory arrest	1 (8%)

Source: Reviewer analysis of PTC-AADC-GT-002 ADAE Dataset
1-Pneumonia includes pneumonia, pneumonia viral, metapneumovirus pneumonia

To assess for potential attribution to eladocagene exuparvovec, SAEs were separated by timepoint after eladocagene exuparvovec administration and shown in Table 17.

Table 17: Serious Adverse Events in the Pivotal Study AADC-002 by Study Timepoint (n=13)

System Organ Class / Adverse Event	Day 0-30 N (%) (N=13)	Day 31-90 N (%) (N=13)	Day 91-Year 1 N (%) (N=13)	Year 1-Year 2 N (%) (N=7)[2]
Cardiac disorders	-	-	-	-
Bradycardia	1 (8%)	-	-	-
Gastrointestinal disorders	-	-	-	-
Vomiting	-	1 (8%)	-	-
General Disorders and Administration Site Conditions	-	-	-	-
Pyrexia	-	-	1 (8%)	-
Infections and Infestations	-	-	-	-
Bacterial infection	-	-	1 (8%)	-
COVID-19			1 (8%)	
Pneumonia[1]	-	-	3 (23%)	2 (15%)
Urinary tract infection	-	-	1 (8%)	-
Nervous system disorders	-	-	-	-

Dyskinesia	1 (8%)	1 (8%)	-	-
Seizure	-	-	-	1 (8%)
Respiratory, thoracic, and mediastinal disorders	-	-	-	-
Bronchospasm	1 (8%)	-	-	-
Respiratory arrest	1 (8%)	-	-	-

Source: Reviewer analysis of AADC-002 ADAE Dataset
1-Pneumonia includes pneumonia, pneumonia viral, metapneumovirus pneumonia
2-Only n=7 of the 13 patients treated in the study have been followed past Year 1

Reviewer Comment:

- *Based on* review of the narratives, consideration of the timing of event in relationship to eladocagene exuparvovec treatment, and clear alternate etiologies, the clinical reviewer assesses the SAEs of bronchospasms, vomiting, pyrexia, bacterial infection, pneumonia, urinary tract infection, and seizure as not considered related to eladocagene exuparvovec. However, this reviewer notes that the following events warrant further discussion and consideration of relatedness:

Bradycardia: This patient experienced a life-threatening SAE of bradycardia on study Day 2 during rotation for a line placement, with a decrease in heart rate to the 60s with sinus pause and subsequent asystole. The patient required chest compressions for 20 seconds and bagging, followed by subsequent recovery to hemodynamic stability. Laboratory results showed a partial pressure of oxygen 166 mm Hg and hemoglobin of 10.2 (units/reference range not reported). Coffee-ground output was noted from the gastrostomy tube. This was assessed by the Applicant as unrelated to the product and related to underlying disease and sensitivity to the sedative dexmedetomidine, required for study procedures.

Respiratory arrest: On the same day as study drug administration and 2 hours after extubation at the conclusion of the surgical procedure, this patient experienced respiratory arrest with hypercarbia >100 mm Hg and acidosis (pH 6.92). Vital signs included 76/43 mm Hg, heart rate of 92 beats/minute, respiratory rate of 14 breaths/minute, and temperature of 34.3^{o}C. Reintubation was performed, followed by development of hypotension requiring vasopressors (epinephrine and norepinephrine). Post-operative CT scan was negative. Two days later, the patient was extubated and remained subsequently stable. This was assessed by the Applicant as unrelated to the study drug and related to underlying disease and increased risk of complications with anesthesia and sedation.

Dyskinesia: This child developed dyskinesia on study Day 27, escalating to the level of an SAE on Day 39 requiring hospitalization and intubation for management. After 3 weeks of management with dopamine antagonists and supportive care, the patient was extubated and improved over the course of 2 months.

Reviewer Comment:

- *Based on the timing of the events of the bradycardia and the respiratory arrest (same day and day after product administration respectively), this reviewer deems it less likely to be attributable to eladocagene exuparvovec. While theoretically, acute imbalances in neurotransmitters (dopamine, epinephrine, and norepinephrine) could precipitate such events, it is unlikely given that the product administers a functional copy of the gene (not the AADC enzyme itself). Therefore, this clinical reviewer notes that it is unlikely that downstream imbalances in neurotransmitters would develop so rapidly after administration. Therefore, the clinical reviewer agrees that these events are more likely due to the anesthesia and sedation required for administration of the product and study procedures (sedated post-operative imaging). However, given that children must undergo sedation for administration of the product, the clinical reviewer recommends that the risk for such events (cardiac and/or respiratory failure) be a consideration for postmarket safety surveillance and highlighted in product labeling.*
- *In reviewing these SAEs, the clinical reviewer notes that the events of dyskinesia are not unexpected given the expected sensitivity to dopamine in children with AADCD. However, the severity of this event merits consideration for inclusion in the product labeling.*

Table 18 shows the SAEs for the patients enrolled in the ex-U.S. supportive studies AADC-010, AADC-011, and AADC-CU-1601. Out of 30 patients treated in these studies, 28 (93%) of patients were followed through Month 12, 17 (57%) through Month 24, 16 (53%) through Month 36, 16 (53%) through Month 48 and 9 (30%) through Month 60.

Table 18: Nonfatal Serious Adverse Events in Ex-U.S. Studies AADC-010, AADC-011, AADC-CU-1601, AADC-1602

System Organ Class / Adverse Event	Number of Patients (%) (N=30)
Cardiac Disorders	-
Bradycardia	1 (3%)
Congenital, familial, and genetic disorders	
Developmental hip dysplasia	3 (10%)
Polydactyly	1 (3%)
Gastrointestinal Disorders	-
Dental Caries	2 (7%)
Diarrhea	1 (3%)
Gastrointestinal hemorrhage[1]	2 (7%)
Gastro-esophageal reflux disease	1 (3%)
Hematochezia	1 (3%)
Hernia[2]	2 (7%)
Peptic Ulcer[3]	2 (7%)
Tongue Ulceration	1 (3%)
Vomiting	1 (3%)
General Disorders and Administration Site Conditions	-
Cyst	1 (3%)
Pyrexia	5 (17%)
Infections and Infestations	-
Cellulitis	1 (3%)
Gastroenteritis[4]	13 (43%)
Gingivitis	1 (3%)
Other Lower Respiratory Tract Infections[5]	4 (13%)
Pneumonia[6]	19 (63%)
Upper Respiratory Tract Infection[7]	6 (20%)
Viral Infection[8]	9 (30%)
Injury, Poisoning, Procedural Complications	-
Femur Fracture	1 (3%)
Joint Dislocation	1 (3%)
Metabolism and Nutrition Disorders	-
Dehydration	7 (23%)
Hypokalemia	1 (3%)
Hyponatremia	1 (3%)
Musculoskeletal and Connective Tissue Disorders	-
Bone Abnormalities[9]	3 (10%)
Nervous System Disorders	-
Cerebrospinal fluid leakage	1 (3%)
Hypoglycemia seizure	1 (3%)
Renal and Urinary Disorders	-
Acute Kidney Injury	1 (3%)

System Organ Class / Adverse Event	Number of Patients (%) (N=30)
Respiratory, Thoracic and Mediastinal Disorders	-
Apnea	1 (3%)
Atelectasis	1 (3%)
Choking	1 (3%)
Paranasal Sinus Inflammation	1 (3%)
Pneumonia Aspiration	2 (7%)
Respiratory Distress	3 (10%)
Respiratory Failure	2 (7%)
Sleep Apnea Syndrome	3 (10%)
Tonsillar Hypertrophy	1 (3%)
Vascular Disorders	-
Cyanosis	2 (7%)
Hypotension	2 (7%)
Shock[10]	5 (17%)

Source: Reviewer analysis of ISS ADAE and AADC-1602 ADAE Datasets
1-Gastrointestinal hemorrhage includes upper gastrointestinal hemorrhage and gastrointestinal hemorrhage
2-Hernia includes hiatus hernia and inguinal hernia
3-Peptic ulcer includes peptic ulcer and gastric ulcer
4-Gastroenteritis includes gastroenteritis and enterocolitis infectious
5-Other lower respiratory tract infection includes bronchiolitis and bronchitis (excludes pneumonia)
6-Pneumonia includes pneumonia, post-procedural pneumonia, pneumonia influenza, pneumonia viral, pneumonia haemophilus, pneumonia adenoviral
7-Upper respiratory tract infection includes upper respiratory tract infection, acute sinusitis, sinusitis
8-Viral infection includes enterovirus infection, exanthema subitem, viral infection, parainfluenza virus infection, enterovirus infection, influenza, COVID-19
9-Bone abnormalities includes Blount's disease, bone deformity, bone disorder, hip deformity, knee deformity, limb deformity
10-Shock includes hypovolemic shock and shock

Table 19 separates the SAEs in the ex-U.S. supportive studies by study timepoint to facilitate assessments of attribution to eladocagene exuparvovec.

Table 19: Serious Adverse Events in Ex-U.S. Studies AADC-010, AADC-011, AADC-CU-1601, AADC-1602 Separated by Study Timepoint (N=30)

System Organ Class / Adverse Event	Day 0-30 N=30 (%)	Day 31-90 N=30 (%)	Day 91-Year 1 N=28 (%)	Year 1-Year 2 N N=17 (%)	Year 2-Year 5 N = 9 (%)	After Year 5 N = 9 (%)
Cardiac Disorders	-	-	-	-	-	-
Bradycardia	-	-	-	-	-	1 (11%)
Cardiac Arrest	-	-	-	-	-	1 (11%)
Congenital, familial, and genetic disorders	-	-	-	-	-	-
Developmental hip dysplasia	-	-	-	-	2 (22%)	1 (11%)
Polydactyly	-	-	-	1 (6%)	-	-
Gastrointestinal Disorders	-	-	-	-	-	-
Dental Caries	-	-	-	1 (6%)	1 (11%)	-
Diarrhea	1 (3%)	-	-	-	-	-
Gastrointestinal hemorrhage[1]	-	-	1 (4%)	-	1 (11%)	1 (11%)
Gastro-esophageal reflux disease	-	-	-	1 (6%)	-	-
Hematochezia	-	-	-	1 (6%)	-	-
Hernia[2]	-	-	-	2 (11%)	1 (11%)	-
Peptic Ulcer[3]	-	-	-	-	1 (11%)	1 (11%)
Tongue Ulceration	-	-	1 (4%)	-	-	-
Vomiting	-	-	-	-	1 (11%)	-
General Disorders and Administration Site Conditions	-	-	-	-	-	-
Cyst	-	1 (3%)	-	-	-	-
Pyrexia	3 (10%)	-	1 (4%)	1 (6%)	-	-

System Organ Class / Adverse Event	Day 0-30 N=30 (%)	Day 31-90 N=30 (%)	Day 91-Year 1 N=28 (%)	Year 1-Year 2 N N=17 (%)	Year 2-Year 5 N = 9 (%)	After Year 5 N = 9 (%)
Infections and Infestations	-	-	-	-	-	-
Cellulitis	-	-	1 (4%)	-	-	-
Gastroenteritis[4]	3 (10%)	2 (7%)	4 (14%)	1 (6%)	6 (67%)	4 (44%)
Gingivitis	-	-	-	-	1 (11%)	-
Other Lower Respiratory Tract Infections[5]	-	2 (7%)	-	-	2 (22%)	-
Pneumonia[6]	6 (20%)	3 (10%)	8 (29%)	5 (29%)	9 (100%)	6 (67%)
Upper Respiratory Tract Infection[7]	2 (7%)	-	3 (11%)	1 (6%)	-	1 (11%)
Viral Infection[8]	-	1 (3%)	2 (7%)	1 (6%)	1 (11%)	4 (44%)
Injury, Poisoning, Procedural Complications	-	-	-	-	-	-
Femur Fracture	-	-	1 (4%)	-	-	-
Joint Dislocation	-	1 (3%)	-	-	-	-
Metabolism and Nutrition Disorders	-	-	-	-	-	-
Dehydration	1 (3%)	1 (3%)	3 (11%)	-	1 (11%)	1 (11%)
Hypokalemia	-	-	-	-	1 (11%)	-
Hyponatremia	-	-	-	-	1 (11%)	-
Musculoskeletal and Connective Tissue Disorders	-	-	-	-	-	-
Bone Abnormalities[9]	1 (3%)	-	-	1 (6%)	2 (22%)	1 (11%)
Nervous System Disorders	-	-	-	-	-	-
Cerebrospinal fluid leakage	1 (3%)	-	1 (4%)	-	-	-
Hypoglycemia seizure	-	-	-	-	1 (11%)	-
Renal and Urinary Disorders	-	-	-	-	-	-
Acute Kidney Injury	-	-	-	-	1 (11%)	-

System Organ Class / Adverse Event	Day 0-30 N=30 (%)	Day 31-90 N=30 (%)	Day 91-Year 1 N=28 (%)	Year 1-Year 2 N N=17 (%)	Year 2-Year 5 N = 9 (%)	After Year 5 N = 9 (%)
Respiratory, Thoracic and Mediastinal Disorders	-	-	-	-	-	-
Apnea	-	-	1 (4%)	-	-	-
Atelectasis	-	-	-	1 (6%)	-	-
Choking	-	-	-	-	1 (11%)	-
Paranasal Sinus Inflammation	-	1 (3%)	-	-	-	-
Pneumonia Aspiration	-	1 (3%)	1 (4%)	-	1 (11%)	-
Respiratory Distress	1 (3%)	-	-	1 (6%)	-	1 (11%)
Respiratory Failure	2 (7%)	-	-	-	-	-
Sleep Apnea Syndrome	-	-	-	1 (6%)	2 (22%)	-
Tonsillar Hypertrophy	-	-	-	1 (6%)	-	-
Vascular Disorders	-	-	-	-	-	-
Cyanosis	-	2 (7%)	-	-	-	-
Hypotension	-	-	-	-	-	2 (22%)
Shock[10]	-	-	1 (4%)	1 (6%)	2 (22%)	-

Source: Reviewer analysis of ISS ADAE and AADC-1602 ADAE Datasets
1-Gastrointestinal hemorrhage includes upper gastrointestinal hemorrhage and gastrointestinal hemorrhage
2-Hernia includes hiatus hernia and inguinal hernia
3-Peptic ulcer includes peptic ulcer and gastric ulcer
4-Gastroenteritis includes gastroenteritis and enterocolitis infectious
5-Other lower respiratory tract infection includes bronchiolitis and bronchitis (excludes pneumonia)
6-Pneumonia includes pneumonia, post-procedural pneumonia, pneumonia influenza, pneumonia viral, pneumonia haemophilus, pneumonia adenoviral
7-upper respiratory tract infection includes upper respiratory tract infection, acute sinusitis, sinusitis
8-viral infection includes enterovirus infection, exanthema subitem, viral infection, parainfluenza virus infection, enterovirus infection, influenza, COVID-19
9-bone abnormalities includes Blount's disease, bone deformity, bone disorder, hip deformity, knee deformity, limb deformity
10-shock includes hypovolemic shock and shock

Reviewer Comment:

- *The event of CSF leakage (progressing to a pseudo-meningocele 5 months after treatment) is assessed as related to the neurosurgical procedure required for eladocagene exuparvovec. Even though this did not occur in pivotal study AADC-002, this merits consideration for inclusion in product labeling given clear attribution to the neurosurgical procedure. Of note, the neurosurgical procedure did not change between the pivotal study and the supportive studies.*
- *Events of cardiac and respiratory failure were already identified in the pivotal study. No other SAEs in the supportive studies that were not observed in the pivotal study were informative to the safety profile of eladocagene exuparvovec.*

8.4.3 Study Dropouts/Discontinuations

Out of the 13 patients treated in pivotal Study AADC-002, 1 patient withdrew after 23 weeks as they were unable to complete in-person visits, 1 patient withdrew from the extension part of the study after 71 weeks of follow-up, and 1 patient declined to enroll in the Extension Phase.

Out of the 30 patients treated in studies AADC-010, AADC-011, and AADC-CU-1601, 3 patients withdrew from the study: 1 patient due to death secondary to influenza B encephalitis (see Section 8.4.1) and 2 patients from the compassionate use study AADC-CU-1601 (reasons not provided) prior to the Month 60 visit due to inability to travel for assessments.

Reviewer Comment:

- *It should be noted that the patient who withdrew after 23 weeks of follow-up in Study AADC-002 experienced the SAE of cardiorespiratory arrest with line placement after administration of the investigational product (see Section 8.4.2)*

8.4.4 Common Adverse Events

Adverse events that occurred within patients enrolled in Study AADC-002 are shown in Table 20.

Table 20: Adverse Events for Patients Enrolled in Study AADC-002

System Organ Class / Adverse Event	**Number of Patients (%) (N=13)**
Blood and Lymphatic System Disorders	-
Anemia	4 (31%)
Lymphadenopathy	1 (8%)
Cardiac Disorders	-
Bradycardia	1 (8%)
Tachycardia	1 (8%)
Eye Disorders	-
Dry eye	1 (8%)
Eye swelling	2 (15%)
Ocular hyperemia	1 (8%)
Oculogyric crisis	3 (15%)
Periorbital edema	1 (8%)
Gastrointestinal disorders	-
Anal fissure	1 (8%)
Constipation	1 (8%)
Diarrhea	8 (62%)
Dysphagia	1 (8%)
Flatulence	1 (8%)
Gastrointestinal hemorrhage[1]	1 (8%)
Gastroesophageal reflux disease	1 (8%)
Hematemesis	1 (8%)
Salivary hypersecretion	3 (23%)
Stomatitis	1 (8%)
Vomiting[2]	5 (38%)

System Organ Class / Adverse Event	**Number of Patients (%) (N=13)**
General disorders and administration site conditions	-
Face edema	1 (8%)
Infusion site bruising	1 (8%)
Injury associated with device	1 (8%)
Puncture site pain	1 (8%)
Pyrexia	10 (77%)
Infections and infestations	-
Bacterial infection	1 (8%)
Clostridium difficile infection	1 (8%)
Conjunctivitis bacterial	1 (8%)
COVID-19[3]	3 (23%)
Gastroenteritis	1 (8%)
Otitis media	2 (15%)
Pneumonia	5 (38%)
Pneumonia, aspiration	1 (8%)
Post viral fatigue syndrome	1 (8%)
Rash	2 (15%)
Upper respiratory tract infection	6 (46%)
Urinary tract infection	1 (8%)
Viral infection	4 (31%)
Injury, poisoning, and procedural complications	-
Contusion	2 (15%)
Fall	1 (8%)
Forearm fracture	1 (8%)
Incision site hemorrhage	1 (8%)
Post-procedural hypotension	1 (8%)
Rash	1 (8%)
Scratch	2 (15%)
Skin pressure mark	1 (8%)
Stoma site discharge	1 (8%)

System Organ Class / Adverse Event	**Number of Patients (%) (N=13)**
Investigations	-
Blood alkaline phosphatase increased	1 (8%)
Blood bicarbonate decreased	1 (8%)
Blood creatinine decreased	1 (8%)
Blood potassium decreased	1 (8%)
COVID-19[3]	2 (15%)
Eosinophil count increased	1 (8%)
Heart rate increased	1 (8%)
Increase in hepatic enzymes	1 (8%)
Lymphocyte count increased	1 (8%)
Viral infection[4]	2 (15%)
White blood cell count increased	1 (8%)
Metabolism and Nutrition Disorders	-
Decreased appetite	1 (8%)
Hyperglycemia	1 (8%)
Hypocalcemia	1 (8%)
Hypoglycemia	2 (15%)
Hypokalemia	3 (23%)
Hypomagnesemia	2 (15%)
Hypophosphatemia	3 (23%)
Polydipsia	1 (8%)
Nervous system disorders	-
Dyskinesia	10 (77%)
Myoclonus	1 (8%)
Seizure	1 (8%)
Psychiatric disorders	-
Insomnia	3 (23%)
Respiratory, thoracic and mediastinal disorders	-
Atelectasis	1 (8%)
Bronchospasm	1 (8%)

System Organ Class / Adverse Event	Number of Patients (%) (N=13)
Epistaxis	1 (8%)
Hypoxia	2 (15%)
Increased upper airway secretion	1 (8%)
Lung hyperinflation	1 (8%)
Respiratory arrest	1 (8%)
Rhinitis, allergic	1 (8%)
Tachypnea	1 (8%)
Upper respiratory tract infection[5]	9 (69%)
Skin and subcutaneous tissue disorders	-
Rash[6]	7 (54%)
Vascular disorders	-
Cyanosis	1 (8%)
Hypotension	4 (31%)

Source: Reviewer analysis of AADC-02 ADAE Dataset
1-Gastrointestinal hemorrhage includes gastrointestinal hemorrhage and upper gastrointestinal hemorrhage
2-Vomiting includes vomiting and discolored vomit
3-COVID-19 includes COVID-19 and SARS-CoV-2 test positive
4-Viral infection includes influenza, rhinovirus infection and vital test positive
5-Upper respiratory tract infection includes cough, nasal congestion, nasopharyngitis, rhinorrhea, sinus congestion, upper respiratory tract congestion, upper respiratory tract infection, viral upper respiratory tract infection
6-Rash includes dermatitis atopic, dermatitis diaper, eczema, impetigo, rash, skin abrasion, skin lesion inflammation, tinea cruris

To facilitate analyses of attribution, adverse events by study timepoint in Study AADC-002 are shown in Table 21.

Table 21: Adverse Events by Timepoint in Study AADC-002

System Organ Class/Adverse Event	Day 0-30	Day 31-90	Day 91-Year 1	Year 1 to Year 2
Blood and Lymphatic System Disorders	-	-	-	-
Anemia	4 (31%)	-	-	-
Lymphadenopathy	-	-	1 (8%)	-
Cardiac Disorders	-	-	-	-
Bradycardia	1 (8%)	-	-	-
Tachycardia	1 (8%)	-	-	-
Eye Disorders	-	-	-	-
Dry eye	-	-	1 (8%)	-
Eye swelling	-	1 (8%)	1 (8%)	-
Ocular hyperemia	-	-	1 (8%)	-
Oculogyric crisis	2 (15%)	-	-	-
Periorbital edema	1 (8%)	-	-	-
Gastrointestinal disorders	-	-	-	-
Anal fissure	-	-	1 (8%)	-
Constipation	-	-	1 (8%)	-
Diarrhea	1 (8%)	2 (15%)	5 (38%)	1 (8%)
Dysphagia	-	-	1 (8%)	-
Flatulence	-	-	1 (8%)	-
Gastrointestinal hemorrhage[1]	1 (8%)	-	-	-
Gastroesophageal reflux disease	-	-	1 (8%)	-
Hematemesis	-	-	1 (8%)	-
Salivary hypersecretion	-	2 (15%)	1 (8%)	-
Stomatitis	-	1 (8%)	-	-
Vomiting[2]	-	3 (23%)	2 (15%)	1 (8%)
General disorders and administration site conditions	-	-	-	-
Face edema	1 (8%)	-	-	-
Infusion site bruising	1 (8%)	-	-	-
Injury associated with device	1 (8%)	-	-	-
Puncture site pain	-	-	1 (8%)	-
Pyrexia	8 (62%)	6 (46%)	8 (62%)	2 (15%)

System Organ Class/Adverse Event	Day 0-30	Day 31-90	Day 91-Year 1	Year 1 to Year 2
Infections and infestations	-	-	-	-
Bacterial infection	-	-	1 (8%)	-
Clostridium difficile infection	1 (8%)	-	-	-
Conjunctivitis bacterial	-	-	1 (8%)	-
COVID-19[3]	-	2 (15%)	1 (8%)	-
Gastroenteritis	-	1 (8%)	-	-
Otitis media	-	-	2 (15%)	-
Pneumonia	1 (8%)	-	3 (23%)	-
Pneumonia, aspiration	1 (8%)	-	-	-
Post viral fatigue syndrome	-	-	1 (8%)	-
Rash	-	1 (8%)	1 (8%)	-
Upper respiratory tract infection	-	1 (8%)	6 (46%)	-
Urinary tract infection	-	-	1 (8%)	-
Viral infection	-	-	4 (31%)	-
Injury, poisoning, and procedural complications	-	-	-	-
Contusion	-	1 (8%)	1 (8%)	-
Fall	-	-	1 (8%)	-
Forearm fracture	-	-	1 (8%)	-
Incision site hemorrhage	-	1 (8%)	-	-
Post-procedural hypotension	1 (8%)	-	-	-
Rash	-	1 (8%)	-	-
Scratch	-	2 (15%)	1 (8%)	-
Skin pressure mark	1 (8%)	-	-	-
Stoma site discharge	-	-	1 (8%)	-
Investigations	-	-	-	-
Blood alkaline phosphatase increased	-	1 (8%)	-	-
Blood bicarbonate decreased	-	1 (8%)	-	-
Blood creatinine decreased	-	1 (8%)	-	-
Blood potassium decreased	1 (8%)	-	-	-
COVID-19[3]	-	-	2 (15%)	-
Eosinophil count increased	-	-	1 (8%)	-
Heart rate increased	1 (8%)	-	-	-
Increase in hepatic enzymes	1 (8%)	1 (8%)	1 (8%)	-
Lymphocyte count increased	-	-	1 (8%)	-
Viral infection[4]	2 (15%)	-	-	-
White blood cell count increased	-	-	1 (8%)	-
Metabolism and Nutrition Disorders	-	-	-	-
Decreased appetite	1 (8%)	-	-	-
Hyperglycemia	1 (8%)	-	-	-
Hypocalcemia	1 (8%)	-	-	-
Hypoglycemia	2 (15%)	-	-	-
Hypokalemia	3 (23%)	1 (8%)	-	-
Hypomagnesemia	2 (15%)	-	-	-

System Organ Class/Adverse Event	Day 0-30	Day 31-90	Day 91-Year 1	Year 1 to Year 2
Hypophosphatemia	3 (23%)	-		-
Polydipsia	-	-	1 (8%)	-
Nervous system disorders	-	-	-	-
Dyskinesia	7 (54%)	5 (38%)	1 (8%)	-
Myoclonus	-	-	1 (8%)	-
Seizure	-	-	-	1 (8%)
Psychiatric disorders	-	-	-	-
Insomnia	1 (8%)	1 (8%)	1 (8%)	-
Respiratory, thoracic and mediastinal disorders	-	-	-	-
Atelectasis	1 (8%)	-	-	-
Bronchospasm	1 (8%)	-	-	-
Dyspnea	-	-	1 (8%)	-
Epistaxis	1 (8%)	-	-	-
Hypoxia	2 (15%)	-	-	-
Increased upper airway secretion	-	1 (8%)	-	-
Lung hyperinflation	1 (8%)	-	-	-
Respiratory arrest	1 (8%)	-	-	-
Rhinitis, allergic	-	1 (8%)	-	-
Tachypnea	1 (8%)	-	-	-
Upper respiratory tract infection[5]	3 (23%)	3 (23%)	7 (54%)	-
Skin and subcutaneous tissue disorders	-	-	-	-
Rash[6]	2 (15%)	2 (15%)	4 (31%)	1 (8%)
Vascular disorders	-	-	-	-
Cyanosis	1 (8%)	-	-	-
Hypotension	4 (31%)	1 (8%)	-	-

Source: Reviewer analysis of AADC-02 ADAE Dataset
1-Gastrointestinal hemorrhage includes gastrointestinal hemorrhage and upper gastrointestinal hemorrhage
2-Vomiting includes vomiting and discolored vomit
3-COVID-19 includes COVID-19 and SARS-CoV-2 test positive
4-Viral infection includes influenza, rhinovirus infection and vital test positive
5-Upper respiratory tract infection includes cough, nasal congestion, nasopharyngitis, rhinorrhea, sinus congestion, upper respiratory tract congestion, upper respiratory tract infection, viral upper respiratory tract infection
6-Rash includes dermatitis atopic, dermatitis diaper, eczema, impetigo, rash, skin abrasion, skin lesion inflammation, tinea cruris

Based on reviewer analysis of the adverse events (including considerations of timing in relation to eladocagene exuparvovec, potential alternative etiologies, and risks of the neurosurgical procedure), Table 22 shows the adverse reactions that occurred in more than one patient (>15%) in Study AADC-002 and are recommended to be included in product labeling. Of note, all adverse reactions occurred within the first 90 days of treatment.

Table 22: Adverse Reactions in ≥15% of Patients With AADC Deficiency in the First Year After Treatment With Eladocagene Exuparvovec

Adverse Reaction	Patients Treated with Eladocagene Exuparvovec N=13 (%)
Dyskinesia	10 (77%)
Pyrexia	5 (38%)
Hypotension	4 (31%)
Anemia	4 (31%)
Salivary hypersecretion	2 (23%)
Hypokalemia	3 (23%)
Hypophosphatemia	3 (23%)
Insomnia	3 (23%)
Hypomagnesemia	2 (15%)

Source: Reviewer analyses of AADC002 ADAE dataset

Review of the adverse events and potential adverse reactions in the supportive studies did not reveal any safety signals that were not observed in the pivotal study.

8.4.5 Clinical Test Results

In Study AADC-002, notable vital sign abnormalities and laboratory abnormalities are noted in the adverse event analyses above in Section 8. No abnormalities suggestive of adeno-associated virus gene therapy class toxicities were observed, including no reported thrombocytopenia or coagulation abnormalities concerning for signs of thrombotic microangiopathy. However, of note, one patient had grade 1 elevations in liver function tests (aspartate aminotransferase and alanine aminotransferase) that began approximately 3 weeks after treatment and persisted until 6 weeks after treatment, thought to possibly related to eladocagene exuparvovec. Levels returned to normal without any intervention required. There were no notable physical examination abnormalities not related to underlying AADCD. Changes in feeding status are highlighted in Section 7.1.10.

Post-operative CT scans were normal in 11 of 13 patients. The two patients with abnormal post-operative CT scan had the following findings: one patient had extensive paranasal sinus opacification related to long-term sinusitis, and one patient had minimal expected pneumocephalus related to surgical burr holes.

Brain MRI findings were largely normal after treatment in patients enrolled in AADC-002. No findings indicative of neuroinflammation, CSF leaks, acute infarction, or intracranial hemorrhage were noted. Two patients had mild findings of brain atrophy noted to be consistent with underlying disease.

8.4.6 Systemic Adverse Events

Refer to the discussion of AEs in Section 8.4.4.

8.4.7 Local Reactogenicity

There is no evidence of local reactogenicity in this submission.

8.4.8 Adverse Events of Special Interest

Dyskinesia

As shown above in Table 22, dyskinesia occurred in 10 out of 13 (77%) children enrolled in Study AADC-002. All patients developed dyskinesia within the first 60 days after treatment, and all events of dyskinesia resolved within 1 year after treatment. Only one patient required hospitalization for the dyskinesia. Patients were responsive to supportive care and anti-dopaminergic agents.

Cerebrospinal Fluid Leaks

No children in Study AADC-002 developed CSF leaks. Three children in the supportive studies developed CSF leaks, with 1 reported as an SAE.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

There is only one dose intended for commercial use (1.8×10^{11} vg/dose). This was the only dose of the commercial product studied in pivotal study AADC-002.

8.5.2 Time Dependency for Adverse Events

Time dependency of adverse events has been highlighted in Table 17, Table 19, and Table 21.

8.5.3 Product-Demographic Interactions

The ability of the data to determine product-demographic interactions is challenging due to the small size of the study population.

8.5.4 Product-Disease Interactions

This product is intended to deliver a functional copy of the *DDC* gene, which is abnormal in patients with AADCD. Therefore, there is a direct product-disease interaction.

8.5.5 Product-Product Interactions

No formal drug interaction studies were performed. Eladocagene exuparvovec is not expected to interact with other drugs.

8.5.6 Human Carcinogenicity

No evidence of carcinogenicity was observed in the clinical development program. There is a theoretical risk for insertional oncogenesis in AAV gene therapy products but none was observed in the clinical studies submitted for review.

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable for this single dose gene therapy product.

8.5.8 Immunogenicity (Safety)

See Section 4.4.4.

8.5.9 Person-to-Person Transmission, Shedding

See Section 4.4.3.

8.6 Safety Conclusions

The expected adverse reactions shown in Table 22 include events such as dyskinesia, salivary hypersecretion, and insomnia likely attributable to dopamine sensitivity in patients with AADCD.

The most significant risks appear to be related to study procedures required for eladocagene exuparvovec, rather than to the gene therapy product itself. Children with AADCD have significant autonomic instability, which places them at additional risk for cardiac and/or respiratory events. In the pivotal study, this was observed in two patients—one who had an event of cardiorespiratory failure during line placement with signs of a concurrent gastrointestinal bleed, and one patient who had an event of respiratory arrest shortly after post-operative extubation. Therefore, it is important that the product labeling include recommendations to providers to ensure close monitoring of such events in patients treated with eladocagene exuparvovec. Additionally, these events were considered for potential postmarketing surveillance (discussed at length in Section 11.6).

However, a limitation of the safety analyses was the very small size of the safety database (only 13 patients treated in the pivotal study with the commercial product). Despite using a different formulation of the product, procedural risks such CSF leaks that occurred in the supportive studies help to inform the potential safety considerations of eladocagene exuparvovec.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

No information was collected on the use of eladocagene exuparvovec during pregnancy.

9.1.2 Use During Lactation

No information was collected on the use of eladocagene exuparvovec during lactation.

9.1.3 Pediatric Use and PREA Considerations

This application is exempt from the Pediatric Research Equity Act due to orphan drug designation. Clinical studies were conducted exclusively in pediatric patients.

9.1.4 Immunocompromised Patients

There are no available data from eladocagene exuparvovec in immunocompromised patients.

9.1.5 Geriatric Use

All clinical studies were conducted in pediatric patients, so there is no information on the geriatric use of eladocagene exuparvovec.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

None.

10. CONCLUSIONS

In summary, the clinical and clinical pharmacology review teams conclude that all criteria for accelerated approval have been met, as follows:

Serious Condition

AADCD is a serious condition, with significant clinical manifestations including global developmental delay, hypotonia, feeding difficulties, oculogyric crises, and autonomic stability. Regardless of phenotype, all patients experience significant disability that impacts quality of life.

Meaningful Advantage Over Available Therapy

Patients with severe AADCD do not respond to available standard of care therapies, including dopamine agonists, MAOIs, and vitamin B6 (pyridoxine). The motor outcomes observed in children enrolled in the pivotal study represent meaningful improvements in

motor function that are not observed in the untreated children with the severe phenotype in the NHDB.

However, patients with the moderate form of the disease have been observed to have rapid improvements after initiation of standard of care therapy, often achieving standing and ambulation after treatment (Wen et al. 2020). Due to the limited case reports and primarily cross-sectional natural history data, an overall responder rate and durability of effect of standard of care is not clear. However, the case reports compiled by (Wen et al. 2020) report. Given that that most of the patients treated in the clinical had improvements limited to only head control and sitting and there is uncertainty in the durability of effect, it is not clear that eladocagene exuparvovec provides a meaningful advantage over available therapy for patients with the moderate phenotype.

Per (Wassenberg et al. 2017), “patients with the mild phenotype can present with predominantly with autonomic symptoms (diarrhea, episodic hypoglycemia, nasal congestion) without evidence movement disorders”. Due to the rarity of the disease and the limited published information on the mild phenotype, the proportion of patients with the mild phenotype who do not have motor impairment has not been characterized. Given that the clinical data was only able to characterize the impact on gross motor outcomes in treated patients, there is uncertainty in how eladocagene exuparvovec could benefit patients with the mild phenotype.

Additionally, eladocagene exuparvovec is a gene therapy product administered directly into the putamen of the brain that comes with significant risks with both the product and the neurosurgical procedure. Oral standard of care therapies have less risks with reported side effects including irritability, weight loss, vomiting, and dyskinesia (Wassenberg et al. 2017).

Demonstrates an Effect on an Endpoint That Is Reasonably Likely to Predict Clinical Benefit

There is uncertainty regarding the proposed CSF HVA biomarker. However, an intermediate clinical endpoint of motor milestone achievement at Week 48 represents early signs of a treatment effect that is reasonably likely to predict long-term clinical benefit. Supportive evidence of a pharmacodynamic effect includes post-treatment increases in CSF HVA and ^{18}F-DOPA uptake on PET scan.

The identified risks of eladocagene exuparvovec are not considered to outweigh the observed benefits in patients with the severe phenotype of AADCD, for which there are no available treatment options and great unmet medical need. However, given the lack of data to demonstrate efficacy in adults (who may have a different response due to lack of neuroplasticity) and other phenotypes of AADCD (mild, moderate), we recommend accelerated approval for children with the severe phenotype of AADCD.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 23: Risk-Benefit Considerations for Eladocagene Exuparvovec

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Aromatic L-amino acid decarboxylase deficiency (AADCD) is a rare, autosomal recessive neurodevelopmental disorder that results in a deficiency in the aromatic L-amino acid decarboxylase (AADC) enzyme. Patients experience deficiencies in dopamine, norepinephrine, norepinephrine, and serotonin. • Clinical manifestations include hypotonia which results in feeding difficulties and global developmental delay (including delayed achievement of motor milestones), autonomic dysfunction, and oculogyric crises. • There is substantial phenotypic heterogeneity in AADCD. Patients with severe disease do not achieve any motor milestones and do not respond to standard of care oral medications (dopamine agonists, monoamine oxidase inhibitors, vitamin B6). Patients with mild phenotype generally do not have significant gross motor dysfunction but are primarily impacted by mild cognitive impairment and autonomic dysfunction. • AADCD is not a neurodegenerative condition – children with the moderate and mild phenotypes can continue to achieve improvements in motor milestones over time.	• AADCD, a rare, autosomal recessive neurodevelopmental disorder in which the AADC enzyme is missing, leads to a deficiency in neurotransmitters key for normal neurologic function. • Clinical presentation is heterogenous. • Children with the severe phenotype experience severe developmental delay (including inability to achieve any or limited gross motor milestones), hypotonia, autonomic dysfunction and cognitive impairment that is reported to not generally respond to standard of care pharmacologic therapies (dopamine agonists, MAOI, pyridoxine and others). • This is a serious disease with significant morbidity and early mortality. • Patients with the mild and moderate phenotypes are able to achieve motor milestones and are reported to have variable improvements on standard of care pharmacologic therapies but likely more so than those with the severe phenotype.
Unmet Medical Need	• There are no FDA-approved treatments for AADCD. • Off label use of oral medications (e.g., dopamine agonists, monoamine oxidase inhibitors, vitamin B6, and others) are recommended for symptomatic management based on expert consensus (Wassenberg et al. 2017) in all patients; those with mild and moderate phenotypes may experience symptomatic response more frequently than those with severe disease.	• There is an unmet medical need for AADCD with no approved disease-modifying treatments. • The unmet medical need is profound for the severe phenotype of AADCD, where there are no current treatment options. Standard of care for the mild and moderate phenotypes is off-label use of oral medications and those have variable success in addressing symptoms.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Clinical Benefit	• The Applicant proposed percent change from baseline to Week 8 in CSF HVA (a byproduct of dopamine breakdown) as a biomarker reasonably likely to predict clinical benefit. To support understanding of CSF HVA as a surrogate endpoint, data was submitted from 22 patients with the severe phenotype of AADCD enrolled in two open-label clinical studies conducted in Taiwan. Multiple uncertainties were identified including uncertainties in the proposed threshold of a minimum of 20% increase from baseline, uncertainty in the significance of the Week 8 timepoint, lack of clear correlation between parameters of CSF HVA (including absolute post-treatment levels, absolute change from baseline and percent change from baseline) and motor outcomes. • In single-arm, open-label study AADC-002 that enrolled and treated 13 children with severe AADCD, improvements in achievement of gross motor milestones were seen in 8 of 12 children (67%) at week 48 and there was no motor milestone achievement in the natural history control (untreated) patients with severe disease phenotype over a long follow up period. These improvements in motor milestone achievement are unexpected when compared to the natural history of severe AADCD. • Additionally, there is uncertainty in the durability of the motor outcomes beyond 1 year after treatment with eladocagene exuparvovec. All patients were followed for less than 2 years. 2 children are showing potential signs of regression in their motor milestones that may indicate a waning of a treatment effect but the extremely limited sample size does not allow definitive conclusions. • Only children with the severe phenotype of AADCD were enrolled in the clinical studies. There is no data assessing effectiveness in patients with the mild and moderate phenotypes. • There is no demonstration of efficacy in adolescents, with the oldest enrolled patient treated at 10 years of age. The motor data suggests more robust outcomes in the youngest treated children but definitive conclusions are limited by the small sample size and short follow up duration (up to 1 year).	• Given the observations of short-term (1 year) clinical benefit in this chronic disease and uncertainty in the durability of the treatment effect, we agree with the Applicant's proposal for accelerated approval, however based on a different surrogate endpoint than the one proposed. • The uncertainties in the CSF HVA biomarker, do not make it appropriate as a surrogate endpoint reasonably likely to predict clinical benefit on neurologic outcomes in the studied population. • The improvement in motor milestones at week 48 represents an intermediate clinical endpoint that is reasonably likely to predict clinical benefit on the neurologic course of severe AADCD and is appropriate to support accelerated approval. The post-approval confirmatory study will be the same study supporting this approval with data generated by following motor milestone achievement in the same 12 patients until at least 60 months (5 years) post-treatment. This is reasonable for verification of the clinical (neurologic) benefit of the product. • Pharmacodynamic results such as post-treatment increases in CSF HVA and putamen specific ^{18}F-DOPA uptake provide confirmatory evidence of effectiveness. • Given that there is no data demonstrating efficacy in adults with any form of the disease or children with the mild and moderate AADCD phenotypes, we recommend approval for treatment of children with the severe phenotype of AADCD.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
	• Pharmacodynamic observations such as post-treatment increases in CSF HVA and putamen specific ^{18}F-DOPA uptake supports the proposed mechanism of action of the product as targeting the single biochemical pathway of the disease. In all 12 patients followed up to 48 weeks in the study AADC-002, CSF HVA and ^{18}F-DOPA uptake increased from baseline after treatment of eladocagene exuparvovec and remained higher than baseline levels at Week 48. These observations in the disease-specific biomarker improvements are consistent with the biomarker improvements seen in the severe AADCD patients treated (with a different version of product) in the supportive, ex-U.S. studies AADC-010 and AADC-011; these patients exhibited motor milestone improvements following treatment.	
Risk	• The safety database is limited to the 13 children treated with the intended commercial product in Study AADC-002. Data from the 2 ex-U.S. studies AADC-010 and AADC-011 in a similar patient population (in terms of disease severity and age) provide a supplemental safety assessment. This additional safety database showed a similar safety profile of the different version of the product but showed additional procedural risks including CSF leaks following the neurosurgical procedure for product administration. • Given the rarity of the disease, it not unexpected that the available safety database is also limited. Despite this limitation, the submitted safety database with respect to number of patients exposed to the product and the duration of exposure appears reasonable to support the safety evaluation and inform the benefit-risk assessment. • Serious adverse events (reported from all studies) included 2 cases of acute cardiac/respiratory failure (likely secondary to post-anesthesia/post-surgical recovery complications) and CSF leaks following the neurosurgical procedure. • The most common adverse reactions reported in >15% of patients in study AADC-002 were dyskinesia (77%), pyrexia (38%), hypotension (38%), anemia (31%), salivary hypersecretion (23%), hypokalemia (23%), hypophosphatemia (23%), insomnia (23%), and hypomagnesemia (15%).	• While there are serious risks of eladocagene exuparvovec identified, in the context of severe AADC, these do not outweigh the clinical benefits observed in the pivotal study AADC-002. • The risks can be mitigated through product labeling to inform patients, providers, and families of the observed risks and inform treatment decisions. Risk mitigation includes close observations. • There are likely unknown risks based on the small safety population that will be further monitored through routine post-marketing surveillance.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	• A REMS was not deemed necessary based on the identified risks in the clinical study that can be mitigated through product labeling and routine post-marketing pharmacovigilance. • However, as discussed in Section 11.6, this reviewer recommends consideration of a FDAAA PMR to evaluate the events of cardiac and/or respiratory failure, meeting the following Section 505(o)(3)(A) criteria "To assess signals of serious risk related to the use of the drug".	• This reviewer recommends a FDAAA PMR to further evaluate events of cardiac and/or respiratory failure in the post-marketing setting.

11.2 Risk-Benefit Summary and Assessment

AADCD is a serious, neurodevelopmental disorder that results from a deficiency in the AADC enzyme leading to deficiencies in dopamine, norepinephrine, epinephrine, and serotonin. Children with the severe phenotype are unable to achieve any motor milestones and experience severe neurologic impairment that does not respond to off-label use of available oral medications. There is a substantial amount of unmet medical need. Eladocagene exuparvovec is an adeno-associated virus gene therapy product that expresses the human *DDC* gene, which encodes the AADC enzyme. After neurosurgical administration of eladocagene exuparvovec, there is an increase in functional AADC enzyme expression.

Clinical data from 12 children with severe AADC treated with eladocagene exuparvovec in a single-arm, open label study demonstrate early evidence showing improvements in motor milestones when compared to untreated children with the same phenotype in the NDHB. Remaining uncertainties in the clinical benefit include durability of effect, potential treatment response in adolescents and adults (where neuroplasticity would be expected to decrease with age), and benefits in patients with the mild and moderate phenotype of the disease.

The observed risks of eladocagene exuparvovec were noted to be risks associated with the neurosurgical procedures (including observed events of cardiac and/or respiratory failure and theoretical risks of CSF leaks, meningoceles, and meningitis) and dyskinesia (related to heightened sensitivity to dopamine in these children who have experienced chronic dopamine deficiency).

Given the devastating nature of severe AADCD and the clinical data supporting the use of eladocagene exuparvovec in children with the severe phenotype, we consider the observed early clinical benefits in motor function to outweigh the identified and theoretical risks. Continued follow-up in a confirmatory study would allow for continued verification of the clinical benefit and may address uncertainties related to durability of effect.

As it relates to children with the mild and moderate phenotypes of the disease, there is no evidence to demonstrate a favorable benefit-risk as they were not studied in the clinical development program.

11.3 Discussion of Regulatory Options

Given the limited duration of follow-up and uncertainty on the durability of effect, the review team agreed with the Applicant’s proposal for accelerated approval rather than traditional approval to permit verification of the clinical benefit in the confirmatory study. However, given uncertainty regarding the proposed CSF HVA biomarker, the review team proposes that the basis of the accelerated approval decision be an intermediate

clinical endpoint motor milestone achievement at Week 48, where early improvements in motor milestones are reasonably likely to predict long-term benefit.

The review team also had discussions on whether approval should be extended to adult patients with AADCD and patients with mild and moderate phenotypes of AADCD. Based on uncertainties in the ability to extrapolate the efficacy to the adult population, and no data to support a favorable benefit-risk in the mild and moderate phenotypes, the clinical reviewer recommends approval for children with the severe phenotype of AADCD.

11.4 Recommendations on Regulatory Actions

Accelerated approval for children with the severe phenotype of AADCD was based on an intermediate clinical endpoint of motor milestone achievement at Week 48.

11.5 Labeling Review and Recommendations

The reviewers recommend the following major changes to the proposed draft label:

- Section 1 (Indication and Usage): Recommend limiting indication to children with the (b) (4) of AADCD. Revisions to reflect that indication is approved under accelerated approval based on change in motor milestone achievement at 48 weeks (rather than CSF HVA). If the decision is made to approve for a broad population (all patients with AADCD regardless of (b) (4) or age), this reviewer recommends that the indications section be limited to the "treatment of (b) (4)" given that 1) there is no data to characterize impacts on (b) (4) and 2) patients with the (b) (4) may not have (b) (4) of their disease.
- Section 2 (Dosage and Administration): Recommend appropriate cross-labeling between the SmartFlow Canula device (reviewed as a de novo submission by the Center for Devices and Radiological Health) and eladocagene exuparvovec.
- Section 4 (Contraindications): Add a contraindication for pediatric patients who have not achieved skull maturity, given that the stereotactic neurosurgical procedure requires skull maturity in order to conduct.
- Section 5 (Warnings & Precautions): Limit to include information from the pivotal study AADC-002 due to difference and product and no additional safety signals observed in the other studies. Add observed events of cardiorespiratory failure to 5.1 and highlight theoretical risks of the procedure, including CSF leak, intracranial bleeding, neuroinflammation, acute infarction, and infection.
- Section 6 (Adverse Reactions): Limit data to Study AADC-002. Update adverse reactions to reflect reviewer analysis discussed in review memo Section 8.
- Section 12 (Clinical Pharmacology): Move all data on CSF HVA and ^{18}F-DOPA uptake from section 14 to section 12. Limit clinical pharmacology data to Study AADC-002.
- Section 14 (Clinical Studies): Present motor data comparing data on children treated in AADC-002 and untreated children in the NHDB.

11.6 Recommendations on Postmarketing Actions

Efficacy

The Applicant proposed to verify the clinical benefit in the post-market setting by following motor milestone achievement in the existing patients in study AADC-002 until 60 months post-treatment.

The recommendation from the clinical reviewer is to enroll and treat new patients in an accelerated approval confirmatory study. This should include treating older children and adolescents (children >10 years of age were not represented in the pivotal study) and assessing motor milestone achievement 5 years after treatment in comparison to an external control. This will serve to verify and describe the clinical benefit across the entire pediatric population with the severe phenotype of AADCD.

Safety

As described in Section 8.4.2, there were two events of cardiorespiratory failure that occurred shortly after product administration. While these events may represent increased sensitivity to anesthesia, surgical procedures and/or other study procedures required to administer eladocagene exuparvovec, this reviewer assesses these events to meet the following criteria of the 2007 Food and Drug Administration Amendments Act: “Assess signals of serious risk related to use of the drug” and recommends a post-marketing safety study to further understand these events. This will also help to further characterize the safety of eladocagene exuparvovec given the small safety database and the known risks of AAV gene therapy.

APPENDIX: ADDITIONAL CLINICAL PHARMACOLOGY INFORMATION AND ANALYSES

1. Study AADC-002: Additional Pharmacodynamics Assessment

1.1 3-OMD and 5-HIAA in CSF

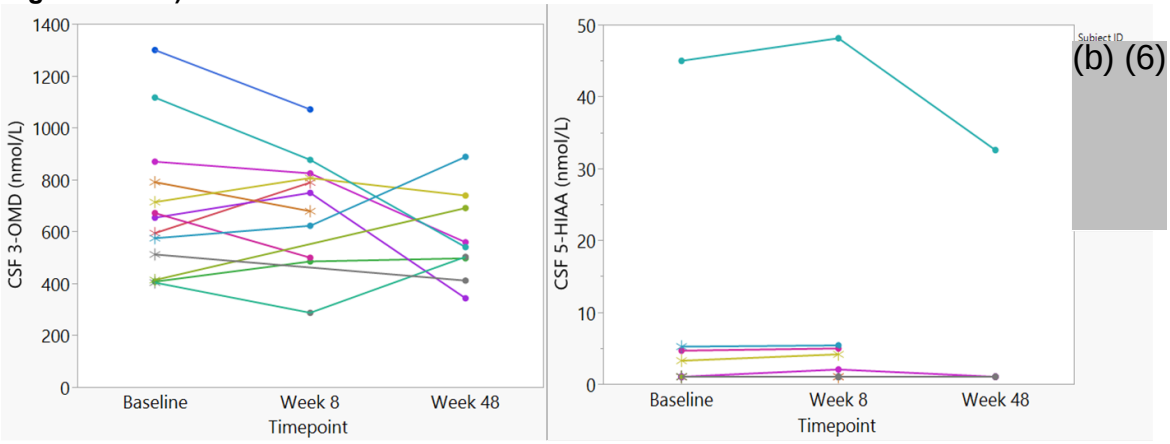
In pivotal Study AADC-002, along with CSF HVA, additional neurotransmitter metabolites in CSF were measured such as 3-OMD (as a metabolite of L-DOPA) and 5-HIAA (as a metabolite of serotonin) using an HPLC-MS/MS method. These were assessed at baseline, Week 8, and Week 48 after the gene therapy.

Changes from baseline in 3-OMD and 5-HIAA were not as evident as those in CSF HVA (Figure 8, Table 24).

3-OMD in CSF was initially anticipated to decrease after the gene therapy by increased activity of the AADC enzyme. However, direction of changes was not consistent across patients; 5 of 11 patients (45.5%) at Week 8 and 5 of 9 patients at Week 48 (55.5%) showed increases from baseline.

A metabolite of serotonin, 5-HIAA, was not anticipated to impact serotonin levels, as the putamen does not contain serotonergic neurons. Changes in 5-HIAA were minimal after the gene therapy.

Figure 8: 3-OMD and 5-HIAA in CSF Over Time by Patient in Study AADC-002 (Left: 3-OMD; Right: 5-HIAA)



Source: Reviewer's analysis based on adlb.xpt of Study AADC-002 and FDAQ14.xpt submitted in Applicant's Responses to Information Requests #12 dated July 1, 2024.
Note: Lower limit of quantification (LLOQ) of 3-OMD and 5-HIAA were both 2 nmol/L, and values reported as <LLOQ was imputed as 0.5*LLOQ; Asterisk (*) presents results obtained in the presence of concomitant dopaminergic agents at the time of measurement.
Abbreviations: CSF, cerebrospinal fluid, 3-OMD, 3-O-methyl-L-DOPA, 5-HIAA, 5-hydroxyindoleacetic acid

Table 24: 3-OMD and 5-HIAA in CSF by Timepoint in Study AADC-002

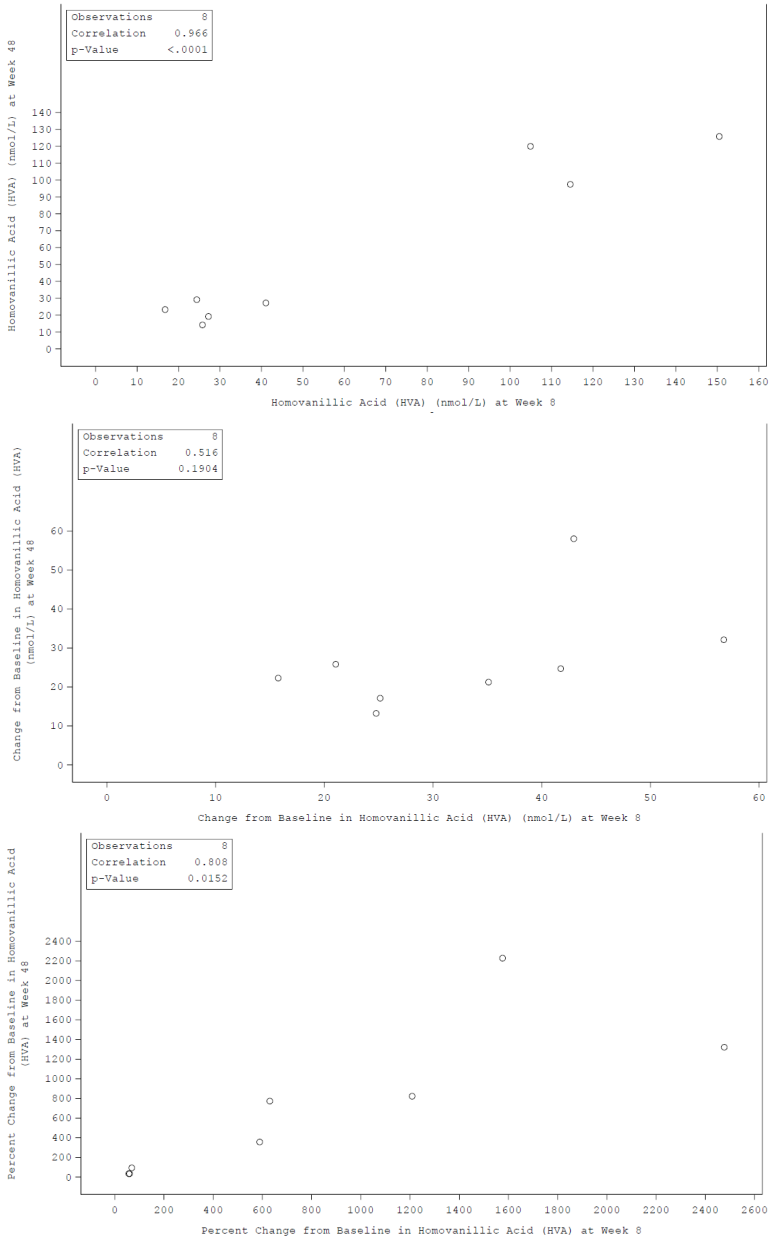
Timepoints	3-OMD Absolute Value (nmol/L)	3-OMD Change from Baseline (nmol/L)	5-HIAA Absolute Value (nmol/L)	5-HIAA Change from Baseline (nmol/L)
Baseline	-	-	-	-
N	13	-	13	-
Mean (SD)	693.13 (272.47)	-	5.16 (12.06)	-
Median (Min, Max)	652.84 (402.88, 1298.97)	-	1.00 (1.00, 44.97)	-
Week 8	-	-	-	-
Na	11	11	12	12
Mean (SD)	698.30 (216.63)	-36.86 (147.31)	5.96 (13.38)	0.46 (0.92)
Median (Min, Max)	748.62 (286.40, 1070.14)	-45.02 (-240.23, 195.12)	1.0 (1.0, 48.11)	0.0 (0.0, 3.14)
Week 48b	-	-	-	-
N	9	9	6	6
Mean (SD)	573.87 (170.17)	-54.78 (296.22)	6.26 (12.88)	-2.07 (5.07)
Median (Min, Max)	539.53 (342.39, 887.45)	25.2 (-576.45, 313.57)	1.0 (1.0, 32.55)	0.0 (0.0, 0.36)

Source: Study AADC-002, Table 14.2.2.6 and Applicant's Responses to Information Requests #12 dated July 1, 2024.
Note: Lower limit of quantification (LLOQ) of 3-OMD and 5-HIAA were both 2 nmol/L, and values reported as <LLOQ was imputed as 0.5*LLOQ; Percent change from baseline = change from baseline/absolute value at baseline x 100.
[a] Patient (b) (6) did not complete the Week 8 visit assessments due to travel limitations. Patient (b) (6) had no 3-OMD value at Week 8 due to no internal standard.
[b] Reviewer calculated the 3-OMD results integrating the additional Week 48 data from 3 patients (ID (b) (6) , and (b) (6)), which were submitted in responses to Information Requests #12 dated July 1, 2024.
Correlation Between CSF HVA Measured at Week 8 and Week 48
Abbreviations: CSF, Cerebrospinal fluid; 3-OMD, 3-O-methyl-L-DOPA; 5-HIAA, 5-hydroxyindoleacetic acid; n, number of patients, SD, standard deviation, Max, maximum; Min, minimum

The Applicant proposed to use "the change from baseline in CSF HVA at Week 8 post-dose" as a surrogate endpoint to reasonably likely predict the clinical benefit of eladocagene exuparvovec. In Study AADC-002, CSF HVA was measured at baseline, Week 8, and Week 48; however, CSF HVA at Week 8 had not been assessed in the previous Studies AADC-010 and AADC-011 (the supportive studies), where CSF HVA was only assessed at Month 12 post dose. For the purposes of data analyses, the Week 48 timepoint in the pivotal study was considered equivalent to the Month 12 timepoint in the supportive studies.

In 8 of 13 patients, CSF HVA levels at Week 8 and Week 48 were both available in the pivotal study. To support a link between CSF HVA observations at Week 8 and Week 48, the Applicant was asked to provide correlation analyses for CSF HVA obtained at two different timepoints: Week 8 and Week 48 (Figure 9). The correlation between changes from baseline at Week 8 and Week 48 was not significant even though the correlations in absolute values and percent change from baseline were statistically significant.

Figure 9: Correlation Analyses Between CSF HVA Levels at Week 8 and Week 48 in Study AADC-002 (Top: Absolute Values; Middle: Change From Baseline; Bottom: Percent Change from Baseline)



Source: Figures 3, 4, and 5, Applicant's Responses to Information Requests #12 dated July 1, 2024

Additionally, substantial intra-patient variability between absolute values at Week 8 and Week 48 was noted: the difference between Week 8 and Week 48 ranged from -24.64 to 15.07 nmol/L, and the percent difference ranged from -44.9% to 38.9% (Figure 2 in Section 4.4.2).

Clinical Pharmacology Reviewer Comment:

- *Given the limited number of observations (N=8) and large intra-patient variability between Week 8 and Week 48, it is uncertain if change from baseline in CSF HVA at Week 8 can reliably represent that of Week 48 or later timepoints.*

1.2 Relationship Between CSF HVA and Highest Motor Milestone

The reviewer visually explored the relationships between CSF HVA and highest motor milestone achievement. Motor milestone achievement based on PDMS-2 was assessed in 12 of 13 patients who received the gene therapy from Week 24 up to Week 48 (n=9), Week 72 (n=1), or Week 96 (n=2); the highest motor milestone that each patient achieved during the study was used in this analysis.

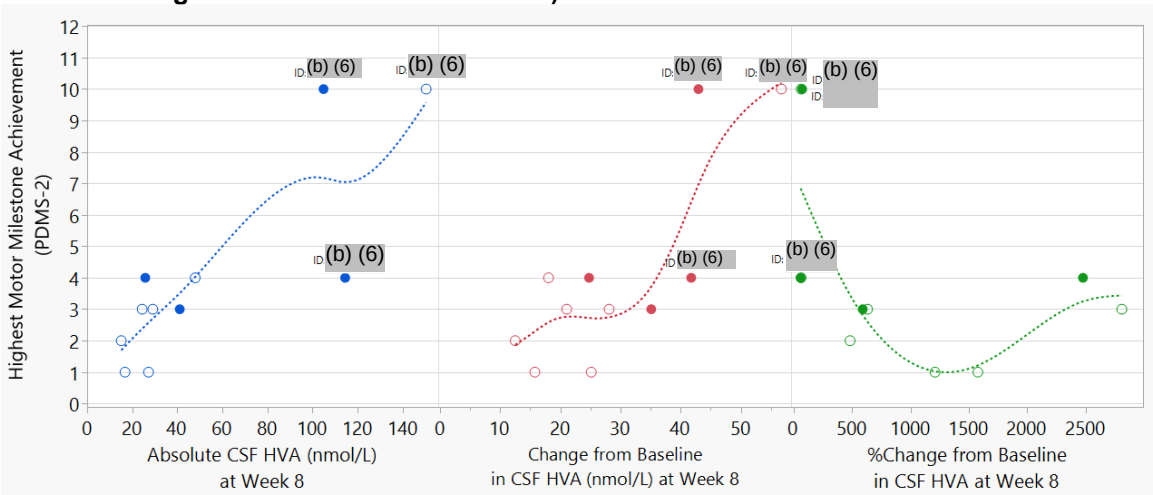
For CSF HVA at Week 8, change from baseline or percent change from baseline did not seem to correlate closely with the degree of highest motor milestone achievement (Figure 10). In other words, from an individual patient level, the same magnitude of change from baseline in CSF HVA (or percent change from baseline) did not result in the same degree of motor milestone achievement.

However, overall, a general trend appeared that higher absolute CSF HVA at Week 8 was associated with higher motor milestone achievement (Figure 10). This trend was also seen in the supportive studies for CSF HVA at Month 12 as well (Figure 5 in Section 7.1.4). It should be noted that absolute CSF HVA post-dose levels are likely affected by pre-treatment baseline levels. For example, there were three patients who showed relatively higher CSF HVA levels at Week 8 and achieved higher motor milestone compared to the other patients (Patient ID: (b) (6)), but their baseline CSF HVA levels had been initially higher than that of the other patients (62 nmol/L, 94 nmol/L, and 73 nmol/L, respectively).

Clinical Pharmacology Reviewer Comment:

- *Intrinsic factors of the three patients (e.g., age, brain size, DDC genotype) may have contributed to the higher CSF HVA levels at baseline.*

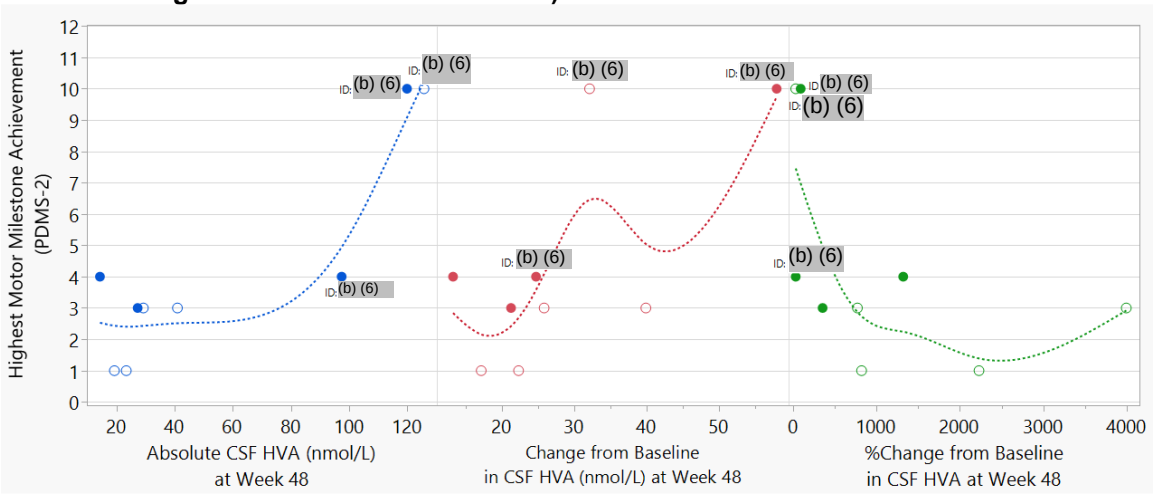
Figure 10: Relationship of CSF HVA at Week 8 and Highest Motor Milestone in Study AADC-002 (Left: Absolute CSF HVA; Middle: Change From Baseline in CSF HVA; Right: Percent Change From Baseline in CSF HVA)



Source: Reviewer's analysis based on FDAQ14.xpt and FDAQ16.xpt, submitted in Applicant's Responses to Information Requests #12 dated July 1, 2024.
Note: Motor milestones assessed on PDMS-2, 0=none, 1=partial head control, 2=full head control, 3=sitting with assistance, 4=sitting unassisted, 5=standing with support, 6=standing away from support, 7=walking with assistance, 8=free walking, 9=walking upstairs with support, 10=walking backward, 11=walking on taped line;
Open circles mean emerging skill and closed circles mean mastery of the skill for the motor milestone.
Dotted lines show smooth curves through the data with a spline method.
Lower limit of quantification (LLOQ) of CSF HVA was 2 nmol/L, and values reported as <LLOQ was imputed as 0.5*LLOQ.
Abbreviations: CSF HVA, homovanillic acid in cerebrospinal fluid; PDMS-2, the Peabody Developmental Motor Scale-2

No clear correlation was found between CSF HVA at Week 48 and highest motor milestone achievement (Figure 11).

Figure 11: Relationship of CSF HVA at Week 48 and Highest Motor Milestone in Study AADC-002 (Left: Absolute CSF HVA; Middle: Change From Baseline in CSF HVA; Right: Percent Change From Baseline in CSF HVA)



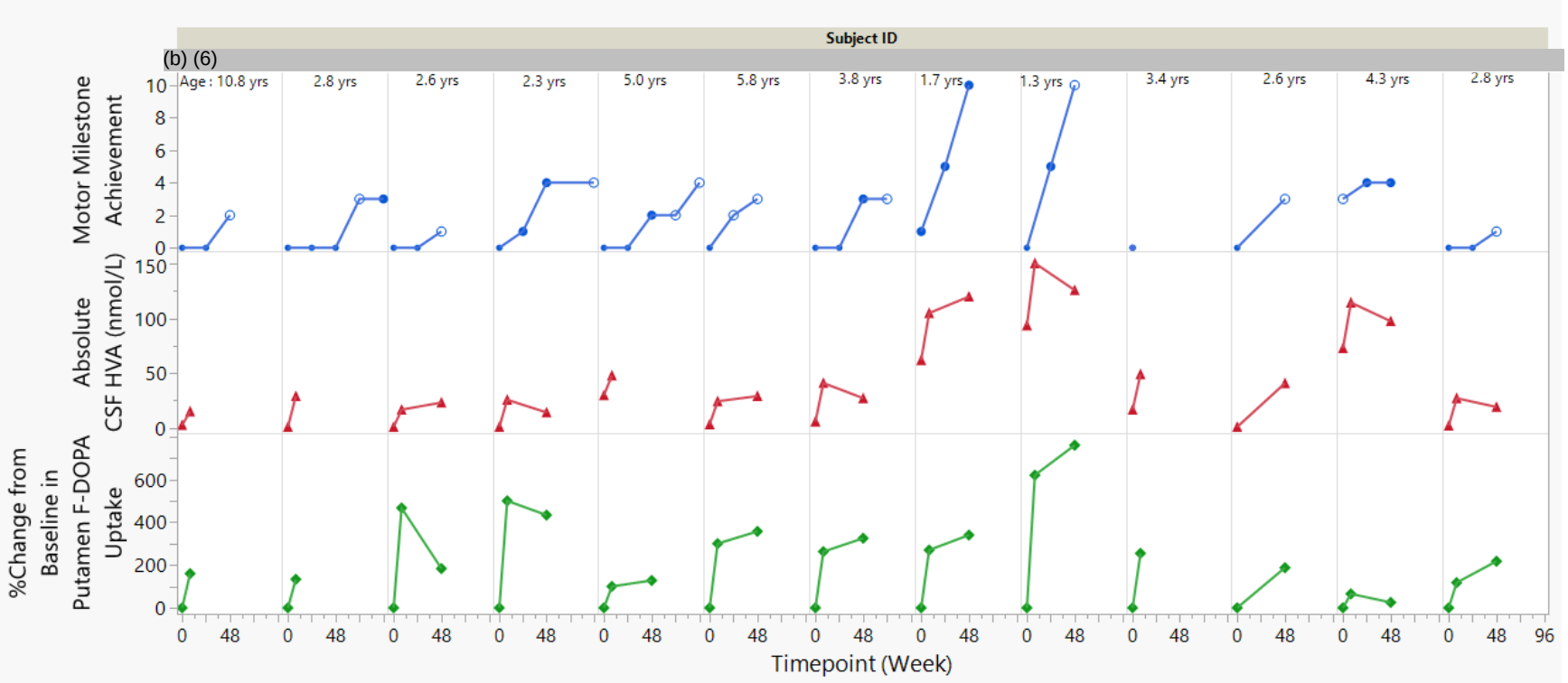
Source: Reviewer's analysis based on FDAQ14.xpt and FDAQ16.xpt submitted in Applicant's Responses to Information Requests #12 dated July 1, 2024.
Note: Motor milestones assessed on PDMS-2, 0=none, 1=partial head control, 2=full head control, 3=sitting with assistance, 4=sitting unassisted, 5=standing with support, 6=standing away from support, 7=walking with assistance, 8=free walking, 9=walking upstairs with support, 10=walking backward, 11=walking on taped line;
Open circles mean emerging skill and closed circles mean mastery of the skill for the motor milestone.
Dotted lines show smooth curves through the data with a spline method.
Lower limit of quantification (LLOQ) of CSF HVA was 2 nmol/L, and values reported as <LLOQ was imputed as 0.5*LLOQ.
Abbreviations: CSF HVA, homovanillic acid in cerebrospinal fluid; PDMS-2, the Peabody Developmental Motor Scale-2

Individual profiles of motor milestone achievement over time are presented in Figure 12 and Figure 13 (by chronological age of patients) along with those of CSF HVA and putamen ^{18}F-DOPA uptake. Overall, CSF HVA and putamen ^{18}F-DOPA uptake increased from Week 8 after the gene therapy, followed by motor function improvement at later timepoints, as early as Week 24 in some patients.

Clinical Pharmacology Reviewer Comment:

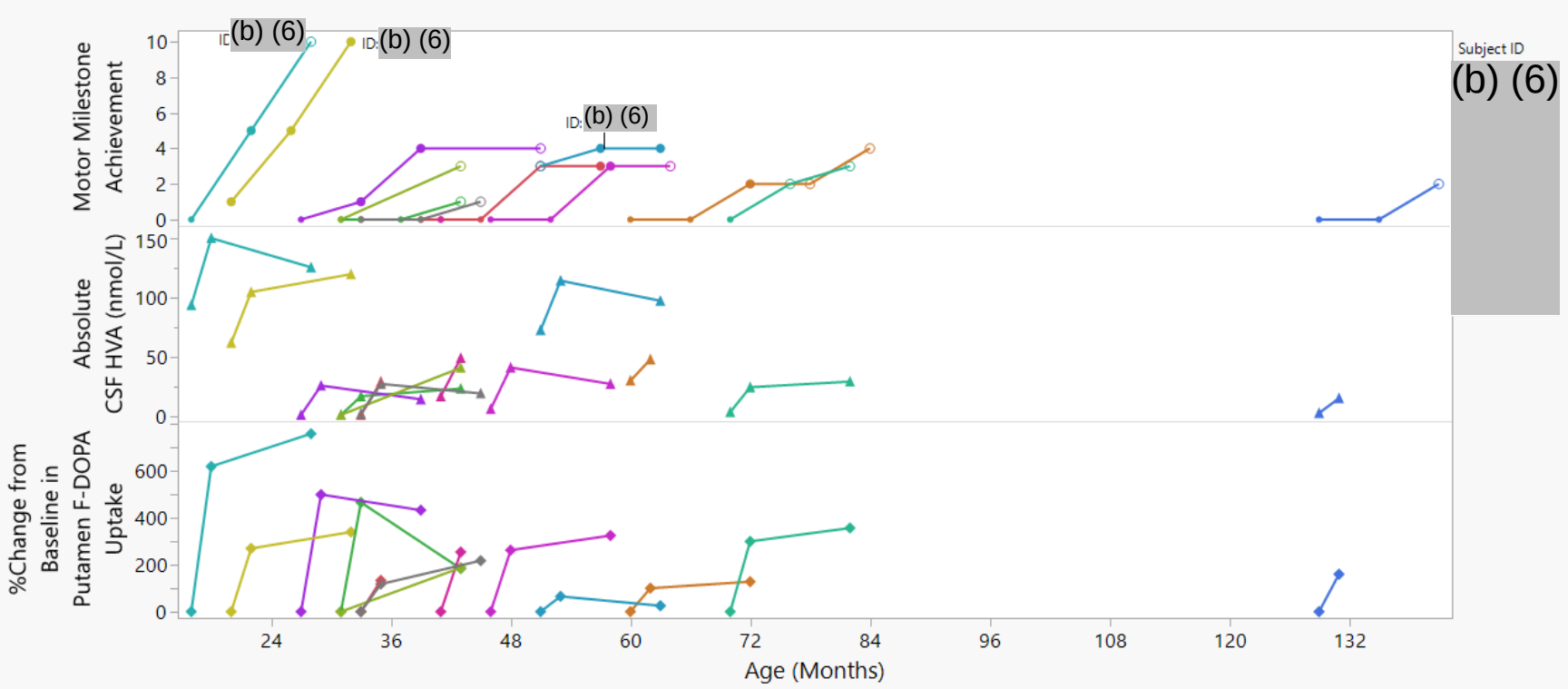
- *Out of 13 patients in Study AADC-002, 7 patients had founder variant (c.714+4A>T; 2 patients with homozygous variant and 5 patients with heterozygous) but due to the large variability and limited number of subjects having the same genotype, any specific trend was not found between different genotypes or within the same genotype group.*

Figure 12: Individual Profiles of Motor Milestone Achievement, CSF HVA, and Putamen Specific ^{18}F-DOPA Uptake in Study AADC-002



Source: Reviewer's analysis based on adnv.xpt of Study AADC-002, and FDAQ14.xpt and FDAQ16.xpt of Applicant's Responses to Information Requests #12 dated July 1, 2024.
Note: Motor milestones assessed on PDMS-2, 0=none, 1=partial head control, 2=full head control, 3=sitting with assistance, 4=sitting unassisted, 5=standing with support, 6=standing away from support, 7=walking with assistance, 8=free walking, 9=walking upstairs with support, 10=walking backward, 11=walking on taped line;
Open circles mean emerging skill and closed circles mean mastery of the skill for the motor milestone.
Lower limit of quantification (LLOQ) of CSF HVA was 2 nmol/L, and values reported as <LLOQ was imputed as 0.5*LLOQ.
%change from baseline = change from baseline/absolute value at baseline x 100.
Abbreviations: CSF HVA, homovanillic acid in cerebrospinal fluid; yrs, yrs old at the time of treatment

Figure 13: Motor Milestone Achievement, CSF HVA, and Putamen Specific ^{18}F-DOPA Uptake by Patient and Chronological Age in Study AADC-002



Source: Reviewer's analysis based on adnv.xpt of Study AADC-002, and FDAQ14.xpt and FDAQ16.xpt of Applicant's Responses to Information Requests #12 dated July 1, 2024.
Note: Motor milestones assessed on PDMS-2, 0=none, 1=partial head control, 2=full head control, 3=sitting with assistance, 4=sitting unassisted, 5=standing with support, 6=standing away from support, 7=walking with assistance, 8=free walking, 9=walking upstairs with support, 10=walking backward, 11=walking on taped line;
Open circles mean emerging skill and closed circles mean mastery of the skill for the motor milestone.
Lower limit of quantification (LLOQ) of CSF HVA was 2 nmol/L, and values reported as <LLOQ was imputed as 0.5*LLOQ.
%change from baseline = change from baseline/absolute value at baseline x 100.
Abbreviations: CSF HVA, homovanillic acid in cerebrospinal fluid

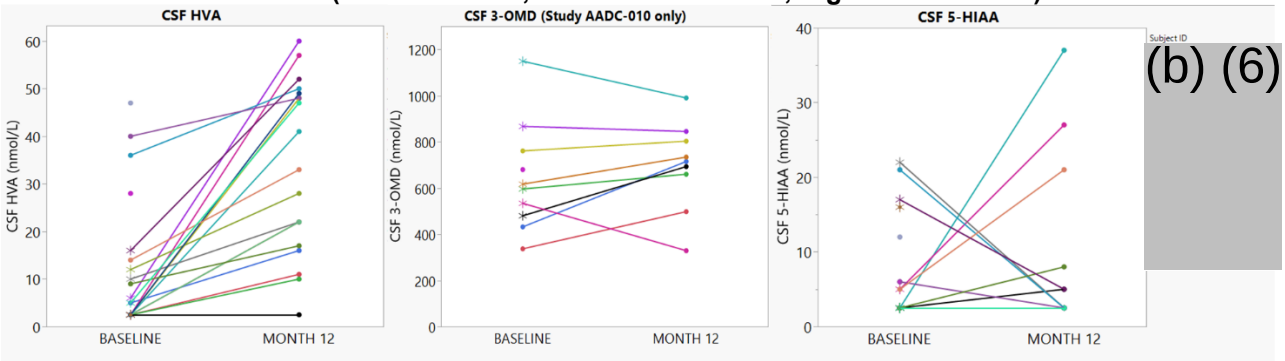
2. Studies AADC-010 and AADC-011: Pharmacodynamics Assessment

2.1 Neurotransmitter Metabolites in CSF

In supportive studies AADC-010 and AADC-011, HVA, 3-OMD (Study AADC-010 only), and 5-HIAA in CSF were measured at baseline and Month 12 using an HPLC-electrochemical detection method (Figure 14, Table 25). The results were in line with the observations in the pivotal study. For CSF HVA, all patients showed an increase at Month 12 after the gene therapy, except for one patient in Study AADC-010 (ID: (b) (6) (b) (6)) who did not show any motor function improvement until Month 84 (see Figure 14). Changes in 3-OMD and 5-HIAA were not apparent, and there were no consistent trends between patients.

Of note, 11 of 22 patients were taking dopaminergic agents (dopamine agonists and MAOIs) at baseline, but none of them were on dopaminergic agents at the time of Month 12 measurement.

Figure 14: CSF Neurotransmitter Metabolites Levels Over Time by Patient in Studies AADC-010 and AADC-011 (Left: CSF HVA, Middle: CSF 3-OMD, Right: CSF 5-HIAA)



Source: Reviewer's analysis based on adlb.xpt of Integrated Summary of Efficacy and FDAQ14.xpt, submitted in Responses to Information Requests #12 dated July 1, 2024
Note: Lower limit of quantification (LLOQ) of HVA and 5-HIAA were 5 nmol/L and LLOQ of 3-OMD was 2 nml/L. Values reported as <LLOQ were imputed as 0.5*LLOQ.
Asterisk (*) presents results obtained in the presence of concomitant dopaminergic agents at the time of measurement.
Abbreviations: CSF, cerebrospinal fluid, HVA, homovanillic acid; 3-OMD, 3-O-methyl-L-DOPA; 5-HIAA, 5-hydroxyindoleacetic acid

Table 25: CSF Neurotransmitter Metabolites by Timepoint in Studies AADC-010 and AADC-011

Analytes	Timepoints	Absolute Value (nmol/L)	Change from Baseline (nmol/L)	Percent Change from Baseline (%)
HVA	Baseline	-	-	-
-	N	22	-	-
-	Mean (SD)	11.5 (13.6)	-	-
-	Median (Min, Max)	5.0 (2.5, 47.0)	-	-
-	Week 12	-	-	-
-	Na	19	19	19
-	Mean (SD)	33.5 (17.9)	24.2 (17.7)	648.5 (707.2)
-	Median (Min, Max)	33.0 (2.5, 60.0)	19.0 (0.0, 54.5)	300.0 (0.0, 2180.0)
3-OMDa	Baseline	-	-	-
-	N	10	-	-
-	Mean (SD)	645.3 (235.9)	-	-
-	Median (Min, Max)	606.5 (337.0, 1149.0)	-	-
-	Week 12	-	-	-
-	N	9	9	9
-	Mean (SD)	696.3 (192.7)	54.9 (162.6)	15.4 (32.8)
-	Median (Min, Max)	715.0 (329.0, 990.0)	64.0 (-205.0, 283.0)	10.7 (-39.4, 65.5)
5-HIAA	Baseline	-	-	-
-	N	22	-	-
-	Mean (SD)	6.5 (6.5)	-	-
-	Median (Min, Max)	2.5 (2.5, 22.0)	-	-
-	Week 12	-	-	-
-	N	19	19	19
-	Mean (SD)	7.1 (9.9)	1.4 (12.5)	113.4 (336.5)
-	Median (Min, Max)	2.5 (2.5, 37.0)	0.0 (-19.5, 34.5)	0.0 (-88.6, 1380.0)

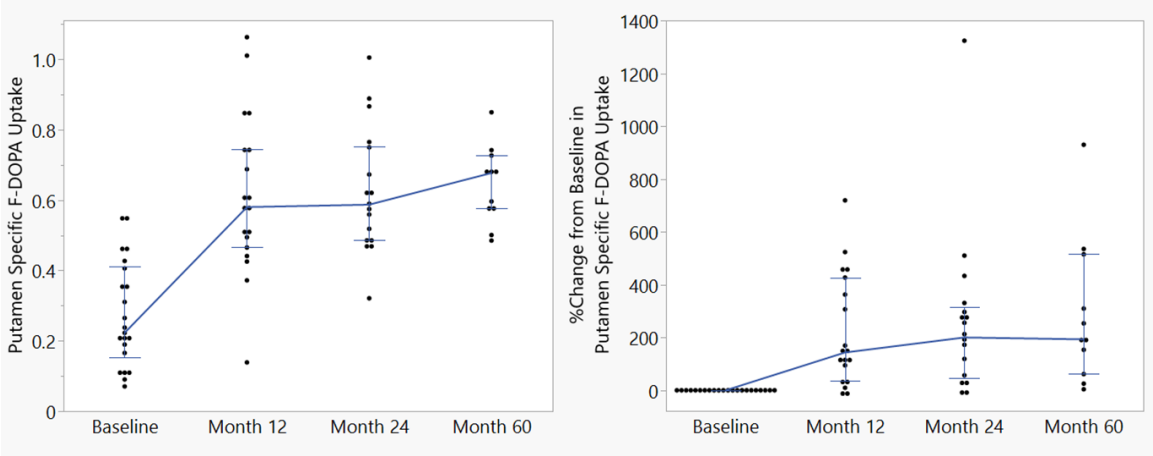
Source: Integrated Summary of Efficacy – Tables, Table 12.1.3.
Note: Lower limit of quantification (LLOQ) of HVA and 5-HIAA were 5 nmol/L and LLOQ of 3-OMD was 2 nmol/L. Values reported as <LLOQ were imputed as 0.5*LLOQ; Percent change from baseline = change from baseline/absolute value at baseline x 100.
[a] 3-OMD was measured only in Study AADC-010.
Abbreviations: CSF, cerebrospinal fluid; HVA, Homovanillic Acid; 3-OMD, 3-O-methyl-L-DOPA; 5-HIAA; 5-hydroxyindoleacetic acid; Max, maximum; Min, minimum; N, number of patients, SD, standard deviation

2.2 Putamen-Specific ^{18}F-DOPA Uptake

In supportive studies AADC-010 and AADC-011, mean bilateral putamen specific uptake of ^{18}F-DOPA was assessed by PET imaging at baseline and Months 12, 24, and 60 after the gene therapy (followed up in Study AADC-1602 at later timepoints than Month 12).

Putamen-specific ^{18}F-DOPA uptake increased from baseline from Month 12 after the gene therapy, which remained sustained by Month 60 (Figure 15, Table 26).

Figure 15: Putamen Specific Uptake of ^{18}F-DOPA Over Time in Studies AADC-010 and AADC-011 (Left: Absolute Values; Right: Percent Change From Baseline)



Source: Reviewer's analysis based on adlb.xpt of Integrated Summary of Efficacy.
Note: The black dots represent values in individual patients. The blue lines represent the median and error bars represent the interquartile ranges. %change from baseline = change from baseline/absolute value at baseline x 100.

Table 26: Putamen-Specific Uptake of ^{18}F-DOPA by Timepoint in Studies AADC-010 and AADC-011

Timepoints	Absolute Value	Change from Baseline	Percent Change from Baseline (%)
Baseline	-	-	-
N	22	-	-
Mean (SD)	0.27 (0.15)	-	-
Median (Min, Max)	0.22 (0.07, 0.55)	-	-
Month 12	-	-	-
N	19	19	19
Mean (SD)	0.61 (0.23)	0.35 (0.27)	220.3 (212.7)
Median (Min, Max)	0.58 (0.14, 1.06)	0.30 (-0.08, 0.87)	143.1 (-14.1, 719.2)
Month 24	-	-	-
N	17	17	17
Mean (SD)	0.63 (0.18)	0.37 (0.26)	261.4 (312.3)
Median (Min, Max)	0.59 (0.32, 1.01)	0.39 (-0.06, 0.93)	200.0 (-10.6, 1323.7)
Month 60	-	-	-
N	11	11	11
Mean (SD)	0.64 (0.11)	0.40 (0.22)	287.9 (276.5)
Median (Min, Max)	0.68 (0.48, 0.85)	0.39 (0.02, 0.66)	192.9 (4.0, 929.8)

Source: Integrated Summary of Efficacy – Tables, Table 13.3.
Note: Percent change from baseline = change from baseline/absolute value at baseline x 100.
Abbreviations: n, number of patients; Max, maximum, Min, minimum; SD, standard deviation

2.3 Relationship Between CSF HVA and Highest Motor Milestone

The reviewer's visual exploration of the relationship between CSF HVA and highest motor milestone achievement in Studies AADC-010 and AADC-011 is presented in Figure 5 and discussed in Section 7.1.4.

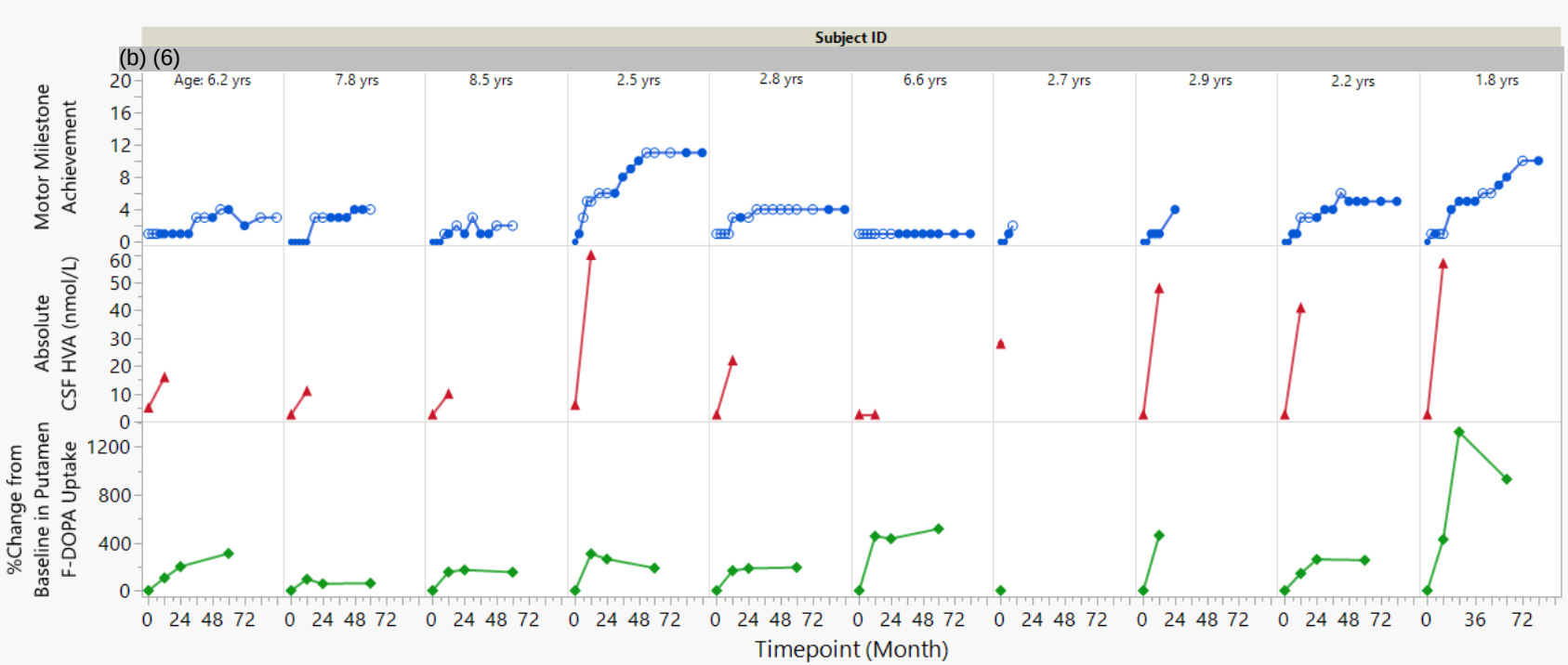
Individual profiles of motor milestone achievement over time are shown in Figure 16 and Figure 17 (by chronological age of patients) along with those of CSF HVA and putamen ^{18}F-DOPA uptake. Overall, motor function improvement occurred after the gene therapy, along with increases in CSF HVA and putamen ^{18}F-DOPA uptake, except for one patient (ID: (b) (6)) who showed no changes in CSF HVA or motor function improvement until Month 84. This patient showed increased ^{18}F-DOPA uptake, though. Of note, anti-AAV2 TAb titer was not higher than that of the other patients.

In some patients (e.g., Patients (b) (6) regression in motor milestone achievement was observed over time.

Reviewer Comment:

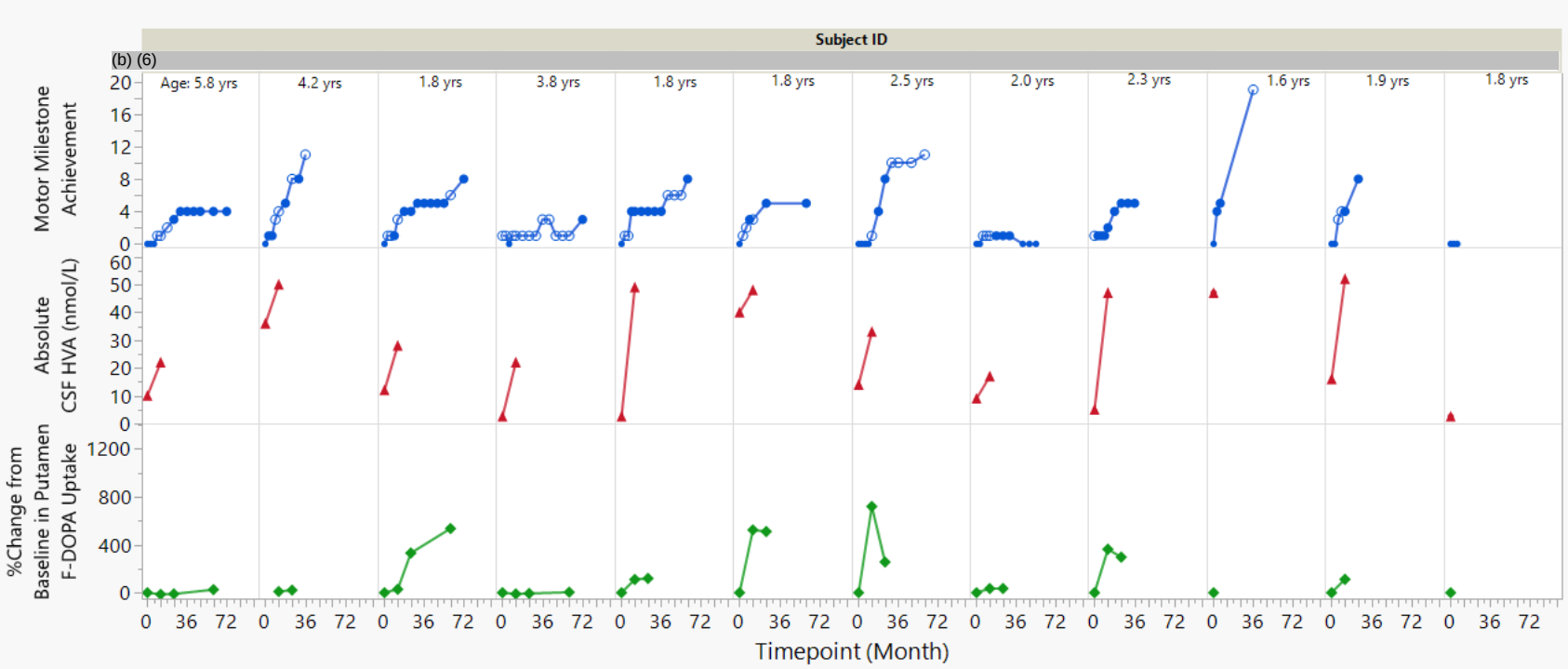
- *In Figure 17, among patients with the same c.714+4A>T homozygous genotype (10/22, 45.5%), variability in response was noted in terms of motor milestone achievement, CSF HVA, and ^{18}F-DOPA uptake was noted. In general, younger patients tended to show earlier improvement of motor function and higher magnitude of changes in CSF HVA and ^{18}F-DOPA uptake.*
- *The regression in motor milestone achievement in these patients suggests possibility that the motor function improvement may not sustain for a long term after the gene therapy.*

Figure 16: Individual Profiles of Motor Milestone Achievement, CSF HVA, and Putamen Specific ^{18}F-DOPA Uptake in Studies AADC-010 and AADC-011



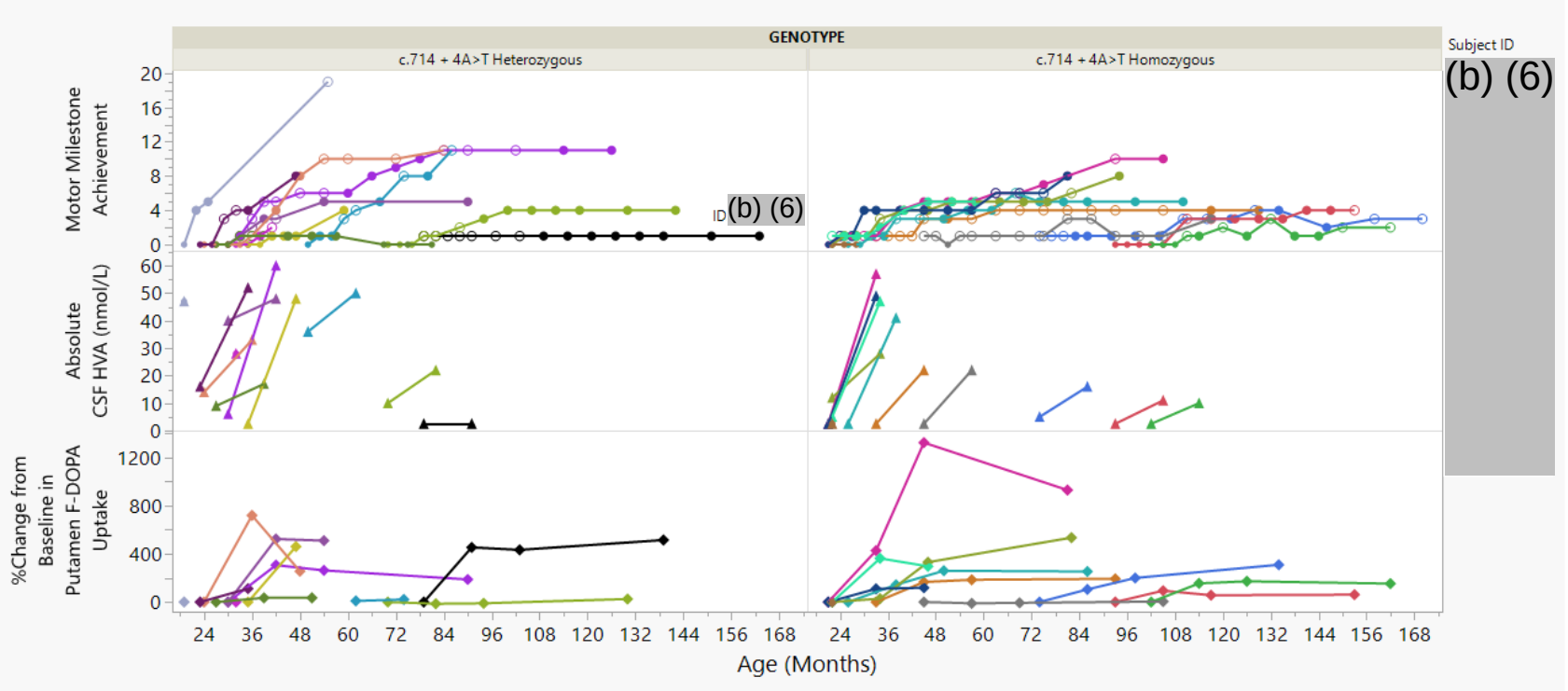
Note: Motor milestones assessed on PDMS-2, 0=none, 1=partial head control, 2=full head control, 3=sitting with assistance, 4=sitting unassisted, 5=standing with support, 6=standing away from support, 7=walking with assistance, 8=free walking, 9=walking upstairs with support, 10=walking backward, 11=walking on taped line, 19 = Running Speed;
Open circles mean emerging skill and closed circles mean mastery of the skill for the motor milestone.
Lower limit of quantification (LLOQ) of CSF HVA was 5 nmol/L, and values reported as <LLOQ was imputed as 0.5*LLOQ.
%change from baseline = change from baseline/absolute value at baseline x 100.
Abbreviations: CSF HVA, homovanillic acid in cerebrospinal fluid, yrs, years old at the time of treatment

(Continued)



Source: Reviewer's analysis based on adfa.xpt of Integrated Summary of Efficacy, and FDAQ14.xpt and FDAQ16.xpt of Applicant's Responses to Information Requests #12 dated July 1, 2024.
Note: Motor milestones assessed on PDMS-2, 0=none, 1=partial head control, 2=full head control, 3=sitting with assistance, 4=sitting unassisted, 5=standing with support, 6=standing away from support, 7=walking with assistance, 8=free walking, 9=walking upstairs with support, 10=walking backward, 11=walking on taped line, 19 = Running Speed;
Open circles mean emerging skill and closed circles mean mastery of the skill for the motor milestone.
Lower limit of quantification (LLOQ) of CSF HVA was 5 nmol/L, and values reported as <LLOQ was imputed as 0.5*LLOQ.
%change from baseline = change from baseline/absolute value at baseline x 100.
Abbreviations: CSF HVA, homovanillic acid in cerebrospinal fluid; yrs, years old at the time of treatment

Figure 17: Motor Milestone Achievement, CSF HVA, and Putamen Specific ^{18}F-DOPA Uptake by Patient, Chronological Age and Genotype in Studies AADC-010 and AADC-011



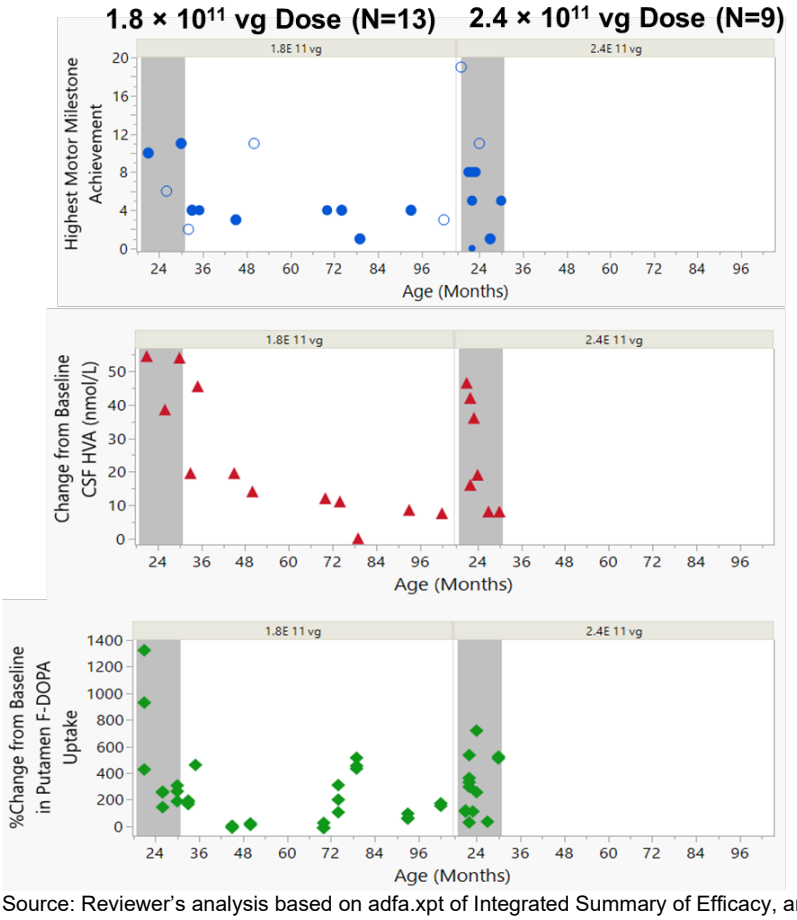
Source: Reviewer's analysis based on adfa.xpt of Integrated Summary of Efficacy, and FDAQ14.xpt and FDAQ16.xpt of Applicant's Responses to Information Requests #12 dated July 1, 2024.
Note: Motor milestones assessed on PDMS-2, 0=none, 1=partial head control, 2=full head control, 3=sitting with assistance, 4=sitting unassisted, 5=standing with support, 6=standing away from support, 7=walking with assistance, 8=free walking, 9=walking upstairs with support, 10=walking backward, 11=walking on taped line, 19 = Running Speed;
Open circles mean emerging skill and closed circles mean mastery of the skill for the motor milestone.
Lower limit of quantification (LLOQ) of CSF HVA was 5 nmol/L, and values reported as <LLOQ was imputed as 0.5*LLOQ.
%change from baseline = change from baseline/absolute value at baseline x 100.
Abbreviations: CSF HVA, homovanillic acid in cerebrospinal fluid

2.4 Dose-Response Relationship

The proposed dose and dosing regimen (i.e., a total dose of 1.8×10^{11} vg as 4 infusions of 0.45×10^{11} vg at two sites per putamen-anterior and posterior) are consistent with the studied dose in Study AADC-002. Since all 13 patients ages 16 to 129 months received the same dose of 1.8×10^{11} vg, dose-response relationship cannot be evaluated in this study.

In Studies AADC-010 and AADC-011, using the product manufactured by Process B, 13 patient ages 21 to 102 months received a total dose of 1.8×10^{11} vg, and the other 9 patients ages 19 to 30 months received 2.4×10^{11} vg (33% higher dose). However, while the data are limited, no dose-dependent trend appeared between two dose groups in terms of the highest motor milestone achieved, change from baseline in CSF HVA, or percent change from baseline in putamen-specific ^{18}F-DOPA uptake, even when was compared between patients with the same age range (19 to 30 months of age) (Figure 18).

Figure 18: Comparison of Highest Motor Milestone Achievement, Change From Baseline in CSF HVA, Percent Change From Baseline in Putamen Specific ^{18}F-DOPA Uptake by Dose Groups (1.8×10^{11} vg vs. 2.4×10^{11} vg) in Studies AADC-010 and AADC-011



Source: Reviewer's analysis based on adfa.xpt of Integrated Summary of Efficacy, and FDAQ14.xpt and FDAQ16.xpt of Applicant's Responses to Information Requests #12 dated July 1, 2024.
Note: Vertical gray area represents age of patients at the time of treatment from 19 to 30 months.
Motor milestones assessed on PDMS-2, 0=none, 1=partial head control, 2=full head control, 3=sitting with assistance, 4=sitting unassisted, 5=standing with support, 6=standing away from support, 7=walking with assistance, 8=free walking, 9=walking upstairs with support, 10=walking backward, 11=walking on taped line, 19 = Running Speed;
Open circles mean emerging skill and closed circles mean mastery of the skill for the motor milestone.
Lower limit of quantification (LLOQ) of CSF HVA was 5 nmol/L, and values reported as <LLOQ was imputed as 0.5*LLOQ.
Putamen specific ^{18}F-DOPA uptake measured at Month 12, 24, and 60 were pooled. %change from baseline = change from baseline/absolute value at baseline x 100.
Abbreviations: CSF HVA, homovanillic acid in cerebrospinal fluid

Table 27: Change in Feeding Status of Patients Treated in Study AADC-002

Patient Status at Study Timepoint (Days Pre/Post-Treatment)	Able To Receive Food By Mouth	Use Of Feeding Tube (Type)	Change in Feeding Status
(b) (6)	-	-	-
Screening (-56)	No	Yes (G-tube)	No
Baseline (-8)	No	Yes (G-tube)	No
Week 48 (337)	No	Yes (G-tube)	No
(b) (6)	-	-	-
Screening (-77)	No	Yes (G-tube)	No
Baseline (-7)	No	Yes (G-tube)	No
Week 24 (185)	Yes	Yes (G-tube)	Yes
Week 48 (338)	Yes	Yes (G-tube)	No
Week 72 (632)	Yes	Yes (G-tube)	No
Week 96 (709)	Yes	Yes (G-tube)	No
(b) (6)	-	-	-
Screening (-63)	Yes	No	No
Baseline (-7)	Yes	No	No
Day 1 (1)	Yes	No	No
Week 48 (336)	Yes	No	No
(b) (6)	-	-	-
Screening (-63)	Yes	No	No
Baseline (-7)	Yes	No	No
Day 1 (1)	Yes	No	No
W96 (701)	Yes	No	No
(b) (6)	-	-	-
Screening (-56)	Yes	Yes (G-tube)	No
Baseline (-7)	Yes	Yes (G-tube)	No
Day 1 (1)	Yes	Yes (G-tube)	No
Week 96 (673)	Yes	Yes (G-tube)	No
(b) (6)	-	-	-
Screening (-63)	Yes	No	No
Baseline (-8)	Yes	No	No
Day 1 (1)	Yes	No	No
(b) (6)	-	-	-
Screening (-70)	No	Yes (G-tube)	No
Baseline (-7)	No	Yes (G-tube)	No
Day 1 (1)	No	Yes (G-tube)	No
Week 48 (337)	No	Yes (G-tube)	No
Week 72 (504)	Yes	No	Yes
(b) (6)	-	-	-

Patient Status at Study Timepoint (Days Pre/Post-Treatment)	Able To Receive Food By Mouth	Use Of Feeding Tube (Type)	Change in Feeding Status
Screening (-76)	Yes	No	No
Baseline (-8)	Yes	No	No
Week 48 (334)	Yes	No	No
(b) (6)	-	-	-
Screening (-82)	Yes	No	No
Baseline (-26)	Yes	No	No
Week 48 (336)	Yes	No	No
(b) (6)	-	-	-
Screening (-62)	Yes	No	No
Baseline (-7)	Yes	No	No
Week 8 (59)	Yes	No	No
(b) (6)	-	-	-
Screening (-97)	Yes	No	No
Baseline (-42)	Yes	No	No
Week 48 (384)	Yes	No	No
(b) (6)	-	-	-
Screening (-65)	Yes	No	No
Baseline (-7)	Yes	No	No
Week 48 (335)	Yes	No	No
(b) (6)	-	-	-
Screening (-70)	Yes	No	No
Baseline (-8)	Yes	No	No
Day 3 (6)	Yes	Yes (NG tube)	Yes*
Week 3 (23)	Yes	No	Yes*
Week 8 (55)	No	Yes (NG tube)	Yes*
Week 12 (86)	Yes	No	Yes*
Week 48 (337)	Yes	No	No

Source: Table 2 in Applicant's Response to Information Request #12
received NG feeding under anesthesia at Week 8
Abbreviations: NG, nasogastric; G, gastric