Policy Number	**RX501.178**
Policy Effective Date	**11/15/2025**

Gene Therapy for Aromatic L-amino Acid Decarboxylase Deficiency

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of and developed by nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For Illinois only: Illinois Public Act 103-0458 [Insurance Code 215 ILCS 5/356z.61] (HB3809 Impaired Children) states all group or individual fully insured PPO, HMO, POS plans amended, delivered, issued, or renewed on or after January 1, 2025 shall provide coverage for therapy, diagnostic testing, and equipment necessary to increase quality of life for children who have been clinically or genetically diagnosed with any disease, syndrome, or disorder that includes low tone neuromuscular impairment, neurological impairment, or cognitive impairment.

Coverage

Eladocagene exuparvovec-tneq (Kebilidi™) **may be considered medically necessary** for individuals if they meet **all** criteria below:

- Meets any 1 of the 3 diagnostic criteria for aromatic L-amino acid decarboxylase deficiency
  - Biallelic pathogenic/likely pathogenic variants in *dopa decarboxylase (DDC)* gene; **OR**
  - One pathogenic/likely pathogenic variant plus a variant of uncertain significance AND aromatic L-amino acid decarboxylase enzyme activity in plasma < 5% **OR** cerebrospinal fluid or plasma neurotransmitter profile consistent with aromatic L-amino acid decarboxylase deficiency (see Policy Guidelines); **OR**
  - Two variants of uncertain significance AND aromatic L-amino acid decarboxylase enzyme activity in plasma < 5% OR cerebrospinal fluid or plasma neurotransmitter profile consistent with aromatic L-amino acid decarboxylase deficiency (see Policy Guidelines);
- Has persistent neurological defects (e.g., autonomic dysfunction, hypotonia, dystonia and other movement disorders, etc.);
- Has anti-AAV2 (Adeno-Associated Virus 2) antibody titer <1:1,200;
- Achieved skull maturity assessed by neuroimaging to allow placement of the stereotactic head frame for surgery.

Eladocagene exuparvovec-tneq (Kebilidi™) **is considered not medically necessary** when the above criteria are not met.

Eladocagene exuparvovec-tneq (Kebilidi™) **is considered experimental, investigational and/or unproven** for all other indications.

Repeat treatment with Eladocagene exuparvovec-tneq (Kebilidi™) **is considered experimental, investigational and/or unproven.**

Policy Guidelines

Recommended Dose
Per the U.S. Food and Drug Administration (FDA) label, the recommended dose is 1.8×10^{11} vector genomes delivered as four 0.08 mL (0.45×10^{11} vg) infusions (two sites per putamen-anterior and posterior) at a rate of 0.003 mL/minute (0.18 mL/hour) for a total of 27 minutes per site, administered in a single stereotactic surgery using a cannula that is FDA-authorized for intraparenchymal infusion.

Dosing Limits
One injection per lifetime.

Supportive Laboratory Findings on Neurometabolites Panel
Cerebrospinal fluid neurotransmitter profile typically demonstrates:

- Low levels of 5-hydroxyindoleacetic acid (5-HIAA), homovanillic acid (HVA), and 3-methoxy-4-hydroxyphenylglycol (MHPG);
- Normal concentrations of pterins (neopterin and biopterin);
- High concentrations of levodopa, 3-O-methyldopa (3-methoxytyrosine; 3-OMD), and 5-hydroxytryptophan (5-HT).

Plasma neurotransmitter (untargeted metabolomics) profile typically demonstrates:
- High level of 3-OMD;
- Low levels of 5-HIAA, vanillylmandelate (VMA), HVA, and dopamine-3-O-sulfate (D3OS);
- Low to normal level of 3-methoxytyramine sulfate (3-MTS);
- Increased urinary concentration of vanillactic acid (VLA).

Other Considerations

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology- "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"- to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Disease-associated change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. American College of Medical Genetics and Genomics and the Association for Molecular Pathology Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence

Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

Definition of Bi-allelic Variant

- Biallelic pathogenic/likely pathogenic variants in *DDC*; **OR**
- One pathogenic/likely pathogenic variant plus a variant of unknown significance; **OR** cerebrospinal fluid (CSF) **OR** plasma neurotransmitter profile consistent with AADC deficiency (see above) **AND** significantly reduced activity of the enzyme AADC in plasma;
- Two variants of unknown significance **AND** CSF **OR** plasma neurotransmitter profile consistent with AADC deficiency (see above) **AND** significantly reduced activity of the enzyme AADC in plasma.

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Description

Aromatic L-amino acid decarboxylase (AADC) deficiency is a rare autosomal recessive neurodevelopmental disorder caused by biallelic pathogenic variants in the *DDC* gene, resulting in reduced or absent activity of the AADC enzyme. This enzyme, expressed in both central and peripheral tissues, catalyzes the conversion of L-DOPA and 5-hydroxytryptophan into the neurotransmitter's dopamine and serotonin, respectively. AADC deficiency leads to impaired synthesis of dopamine, serotonin, norepinephrine, and epinephrine, contributing to a broad spectrum of clinical manifestations. The phenotypic spectrum is heterogenous and reflect deficits in monoaminergic neurotransmission. Phenotype ranges from mild (e.g., mild delay in developmental milestones, ambulatory without assistance, mild intellectual disability) to severe (e.g., no or very limited developmental milestones, fully dependent on caregivers). Approximately 80% of affected individuals present with severe phenotype. Dopamine deficiency primarily contributes to motor symptoms such as hypotonia, dystonia, delayed motor development, and oculogyric crises; norepinephrine and epinephrine deficiencies affect autonomic functions including ptosis, hypoglycemia, and hypotension; serotonin deficiency may impair cognition, voluntary movement, and emotional regulation. Prior to the approval of eladocagene exuparvovec, no U.S. Food and Drug Administration (FDA)-approved therapies

were available. Standard of care involved off-label use of oral medications such as dopamine agonists, monoamine oxidase inhibitors, and pyridoxine, though their efficacy and durability remain poorly characterized due to limited case reports. Eladocagene exuparvovec is a recombinant adeno-associated virus serotype 2 based vector gene therapy product containing the complementary DNA of the human *DDC* gene under the control of the cytomegalovirus immediate-early promoter. It is produced in human embryonic kidney cells by recombinant DNA technology. It is administered in a single stereotactic surgery using a cannula that is FDA-authorized for intraparenchymal infusion.

Aromatic L-amino Acid Decarboxylase Deficiency

Aromatic L-amino acid decarboxylase (AADC) deficiency is a is a rare autosomal recessive disorder caused by pathogenic variants in the *DDC* gene, which encodes the AADC enzyme). (1) This enzyme is essential for synthesizing key neurotransmitters dopamine and serotonin by converting their precursors, L-DOPA and 5-hydroxytryptophan, respectively. AADC is expressed in both central and peripheral tissues. Loss or reduction of AADC activity leads to impaired production of dopamine, serotonin, norepinephrine, and epinephrine, resulting in accumulation of precursors and reduced levels of neurotransmitter metabolites. (2)

Clinical symptoms typically emerge in infancy and vary widely. (3, 2) This variability in clinical presentation is related to deficiencies in dopamine, epinephrine, norepinephrine, and serotonin. Generally, decreased dopamine levels are responsible for movement-related symptoms such as hypotonia, dystonia, delayed motor development, and oculogyric crisis. Epinephrine and norepinephrine deficiencies affect autonomic functions such as ptosis, hypoglycemia, or hypotension. Serotonin deficiency can affect cognitive function, voluntary movement, and emotional state. AADC deficiency is broadly categorized into mild, moderate, and severe phenotypes.

- The severe phenotype is characterized by profound motor impairment, including the absence of head control and failure to achieve motor milestones. Affected individuals often experience severe hypotonia, feeding difficulties, oculogyric crises (prolonged dystonic eye and facial movements), and autonomic dysfunction. These patients are fully dependent on caregivers and may face early mortality due to complications from hypotonia and autonomic instability.
- The moderate phenotype includes patients who attain some motor milestones, such as head control, sitting, or standing, but are unable to walk independently. Symptoms are less severe than in the severe form but still significantly impact daily function.
- The mild phenotype involves less pronounced motor impairment, with individuals often achieving independent ambulation. These patients may live into adulthood and primarily exhibit autonomic symptoms, sleep disturbances, and behavioral issues, with minimal or no motor dysfunction.

Approximately 80% of patients exhibit a severe phenotype (3) and require lifelong care. Disease symptoms do not spontaneously improve, and death often occurs in the first decade of life. The disease significantly impacts the quality of life of patients and their caregivers.

Epidemiology

Prevalence of AADC deficiency globally and within the United States is unknown, with fewer than 400 confirmed cases reported worldwide to date. (4) Wassenberg et al. (2017) has identified 117 case reports in the literature, and estimated prevalence is roughly 1-2 in 1,000,000 newborns per the National Organization for Rare Disorders. (2) The condition appears to be more common in certain Asian populations, particularly in Taiwan, China, and Japan, likely due to a founder mutation. (5, 1)

Diagnosis

AADC deficiency is frequently underdiagnosed or misdiagnosed due to its rarity and overlapping symptoms with more common neurological disorders such as cerebral palsy or epilepsy. (6, 7) Although clinical signs typically emerge within the first few months of life, diagnosis is often delayed until childhood or even adulthood. Data from international patient registries show that while the average age of symptom onset is around 2.5 to 2.7 months, the average age at diagnosis can range from 9 months to over 3 years, with some cases diagnosed as late as the third decade of life. (8, 2) This delay can lead to inappropriate management, missed opportunities for early intervention, and worsening of disease-related complications. Timely and accurate diagnosis is essential to initiate appropriate therapies, support developmental outcomes, and reduce the burden on patients and caregivers. (9, 3) Core diagnostic tests for AADC deficiency include single gene or genetic panel testing, CSF neurotransmitter metabolites panel, and a plasma AADC enzyme assay. (2) To confirm a diagnosis of AADC deficiency, at least 2 of the 3 core diagnostic tests should be positive. See Table 1.

Table 1. Diagnostic Tests to Confirm AADC Deficiency (1, 2)

Test	Description
CSF neurotransmitter metabolites panel	• Decreased 5-HIAA, HVA, and MHPG, plus • Increased 3-OMD, L-dopa, and 5-HTP, plus • Normal pterins
Single gene or genetic panel testing	Pathogenic variants in the DDC gene
Plasma enzyme assay	Plasma enzyme assay

3-OMD: 3-O-methyldopa; 5-HIAA: 5-hydroxyindoleacetic acid; 5-HTP: 5-hydroxytryptophan; AADC: aromatic L-amino acid decarboxylase; CSF: cerebrospinal fluid; DDC: dopa decarboxylase; HVA: homovanillic acid; L-dopa: levodopa; MHPG: 3-methoxy-4hydroxyphenylglycol.

AADC deficiency is currently not on the Recommended Uniform Screening Panel (RUSP) list of health conditions that experts recommend newborn screening in the U.S. There is growing interest and research around the potential for newborn screening for AADC deficiency. A specific test that measures 3-O-methyldopain dried blood spots has been evaluated in a clinical trial in Taiwan as a candidate screening test. (10)

Treatment

Until recently, there were no FDA-approved therapies for AADC deficiency. Current approach has relied on off-label use of oral medications such as dopamine agonists, monoamine oxidase inhibitors, and pyridoxine (vitamin B6). These treatments have shown limited and variable

effectiveness. (11) Patients with the severe phenotype typically show no improvement in motor function. In contrast, individuals with mild or moderate phenotypes may experience notable gains in motor milestones such as improved head control, sitting, standing, or walking following dopamine agonist therapy. Additional benefits may include reductions in hypotonia, oculogyric crises, and autonomic symptoms. (7) However, due to the rarity of the disease and the limited number of published case reports, the response rate and long-term effectiveness of these therapies remain poorly characterized. Current management strategies may also be limited by undesirable side effects, which may lead to discontinuation of therapy. Consequently, there remains a significant unmet medical need for an FDA-approved therapy that can address the underlying cause of AADC deficiency across all phenotypes.

Regulatory Status

On November 13, 2024, eladocagene exuparvovec-tneq suspension (Kebilidi™) was approved by the U.S. Food and Drug Administration (FDA) for the treatment of adult and pediatric individuals with aromatic 13 L-amino acid decarboxylase (AADC) deficiency. This indication was approved under accelerated approval based on change from baseline in gross motor milestone achievement at 48 weeks post-treatment. Continued approval for this indication may be contingent upon verification and description of benefit in a confirmatory clinical trial.

Eladocagene exuparvovec-tneq was approved as Upstaza by the European Medicines Agency on July 18, 2022, by the United Kingdom's Medicinal Health Products Regulatory Agency in November 2022, and by Israel Ministry of Health in February 2023 for pediatric patients 18 months and older with the severe phenotype of AADC deficiency.

Rationale

Medical policies assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trials preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less

common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Aromatic L-amino Acid Decarboxylase Deficiency

Clinical Context and Therapy Purpose

The purpose of eladocagene exuparvovec-tneq in individuals with aromatic L-amino acid decarboxylase (AADC) deficiency is to provide a treatment option that is an improvement on existing therapies. Potential benefits of this one-time therapy may include the following:

- Novel mechanism of action or approach may allow successful treatment of patients for whom other available treatments have failed.
- Successful treatment may reduce the potential for disease and standard treatment-related morbidity and mortality and improve quality of life.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population(s) of interest are individuals with AADC deficiency.

Interventions

The therapy being considered is eladocagene exuparvovec.

Eladocagene exuparvovec is a recombinant adeno-associated virus serotype 2-based gene therapy designed to deliver a copy of the *DDC* gene that encodes the AADC enzyme. Intraputaminal infusion of eladocagene exuparvovec results in AADC enzyme expression and subsequent production of dopamine in the putamen.

Comparators

The off-label use of the following therapies is considered standard of care (SoC)- dopamine agonists, monoamine oxidase inhibitors, and pyridoxine. (2) Patients with the severe phenotype of AADC deficiency do not demonstrate any improvements in motor function in response to these SoC therapies. Initiation of dopamine agonists in patients with the mild and moderate phenotype can result in rapid improvements in gross motor function and achievement of new motor milestones (including improvements in head control, sitting, standing and walking) that would be unexpected in these phenotypes. Improvements in hypotonia, oculogyric crises, and autonomic dysfunction have also been reported. (7) Due to the rarity of the disease and the limited case reports published in the literature, both responder rate and durability of standard of care medications is not characterized. There remains an unmet medical need for an FDA-approved treatment to address AADC deficiency, regardless of phenotype.

Outcomes

The general outcomes of interest are overall survival, disease-specific survival, change in disease status, functional outcomes, quality of life, treatment-related morbidity, and treatment-related mortality (Table 2). Follow-up at 15 years is of interest to monitor outcomes.

Table 2. Health Outcome Measures Relevant to Aromatic L-amino Acid Decarboxylase Deficiency

Outcome	Measure (Units)	Description and Administration	Thresholds for Improvement/Decline or Clinically Meaningful Difference (if known)
PDMS-2	PDMS-2 is a scale composed of 6 subtests that measure the motor abilities of the subject. Each item is scored as 0 (having no ability), 1 (an emerging skill), or 2 (mastery of the motor milestone), and scores are summed to give a total PDMS-2 score	20-30 minutes for each motor-related subtest or 45-60 minutes for entire assessment. This early childhood motor development program contains six subtests that assess the motor skills of children. 1. Reflexes: The subtest measures a child's ability to automatically react to environmental events. 2. Stationary: The subtest measures a child's ability to sustain control of his or her body within its center of gravity and retain equilibrium. 3. Locomotion: The subtest measures a child's ability to move from one place to another. The actions measured include crawling, walking, running, hopping, and jumping forward. 4. Object Manipulation: The subtest measures a child's ability to manipulate balls. Examples of the actions measured include catching, throwing, and kicking. 5. Grasping: The subtest measures a child's ability to use his or her hands. 6. Visual-Motor Integration: The subtest measures a	PDMS-2 is interpreted by comparing a child's performance on six subtests to a standardized sample of children. Scores are converted to age equivalents, percentile ranks, scaled scores, and composite index scores, including Gross Motor Quotient, Fine Motor Quotient, and Total Motor Quotient. These scores help determine a child's motor competence relative to their peers and identify areas of strength and weakness.

		child's ability to use his or her visual perceptual skills to perform complex eye-hand coordination tasks such as reaching and grasping for an object, building with blocks, and copying designs.	

PDMS: Peabody Developmental Motor Scale, Second Edition.
Cite: Folio R, Fewell R. Peabody developmental motor scales-2 (2nd ed.). Austin, TX: Pro-Ed; 2000

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

The clinical development program is summarized in Table 3 and consists of multiple interventional and observational studies. All studies are single-arm, open-label trials. The severity of AADC deficiency, the rarity of the disease, the lack of authorized treatment options, and the risk of disease progression precluded the conduct of a RCT in the target patient population. The FDA approval was based on the pivotal AADC-002 single-arm study. The manufacturer proposed using the surrogate outcomes of cerebrospinal fluid homovanillic acid as the primary endpoint to support accelerated approval. FDA reviewers concluded that the evidence was insufficient to establish HVA as a surrogate reasonably likely to predict clinical benefit and recommended using motor milestone achievement as the primary efficacy endpoint. However, motor milestone achievement was planned to be assessed at 2 years of age. However, up to the March 1, 2024 data cut, the median duration of follow-up among the treated patients was only 82 weeks (range 23 to 109 weeks). Consequently, motor milestone achievement at week 48 was used instead as an intermediate clinical efficacy endpoint to support accelerated approval in FDA's review of the application. All patients (except for one subject who withdrew at 23 weeks) reached 48 weeks of follow-up. (12, 13)

The natural history cohort was sourced from a comprehensive review of published AADC deficiency literature through July 2022 which identified 156 publications that met the inclusion criteria. These 156 studies reported data on 288 unique patients with high-quality data that identified them as unique patients with high certainty. Disease phenotype (severity) was

classified based on the achievement of motor milestones at the age of 24 months. The disease phenotypes were adjudicated to identify those that had similar disease characteristics (severe phenotype) as those included in clinical trials for eladocagene exuparvovec-tneq and hence could be used as a historical control. After adjudication, a group of 51 unique patients who had not participated in clinical studies for eladocagene exuparvovec-tneq and had similar disease phenotypes to the study patients (described as having no or little motor milestone achievement at 24 months) in the gene therapy clinical studies. These patients were used as a control group to compare acquisition of motor milestones with eladocagene exuparvovec-tneq-treated patients in study AADC-002. Among the 51 pediatric patients with the severe phenotype who were included in the natural history cohort, 8 pediatric patients were further excluded by the FDA clinical review teams. Among these eight pediatric patients, three likely did not have the severe phenotype.

Table 3. Summary of the Clinical Development Program for Eladocagene Exuparvovec

Study	NCT No.	Phase	Study Population	Status	Study Dates	Design	Sample Size	Follow-up
Pivotal Study								
AADC-002	NCT04903288	2	Individuals with genetically confirmed AADC deficiency	Ongoing	2021-2028	Single arm, multi-center	13	60 mo
Supportive Studies								
AADC-CU/1601	Not available	Compassionate Use Study	Individuals aged ≥2 years with a confirmed diagnosis of AADC deficiency (i.e., per CSF neurotransmitter metabolite profile or presence of 1 pathogenic variant in the DDC gene)	Ongoing	NA	Single arm	8	60 mo
AADC-010	NCT01395641	1/2	Individuals aged ≥2 years with a confirmed diagnosis of	Completed and published (14, 15)	2014-2022	Single arm, single center	10	60 mo

			AADC deficiency (i.e., per CSF neurotransmitter metabolite profile or presence of >1 pathogenic variant in the DDC gene)			(Taiwan)		
AADC-011	NCT02926066	2b	Individuals aged ≥2 years with a confirmed diagnosis of AADC deficiency (i.e., per CSF neurotransmitter metabolite profile or presence of >1 pathogenic variant in the DDC gene)	Completed and published (15)	2016 - 2022	Single arm, single center (Taiwan)	12	12 mo
AADC-1602	Not available	-	Pooled analysis of participants across 3 single-arm clinical trials (AADC-CU/1601, AADC-010, and AADC-011)	Ongoing	-	Pooled analysis	30	-

AADC: Aromatic L-amino acid decarboxylase; CSF: cerebrospinal fluid; DDC: dopa decarboxylase; mo: months; NA: not available; NCT: national clinical trial.

Pivotal Study

Study characteristics, baseline patient characteristics, and results are summarized in Tables 4 to 6, respectively.

AADC-002 is an open-label, single arm study that enrolled 13 pediatric patients with genetically confirmed, severe AADC deficiency who had achieved skull maturity assessed with neuroimaging. The main efficacy outcome measure was gross motor milestone achievement evaluated at week 48 and assessed using the Peabody Developmental Motor Scale, Second

Edition (PDMS-2). Patients treated with eladocagene exuparvovec were compared to an external untreated natural history cohort of 43 pediatric patients with severe AADC deficiency who had at least one motor milestone assessment after 2 years of age. Twelve of the 13 patients had the severe phenotype of AADC deficiency, defined as having no motor milestone achievement at baseline and no clinical response to standard of care therapies. The one remaining patient had a "variant" of the severe disease phenotype, with the ability to sit with assistance but with lack of head control. One study participant who withdrew consent at week 23 and dropped out of the study was excluded from the analysis. Eight (67%) of the 12 treated patients achieved a new gross motor milestone at week 48: 3 patients achieved full head control, 2 patients achieved sitting with or without assistance, 2 patients achieved walking backwards and the patient with the "variant" severe phenotype was able to sit unassisted. The two patients who achieved walking backwards at week 48 were treated before 2 years of age. The four patients who were unable to achieve new gross motor milestones at week 48 were treated between the ages of 2.8 and 10.8 years. In comparison, none of the 43 untreated patients with the severe phenotype had documented motor milestone achievement at last assessment at a median age of 7.2 years (range 2 to 19 years). No formal statistical hypothesis testing was planned in study AADC-002, and sample size was not based on statistical power consideration, rather, it was based on feasibility. (12)

Table 4. Summary of Pivotal Study

Study	Study Type	Country	Dates	Participants	Treatment	Follow-up
AADC-002 (NCT04903288) (13, 16)	Single-arm, prospective	U.S., Israel, and Taiwan	2010-2018	Inclusion criterion • Pediatric patients aged ≥1 year with genetically confirmed AADC deficiency • Cranium sufficiently developed to allow placement of stereotactic frame for surgery Exclusion criterion • Anti-AAV2 antibody titer >1:1,200 Co-primary endpoints at week 8 (as per protocol):	Eladocagene exuparvovec at 1.8 X 10^{11} vg by bilateral infusion into the putamen in a single operative session (n=13) Patients also received standard of care for their AADC deficiency during the study.	Intended follow-up: 60 months Actual follow-up at the time of FDA approval: 82 weeks (range 23 to 109 weeks). All patients (except for one subject who withdrew at 23 weeks) reached 48 weeks of follow-up.

				• Change from baseline in CSF HVA at week 8 • AEs associated with the SmartFlow MR-compatible ventricular cannula during the 8-week trial period <u>Secondary endpoints:</u> • Change from baseline in bilateral putaminal-specific 18F-DOPA uptake, as measured by PET analysis at week 8 and week 48 • Change from baseline in CSF HVA at week 48; • Attainment of key motor milestones during the 60 months after administration of eladocagene exuparvovec-tneq, as measured by the PDMS-2 • Overall safety profile of eladocagene		

				exuparvovec-tneq during the study		

AADC: aromatic L-amino acid decarboxylase; AAV2: Adeno-associated virus type 2; AE: adverse events; CSF: cerebrospinal fluid; DOPA: dopamine; FDA: food and drug administration; HVA: homovanillic acid; MR: magnetic resonance; PET: positron emission tomography; PDMS-2: Peabody developmental motor scales-second edition; U.S.: United States; VG: vector genome.

Table 5. Summary of Baseline Demographics and Disease Characteristics in the Pivotal Study (12)

Characteristic	**All patients (N=13)**
Age (months), mean (±SD)	
At symptom onset	2.0 (1.84)[a]
At diagnosis	13.3 (10.7)[b]
At screening	42.8 (29.9)
At gene therapy	45.2 (29.5)
Male, n (%)	6 (46.2)
Height, cm, mean (±SD)	92.4 (15.3)
Weight, kg, mean (±SD)	12.6 (5.2)
Ethnicity, n (%)	
Hispanic or Latino	2 (15.4)
Not Hispanic or Latino	10 (76.9)
Unknown	1 (7.7)
Race, n (%)	
Asian-Chinese	10 (76.9)
White	2 (15.4)
Other	1 (7.7)
Genotype, n (%)	
Homozygous	2 (15.4)
Heterozygous	11 (84.6)

[a] n=11

[b] n=12

SD: standard deviation

Table 6. Summary of Results in the Pivotal Study (12)

Motor Milestone at Mastery Level[a], n (%)	**At Baseline (n=13)**	**Week 48 (n=12)**	**Natural History Cohort/External Control (n=43)**
Full head control	0 (0)	8 (67%)	0 (0)
Sitting with assistance	0 (0)	5 (42%)	0 (0)
Sitting unassisted	0 (0)	4 (33%)	0 (0)
Standing with support	0 (0)	2 (17%)	0 (0)

Walking with assistance	0 (0)	2 (17%)	0 (0)

[a] Motor milestones achieved at mastery level is defined as earning a score of 2 on the Peabody developmental motor scales- second edition.
Note: Motor milestones are acquired sequentially, i.e., in the following order: full head control to walking with assistance. The study is still ongoing with only 3 patients having motor assessment at week 72 and week 96 visit by May 20, 2024.

The purpose of the study limitations tables (see Tables 7 and 8) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement. Multiple limitations were noted. The FDA approved eladocagene exuparvovec based on new motor milestone achievement at week 48 compared to an untreated natural history cohort. While FDA describes the post hoc analysis of motor milestone achievement as an intermediate endpoint as the basis for accelerated approval, for the purpose of this review motor milestone achievement is considered a clinically meaningful outcome and appropriate for evaluating clinical benefit. The primary source of uncertainty stems from the post hoc nature of the analysis and the strong assumption of comparability between the treated cohort and the external historical control. Single-arm studies are inherently vulnerable to bias due to potential unmeasured differences between groups. Additionally, the natural history cohort data were sparse and inconsistent with highly variable time spans between the first and last reported motor milestone assessments (e.g., some did not have data at earlier age). This limits the ability to match patients and compare outcomes at equivalent time points between the groups. Despite these limitations, the use of single-arm studies and external controls is considered methodologically acceptable in the context of a rare disease with no approved therapies. Several contextual factors support the conclusion of clinical benefit.

- All enrolled patients had severe AADC deficiency, were at least two years old at baseline, exhibited poor or absent head control, and had no response to standard therapies. A substantial proportion achieved motor milestones by week 48 that exceeded expectations based on the natural history of the disease.
- The observed treatment effect was large, which increases confidence in the findings and reduces the likelihood that the results are solely attributable to bias or confounding.
- Pharmacodynamic data demonstrated post-treatment increases in levels of homovanillic acid in the CSF as a downstream metabolite of dopamine and putamen specific 18F-DOPA uptake indicating increases in AADC activity.
- Known risks, including procedural complications and dyskinesia, are considered manageable with appropriate monitoring and treatment. These risks are deemed acceptable given the severity of AADC deficiency and the absence of alternative treatment options.

Nonetheless, important limitations remain: First, limited sample size limit the precision of estimates, particularly for adverse events. Rare but serious harms may not be captured in clinical trials, and long-term safety remains uncertain. Second, the available data primarily reflect outcomes in patients with severe disease; evidence for treatment effects in milder phenotypes is limited.

Table 7. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
AADC-002 (16)	5. Other majority (76.9%) of patients are Asian in this study		5. Other (external historical control)		1. Not sufficient duration for benefit; 2. Not sufficient duration for harms

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.

[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 8. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
AADC-002 (16)	1. Participants not randomly allocated; 4. Inadequate control for selection bias	1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician;			1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Section Summary: Aromatic L-amino Acid Decarboxylase Deficiency

The primary evidence supporting the safety and effectiveness of eladocagene exuparvovec was derived from an open-label, single-arm study involving 13 pediatric patients with genetically confirmed AADC deficiency. Effectiveness was assessed at 48 weeks based on the achievement of new gross motor milestones, measured using the PDMS-2 scale, and compared to an external, untreated natural history cohort. One participant withdrew consent at week 23 and was excluded from the final analysis. Among the remaining 12 treated patients, 8 (67%) achieved at least one new gross motor milestone by week 48. Specifically, 3 patients achieved full head control, 2 patients achieved sitting (with or without assistance), 2 patients achieved walking backward, and 1 patient with a variant severe phenotype achieved unassisted sitting. In contrast, none of the 43 untreated patients with severe AADC deficiency in the natural history cohort had documented motor milestone achievement at their last assessment at a median age of 7.2 years (range 2 to 19 years). Notable limitations include 1) Single-arm design and reliance on an external historical control introduce potential biases and limit the ability to accurately estimate treatment effects; 2) Limited number of participants reduces statistical precision, particularly for safety outcomes. Rare but serious adverse events may not be captured, and long-term safety remains uncertain; 3) The data primarily reflect outcomes in patients with severe phenotypes; evidence for efficacy in milder forms of AADC deficiency is limited; and 4) Long-term durability of treatment benefits and safety remain uncertain. Despite these limitations, the study design is considered methodologically acceptable in the context of a rare disease with no approved therapies. Several contextual factors support the conclusion of clinical benefit including large treatment effect size, which increases confidence in the findings and reduces the likelihood that the results are solely attributable to bias or confounding. Pharmacodynamic data also demonstrated post-treatment increases in levels of homovanillic acid in the CSF as a downstream metabolite of dopamine and putamen specific 18F-DOPA uptake indicating increases in AADC activity. Known risks, including procedural complications and dyskinesia, are considered manageable with appropriate monitoring and treatment. These risks are deemed acceptable given the severity of AADC deficiency and the absence of alternative treatment options.

Summary of Evidence
For individuals with AADC deficiency who receive eladocagene exuparvovec, the evidence includes an open-label, single-arm study compared with an external natural history cohort. Relevant outcomes are overall survival, disease-specific survival, change in disease status, functional outcomes, quality of life, treatment-related morbidity and treatment-related mortality. The single-arm study enrolled 13 pediatric patients with genetically confirmed AADC deficiency. Effectiveness was assessed at 48 weeks based on the achievement of new gross motor milestones, measured using the PDMS-2 scale, and compared to an external, untreated natural history cohort. One participant withdrew consent at week 23 and was excluded from the final analysis. Among the remaining 12 treated patients, 8 (67%) achieved at least one new gross motor milestone by week 48. Specifically, 3 patients achieved full head control, 2 patients achieved sitting (with or without assistance), 2 patients achieved walking backward, and 1 patient with a variant severe phenotype achieved unassisted sitting. In contrast, none of the 43 untreated patients with severe AADC deficiency in the natural history cohort had documented motor milestone achievement at their last assessment at a median age of 7.2 years (range 2 to 19 years). Notable limitations include 1) Single-arm design and reliance on an external historical control introduce potential biases and limit the ability to accurately estimate treatment effects. 2) Limited number of participants reduces statistical precision, particularly for safety outcomes. Rare but serious adverse events may not be captured, and long-term safety remains uncertain. 3) The data primarily reflects outcomes in patients with severe phenotypes; evidence for efficacy in milder forms of AADC deficiency is limited. 4) Long-term durability of treatment benefits and safety remains uncertain. Despite these limitations, the study design is considered methodologically acceptable in the context of a rare disease with no approved therapies. Several contextual factors support the conclusion of clinical benefit including large treatment effect size, which increases confidence in the findings and reduces the likelihood that the results are solely attributable to bias or confounding. Pharmacodynamic data also demonstrated post-treatment increases in levels of homovanillic acid in the CSF as a downstream metabolite of dopamine and putamen specific 18F-DOPA uptake indicating increases in AADC activity. Known risks, including procedural complications and dyskinesia, are considered manageable with appropriate monitoring and treatment. These risks are deemed acceptable given the severity of AADC deficiency and the absence of alternative treatment options. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements
National Institute for Health and Care Excellence
The National Institute for Health and Care Excellence published a highly specialized technologies guidance report on eladocagene exuparvovec for treating AADC deficiency on April 19, 2023. (17) The guidance makes the following recommendations:

"Eladocagene exuparvovec is recommended, within its marketing authorization, as an option for treating AADC deficiency in people 18 months and over with a clinical, molecular and genetically confirmed diagnosis of AADC deficiency with a severe phenotype. Eladocagene

exuparvovec is only recommended if the company provides it according to the commercial arrangement."

International Working Group on Neurotransmitter Related Disorders (iNTD)
In 2017, the iNTD conducted a systematic literature review on AADC deficiency and developed treatment guidelines. (2) These guidelines state "Gene therapy for AADC deficiency is currently under development in a research setting. Clinical trial results will determine whether further implementation of this promising therapy may occur in the future." as they were published prior to the U.S. or EU approval of eladocagene exuparvovec.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	C9399, J3490, J3590

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
11/15/2025	Document updated. Coverage revised to consider eladocagene exuparvovec-tneq (Kebilidi) medically necessary when criteria listed in Coverage are met. References 1-4, 6-17 added. Title changed from Eladocagene exuparvovec-tneq.
04/15/2025	New medical document. Eladocagene exuparvovec-tneq (Kebilidi) for the treatment of adult and pediatric patients with aromatic L-amino acid decarboxylase (AADC) deficiency is considered not medically necessary as a clinical benefit has not been established. Eladocagene exuparvovec-tneq (Kebilidi) for the treatment of all other indications is considered experimental, investigational and/or unproven.