Genetics in Medicine Open (2025) ■, 103471

ELSEVIER

Genetics in Medicine OPEN
An Official Journal of the ACMG

www.journals.elsevier.com/genetics-in-medicine-open

ACMG THERAPEUTICS BULLETIN

Kebilidi (eladocagene exuparvovec-tneq) for adults and children with aromatic L-amino acid decarboxylase (AADC) deficiency: A therapeutics bulletin of the American College of Medical Genetics and Genomics (ACMG)

Julie M. Porter[1], Andrés Morales Corado[2], Kuntal Sen[3], Sarah H. Elsea[4]; on behalf of the ACMG Therapeutics Committee[5,*]

ARTICLE INFO

Article history:
Received 30 October 2025
Accepted 31 October 2025
Available online xxxx

Keywords:
Aromatic L-amino acid decarboxylase deficiency
Eladocagene exuparvovec-tneq
Gene therapy
Kebilidi

Background

Aromatic L-amino acid decarboxylase (AADC) deficiency (OMIM 608643) is a rare autosomal recessive neurodevelopmental disorder caused by biallelic loss-of-function pathogenic variants in *DDC* (HGNC:2719).[1] AADC catalyzes an intermediate step in the synthesis of multiple neurotransmitters.[2] Deficiency of this enzyme results in decreased synthesis of dopamine, serotonin, norepinephrine, and epinephrine. Clinical presentation typically consists of nonspecific findings in early infancy, including hypotonia, developmental delay, and feeding difficulties. More specific features include oculogyric crises, dystonia, and autonomic dysfunction. Additionally, sleep and mood disturbances are often seen. There is a spectrum of disease severity, with about 80% of affected individuals experiencing severe

This article was a work product of the Therapeutics Committee of the ACMG and the Article Publishing Charge (APC) was waived. No industry sponsorship was received for this work.

The Board of Directors of the American College of Medical Genetics and Genomics approved this bulletin on 21 October 2025.

*Correspondence: ACMG. *Email address:* documents@acmg.net

Affiliations are at the end of the document.

doi: https://doi.org/10.1016/j.gimo.2025.103471

symptoms with very limited motor function and intellectual development and 5% to 10% with milder symptoms that may eventually walk independently and demonstrate less severe intellectual disability.[1,2] The minimal estimated prevalence of AADC deficiency based upon gnomAD *DDC* variant analysis is 1:1,374,129 with a higher carrier frequency in East Asian populations due to a founder variant, NM_001082971.2:c.714+4A>T (IVS6+4A>T), NC_000007.14:g.50528133T>A, resulting in an estimated prevalence of 1/65,266.[3]

Management

International consensus guidelines for the management of AADC deficiency have been published.[4] Treatment generally focuses on replacement or scavenging of the affected neurotransmitters with off-label medication use. Dopamine agonists and monoamine oxidase inhibitors are both standard of care, although their efficacy is limited in AADC deficiency. Additionally, pyridoxine (vitamin B6) is a cofactor of AADC, and supplementation may increase residual enzyme activity. Other medications that may be used for symptomatic treatment include anticholinergics to treat autonomic symptoms, dystonia, and oculogyric crisis; melatonin for sleep; and benzodiazepines in specific settings, such as prolonged oculogyric crisis.[1,4] However, even with optimal treatment, affected individuals typically still have significant symptoms and require supportive care.

Newly Approved Therapy

Indication and approved treatment population

Eladocagene exuparvovec-tneq is a recombinant adeno-associated virus 2-based gene replacement therapy approved by the US Food and Drug Administration (FDA) on November 14, 2024 (trade name: Kebilidi)[5] and the European Medicines Agency on July 18, 2022 (trade name: Upstaza).[6] In the United States, it is approved for adult and pediatric individuals with AADC deficiency of any severity who have achieved skull maturity. Eladocagene exuparvovec-tneq was approved via the Accelerated Approval pathway. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory clinical trial.

The application received Priority Review and Orphan Drug designation and was granted a rare pediatric disease priority review voucher by the FDA.[7]

Mechanism of action

Eladocagene exuparvovec-tneq is delivered in 1 session via 4 stereotactically guided intraputaminal infusions (2 anterior and 2 posterior) using the SmartFlow Neuro Cannula that is FDA-authorized for this administration.[5] Each infusion consists of 0.45×10^{11} vector genomes, for a total standard dose of 1.8×10^{11} vector genomes. It is designed to provide a functional copy of *DDC* within the putamen, resulting in restored AADC expression and dopamine production. Dopamine production is evidenced by homovanillic acid (a metabolite of dopamine) in the cerebral spinal fluid (CSF) and ^{18}F-DOPA (a positron-emitting fluorine-labeled precursor to dopamine) uptake in treated individuals.[5,8]

Outcomes and efficacy

An open-label single-arm study (NCT04903288) enrolled 13 affected participants with severe AADC deficiency and compared with a cohort of 43 affected individuals from a natural history study.[9] The median participant age was 2.8 years (1.3-10.8 years) in the intervention group and 7.2 years (2-19 years) in the natural history study. Twelve of the 13 participants completed the study to the 48-week endpoint; 1 withdrew. Eight of the 12 treated participants achieved progress in gross motor milestones during the trial period, whereas no motor milestones had been documented in those of the untreated natural history study.[5]

Earlier studies performed in Taiwan also demonstrated efficacy.[8,10,11] An open-label phase 1/2 trial of 10 children median age 2.71 years (1.67-8.42 years) demonstrated improvement in the Peabody Developmental Motor Scales, the Alberta Infant Motor Scale, and Bayley-III scales at 12 months after treatment, as well as an increase in CSF homovanillic acid levels.[8] At baseline, none of the participants had head control, and all gained motor milestones. Notably, those who were youngest at the time of gene therapy administration showed more improvement than older participants.[4] A long-term follow-up study that included a total of 26 participants demonstrated that efficacy was maintained over 5 years after administration, typically with improvement over the first 1 to 3 years followed by a plateau.[10]

Adverse effects and toxicity

Most common adverse reactions seen in greater than 15% of subjects were dyskinesia, pyrexia, hypotension, anemia, salivary hypersecretion, hypokalemia, hypophosphatemia, insomnia, hypomagnesemia, and procedural complications.[5,8,10] Procedural complications included nonfatal respiratory and cardiac arrest within 24 hours of procedure[5] and CSF leakage.[10] Dyskinesia was the most common adverse event, occurring in 10 of 13 (77%) of participants in the US trial[5] and 24 of 26 (92%) individuals in the Taiwan studies.[10] Dyskinesia typically began within 3 months after AAV dosing and continued for an additional 1 to 5 months, followed by resolution within 10 months of treatment.[5,10] The dyskinesia is likely secondary to dopamine receptor

hypersensitivity and can be managed using dopamine antagonists if needed.[5] There are no clinical data regarding the use of eladocagene exuparvovec-tneq in pregnant individuals nor its effects on lactation or fertility. In addition, it has not been studied in children younger than 16 months of age.[5] Eladocagene exuparvovec-tneq does not carry any boxed warnings.

Additional Considerations

The administration of eladocagene exuparvovec-tneq is unique because it is the first FDA-approved intraputaminal gene therapy and requires collaboration between neurosurgeons, neurologists, and geneticists for delivery and management. Additional clinical trials for AADC deficiency include (1) a phase 1 investigator-initiated study of an intrastriatal injection of AAV9 gene therapy of VGN-R09b in China (NCT05765981), (2) a dose escalation of VGN-R09b directed to the putamen in pediatric participants in China (NCT06432140), and (3) a phase 1 investigator-initiated study of AAV2-hAADC delivered to the substantia nigra pars compacta and ventral tegmental area in children with AADC deficiency (NCT02852213).[12]

Conflict of Interest

All workgroup members receive a salary for providing clinical services that may be relevant to the content of this document in either the laboratory or patient care setting at their listed affiliations. The following workgroup members have additional conflicts of interest: Sarah H. Elsea serves as Chair of the ClinGen DDC-VCEP and has received grant funding from PTC Therapeutics to support the team curation of the DDC gene. The other authors declare no additional conflicts of interest.

Affiliations

[1]Division of Medical Genetics, Department of Pediatrics, University of Utah, Salt Lake City, UT; [2]Division of Clinical Genetics, Department of Pediatrics, Columbia University Vagelos College of Physicians and Surgeons, New York, NY; [3]Division of Neurogenetics and Neurodevelopmental Pediatrics, Children's National Hospital, Washington, DC; [4]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX; [5]American College of Medical Genetics and Genomics, Bethesda, MD

References

1. Blau N, Pearson TS, Kurian MA, et al. Aromatic L-amino acid decarboxylase deficiency. In: Adam MP, Feldman J, Mirzaa GM, et al., eds. *GeneReviews*. University of Washington, Seattle; 2023. Accessed June 14, 2025. https://www.ncbi.nlm.nih.gov/books/NBK595821/
2. Brun L, Ngu LH, Keng WT, et al. Clinical and biochemical features of aromatic L-amino acid decarboxylase deficiency. *Neurology*. 2010;75(1):64-71. http://doi.org/10.1212/WNL.0b013e3181e620ae
3. Park JE, Lee T, Ha K, Cho EH, Ki CS. Carrier frequency and incidence of aromatic L-amino acid decarboxylase deficiency: a gnomAD-based study. *Pediatr Res*. 2023;94(5):1764-1770. http://doi.org/10.1038/s41390-023-02685-0
4. Wassenberg T, Molero-Luis M, Jeltsch K, et al. Consensus guideline for the diagnosis and treatment of aromatic L-amino acid decarboxylase (AADC) deficiency. *Orphanet J Rare Dis*. 2017;12(1):12. http://doi.org/10.1186/s13023-016-0522-z
5. KEBILIDI (eladocagene exuparvovec-tneq) suspension, for intraputaminal infusion. United States Food and Drug Administration. Accessed July 7, 2025. https://www.fda.gov/media/183530/download
6. Upstaza. European Medicines Agency. Accessed July 7, 2025. https://www.ema.europa.eu/en/medicines/human/EPAR/upstaza#
7. FDA approves first gene therapy for treatment of aromatic L-amino acid decarboxylase deficiency. United States Food and Drug Administration. Accessed July 7, 2025. https://www.fda.gov/news-events/press-announcements/fda-approves-first-gene-therapy-treatment-aromatic-l-amino-acid-decarboxylase-deficiency
8. Chien YH, Lee NC, Tseng SH, et al. Efficacy and safety of AAV2 gene therapy in children with aromatic L-amino acid decarboxylase deficiency: an open-label, phase 1/2 trial. *Lancet Child Adolesc Health*. 2017;1(4):265-273. http://doi.org/10.1016/S2352-4642(17)30125-6
9. A study of smartflow magnetic resonance (MR) compatible ventricular cannula for administering eladocagene exuparvovec to pediatric participants. Parametric Technology (Corporation) Therapeutics. Accessed July 7, 2025. https://clinicaltrials.gov/study/NCT04903288
10. Tai CH, Lee NC, Chien YH, et al. Long-term efficacy and safety of eladocagene exuparvovec in patients with AADC deficiency. *Mol Ther*. 2022;30(2):509-518. http://doi.org/10.1016/j.ymthe.2021.11.005
11. Hwu WL, Lee HM, Peipert JD, et al. Clinically meaningful improvements after gene therapy for aromatic L-amino acid decarboxylase deficiency (AADCd) in the Peabody Developmental Motor Scale, Second Edition (PDMS-2) and correlation with Bayley-III scores and motor milestones. *Orphanet J Rare Dis*. 2025;20(1):58. http://doi.org/10.1186/s13023-025-03584-9
12. Bankiewicz K. A single-stage, adaptive, open-label, dose escalation safety and efficacy study of AADC deficiency in pediatric patients (AADC). ClinicalTrials.gov. Accessed July 7, 2025. https://clinicaltrials.gov/study/NCT02852213?a=6