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ORIGINAL ARTICLE

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Gene therapy for aromatic L-amino acid decarboxylase deficiency: Requirements for safe application and knowledge-generating follow-up

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Abstract

The autosomal recessive defect of aromatic L-amino acid decarboxylase (AADC) leads to a severe neurological disorder with manifestation in infancy due to a pronounced, combined deficiency of dopamine, serotonin and catecholamines. The success of conventional drug treatment is very limited, especially in patients with a severe phenotype. The development of an intracerebral

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AAV2-based gene delivery targeting the putamen or substantia nigra started more than 10 years ago. Recently, the putaminally-delivered construct, Eladocagene exuparvovec has been approved by the European Medicines Agency and by the British Medicines and Healthcare products Regulatory Agency. This now available gene therapy provides for the first time also for AADC deficiency (AADCD) a causal therapy, leading this disorder into a new therapeutic era. By using a standardized Delphi approach members of the International Working Group on Neurotransmitter related Disorders (iNTD) developed structural requirements and recommendations for the preparation, management and follow-up of AADC deficiency patients who undergo gene therapy. This statement underlines the necessity of a framework for a quality-assured application of AADCD gene therapy including Eladocagene exuparvovec. Treatment requires prehospital, inpatient and posthospital care by a multidisciplinary team in a specialized and qualified therapy center. Due to lack of data on long-term outcomes and the comparative efficacy of alternative stereotactic procedures and brain target sites, a structured follow-up plan and systematic documentation of outcomes in a suitable, industry-independent registry study are necessary.

KEYWORDS

AADCD, Aromatic L-amino acid decarboxylase, Eladocagene exuparvovec, gene therapy, iNTD registry, neurotransmitter

1 | INTRODUCTION/ BACKGROUND

Aromatic L-amino acid decarboxylase (AADC; EC 4.1.1.28) catalyzes the final step of the biosynthesis of the monoamine neurotransmitters serotonin and dopamine. AADC deficiency (AADCD, OMIM 608643) is a rare autosomal recessive neurometabolic disorder (*DDC* gene; 7p12.2-p12.1, chr7[hg19]: 50526134–50 633 154) characterized by impaired synthesis of the catecholamines (dopamine, epinephrine, and norepinephrine) and serotonin (Figure 1). The disease prevalence varies between different countries and ethnic origin. The highest incidence of 1/32000 is reported in Taiwan due to the presence of a common founder mutation (IVS6 + 4A > T).[1] Preliminary results from newborn screening studies in central Europe confirmed the former estimated prevalence of 1–2 in around 500 000 newborns (unpublished results from pilot newborn screening studies in Germany).

AADCD typically presents with hypotonia, dystonia, oculogyric crises, and developmental delay.[2,3] Sleep disturbances, autonomic dysfunction, and intellectual disability are additional disease features. While the vast majority of the patients develop symptoms in the first 6 months of life, the age at diagnosis varies significantly (mean 3.4 years, range 28 days–32 years).[2–4] Since AADC mediates the final step in the synthesis of dopamine and serotonin, supplementation with the immediate precursors (levodopa and 5-hydroxytryoptophan, respectively) is not a viable treatment strategy. Current drug treatment approaches aim to enhance the residual activity of the AADC enzyme, potentiate dopamine receptor action or slow down the degradation of serotonin and dopamine. These approaches have extremely limited efficacy in controlling disease-related symptoms, as addressed by a recent consensus guideline.[5]

Novel and innovative forms of therapy including antisense oligonucleotides, small molecules and gene therapies are successively being approved for rare diseases.[6,7] Within the group of orphan drugs, a rising number of so-called advanced therapy medicinal products (ATMPs) including recombinant nucleic acids, somatic cell therapeutics, and biotechnologically produced tissues or tissue products undergo market approval. While these have high therapeutic potential, in many cases only limited data are available on the long-term course of treatment at the time of approval (European Parliament 2007[8,9]). Nevertheless, gene therapy often represents a first therapeutic approach that targets the primary disease process, especially for congenital neurometabolic diseases.

With the European market approval of Eladocagene exuparvovec (Upstaza®) the therapeutic landscape of AADCD has changed. The product contains a vector

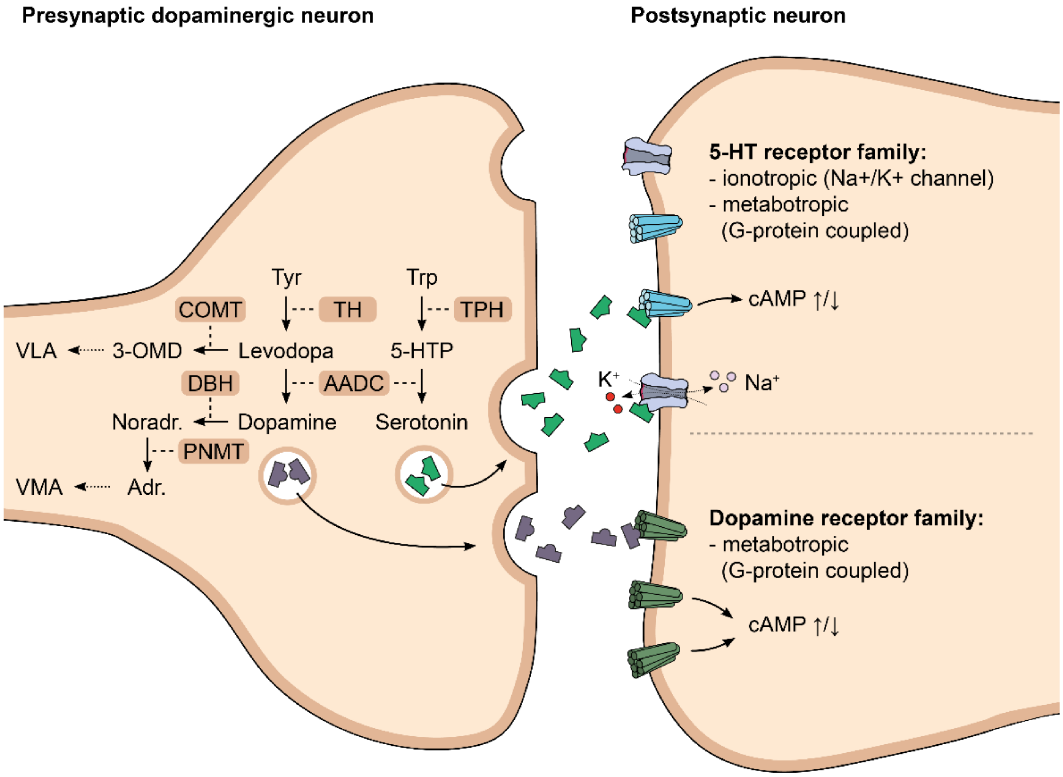

FIGURE 1 Synthesis, release and mode of action of monoamine neurotransmitters. Synthesis of dopamine and serotonin in presynaptic dopaminergic neurons, conversion to epinephrine and norepinephrine, and the effects of the neurotransmitters on corresponding receptor families. AADC, aromatic L-amino acid decarboxylase; Adr., epinephrine; cAMP, cyclic adenosine monophosphate; COMT, catechyl-O-methyltransferase; DßH, phenylethanolamine N-methyltransferase; noradr., norepinephrine; PNMT, phenylethanolamine N-methyltransferase; Trp, tryptophan; Tyr, tyrosine; VLA, vanillin lactate; VMA, vanillin mandelic acid; 3-OMD, 3-O-methyldopa; 5-HT, 5-hydroxy-trypatmine; 5-HTP, 5-hydroxy-tryptophan.

consisting of a recombinant adeno-associated virus, serotype 2 (rAAV2) with the complementary human *DDC* gene (rAAV2-hAADC) and provides the first therapy for AADCD directed towards the primary underlying cause of the disease.

1.1 | Gene therapy for AADCD: concept

Dopamine synthesis takes place in dopaminergic neurons in the central nervous system. These neurons are located in the pars compacta of the substantia nigra (SNpc) and ventral tegmental area (VTA) in the midbrain and send projection axons to the basal ganglia (caudate, putamen, and nucleus accumbens) as well as the prefrontal cortex.

Effective treatment of AADCD relies upon delivery of the gene vector to neurons deep in subcortical regions of the brain. To achieve this, the single application of AAV2-hAADC is performed during a stereotactic neurosurgical procedure with bilateral placement of cannula into the target brain structure. Two different surgical approaches for gene delivery have been investigated for this disease. Eladocagene exuparvovec is delivered to the bilateral putamen based on previous clinical trials for gene delivery to the putamen in adults with Parkinson's disease.[10,11] The second approach, which does not use Eladocagene exuparvovec but a similar vector, targets midbrain dopaminergic neurons in the SNpc and VTA and is currently under investigation in clinical trials (ClinicalTrials.gov Identifier: NCT02852213).[12]

Internalization of the vector occurs by endocytosis (Figure 2). By means of endosomal-lysosomal degradation processes, the viral capsid is removed and the viral genome including the *DDC* transgene is translocated into the nucleus. The *DDC* transgene persists as a circular extrachromosomal episome. It is known from other (systemic) gene therapy approaches with AAV vectors that integration into the host DNA is theoretically possible and can be associated with the risks of oncogenic transformation.[13,14] The risk of this so-called *insertional mutagenesis* occurring after intracerebral application of rAAV2-hAADC can only be assessed by long-term follow-up.

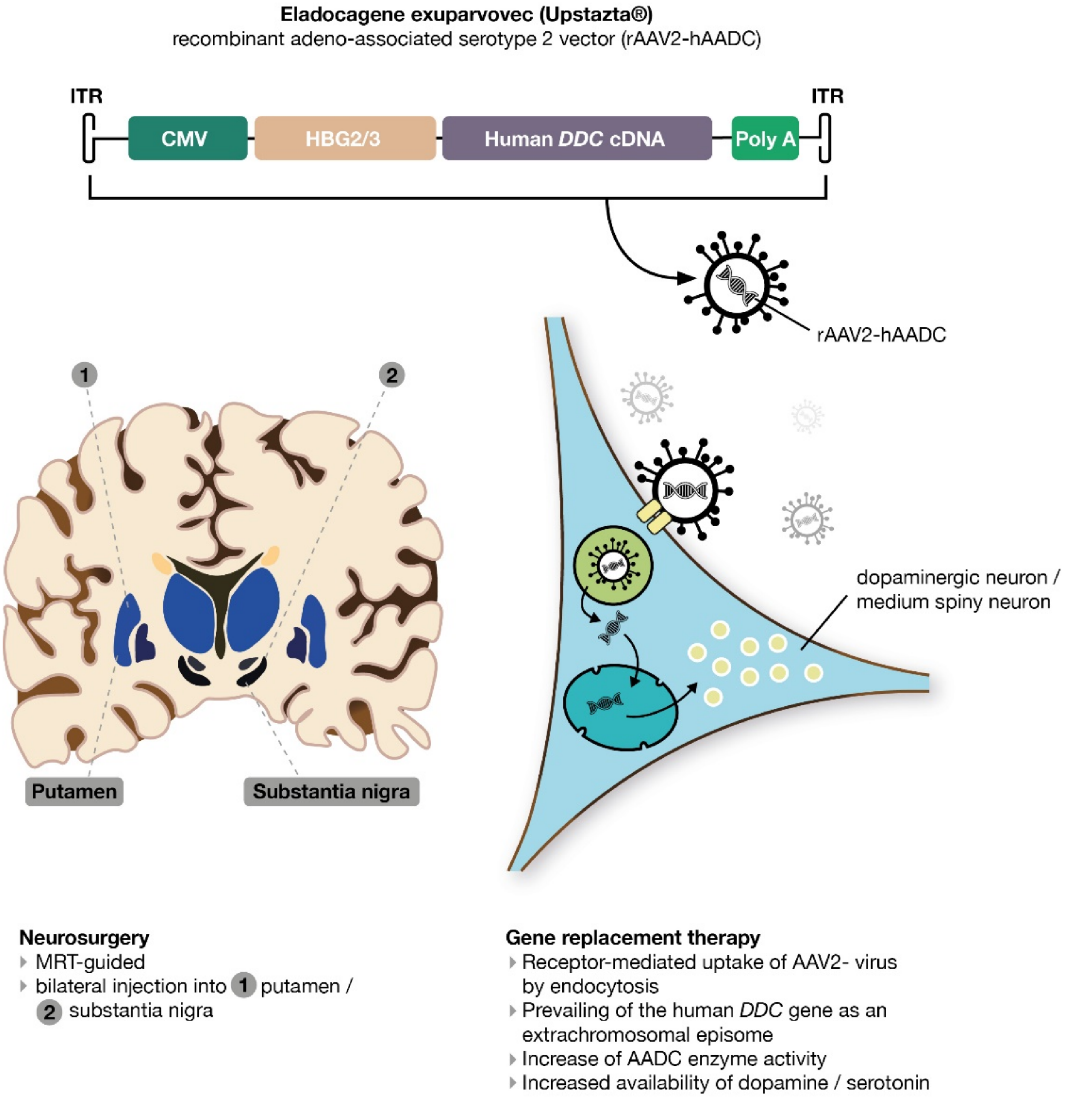

FIGURE 2 Treatment with rAAV2-hAADC. Illustration of the recombinant adeno-associated serotype 2 vector (rAAV2-hAADC) under control of the CMV promoter and the individual steps leading to the enhancement of AADC enzyme activity. AADC, aromatic L-amino acid decarboxylase; CMV IEP, cytomegalovirus immediate early promoter/enhancer; HBG2/3, human β-globin partial intron 2/partial exon 3; ITR, inverted terminal repeat.

1.1.1 | Gene therapy for AADCD: existing clinical data (Putamen)

Three clinical trials (phase I; phase I/II and IIb) with a total of 26 pediatric AADCD patients in Taiwan were performed and results of safety, efficacy and long-term follow-up have been published.[15,16] Over the course of 12 months, patients treated at a mean age of 4.1 ± 2.2 years (range 1.7–8.5 years) achieved improvements in motor skills (as measured by an increase in Alberta Infant Motor Scale [AIMS] and Peabody Developmental Motor Scale, Second Edition [PDMS-2] scores). Additionally, an increase in cognitive and language function was achieved, with sustained efficacy at >5 years of follow-up in 11 patients who were followed to this stage (mean 5.4 ± 2.6 years, range 2.0–10.2 years). In addition, a significant improvement in body weight, mood, sweating, temperature control, oculogyric crises, and caregiver's quality of life was observed.

Kojima et al. conducted an open-label phase I/II study in Japan using the same surgical procedure and vector in 6 AADCD patients (mean age 10.8 years, range 4–19 years), five of them with severe, one with moderate clinical phenotype.[17] During an observational period of 2 years, all patients demonstrated improvements in motor function, including four patients older than 10 years. The one patient with a moderate disease phenotype, who was able to walk with support before gene therapy achieved independent walking.

Very recently, François-Heude et al. reported the first European compassionate experience of intraputaminal delivery of Eladocagene exuparvovec in two children aged >10 years with a severe form of AADCD.[18] In accordance with previous reports motor symptoms significantly improved,[17] although in slower pace compared to young patients. The improvement of nonmotor symptoms lead to an increased quality of life.[18] The most frequent adverse events were pyrexia during the immediate postoperative course, and transient dyskinesia approximately 3–4 weeks after surgery, which were attributed to hypersensitivity of the dopaminergic system.[12,17,18]

In July 2022, PTC Therapeutics, Inc. received the marketing authorization of Eladocagene exuparvovec (Upstaza®) for the intraputaminal administration from the European Medicines Agency (EMA) and in February 2023 from the British Medicines and Healthcare products Regulatory Agency (MHRA) on the basis of data from the Taiwanese Phase I/II studies. Approval was granted for treating AADCD in people 18 months and over with a clinical, molecular and genetically confirmed diagnosis of AADCD with a severe phenotype.

1.1.2 | Gene therapy for AADCD: Existing clinical data (Midbrain)

Another gene therapy study, not using Eladocagene exuparvovec but a similar vector, targets the SNpc and VT for intracerebral injection based on the hypothesis that direct transduction of dopaminergic midbrain neurons would be beneficial (ClinicalTrials.gov Identifier: NCT02852213). In the initial open-label phase I/II study of seven patients (age range 4–9 years) with a severe disease phenotype, oculogyric crises resolved completely within 3 months in 6/7 patients, and all patients made significant motor developmental gains, with 6/7 attaining normal head control and 4/7 attaining the ability to sit independently within 12 months of surgery.[12]

In summary, the two novel gene therapies for AADCD that directly target the cause of the disease are promising, but it must be kept in mind that not all aspects regarding safety and efficacy are yet known given the relatively small number of patients treated to date. Therefore, the indication, use, and follow-up of this therapies in AADCD require a multidisciplinary approach in a center with expertise in rare movement disorders.

Experience with onasemnogene abeparvovec (Zolgensma®), a comparably novel treatment for spinal muscular atrophy, has shown the need to link treatment to a specialized center and ensure outpatient follow-up for at least 12 months and long-term follow-up of 15 years after administration.[19] A structured treatment plan can be the basis for application-related data collection, which may provide answers to important clinical and scientific questions in the future. This includes the question of which of the two approaches is most beneficial to patients in terms of safety and efficacy.

This consensus statement summarizes the structural requirements for the safe use of AADCD gene therapy including Eladocagene exuparvovec, outlines the mandatory personnel, temporal, and financial resources, and proposes quality criteria for the use of this therapy in a multidisciplinary setting.

2 | METHODS

2.1 | Consensus building

The International Working Group on Neurotransmitter related Disorders (iNTD) is an international network of clinical and scientific experts in the field of primary and secondary neurotransmitter disorders. The executive board (EB) is the operating board of the iNTD and is composed of up to 10 members elected by the iNTD members. All EB members are experienced in the care of patients with AADCD. Some of them have been actively involved in AADCD gene therapy studies or individual treatment attempts.

Due to the challenges expected to arise following the approval of Eladocagene exuparvovec, the EB decided to perform a two-step Delphi procedure to prepare statements regarding the requirements for safe application and knowledge-generating follow-up of patients who have received AADC gene therapy.

2.2 | The Delphi procedure for consensus finding.

The expert group consisted of the neurometabolic experts Thomas Opladen (Heidelberg University Hospital, Germany), Manju Kurian (Great Ormond Street Hospital, London, U.K.), Toni Pearson (Nationwide Children's Hospital, Columbus, U.S.A.), Àngels Garcia Cazorla (Sant Joan de Déu Barcelona Children's Hospital, Spain), Vincenzo Leuzzi (Università degli Studi di Roma La Sapienza, Rome, Italy), Roser Pons (First Department of Pediatrics of the National and Kapodistrian University of Athens, Athens, Greece), Michèl Willemsen (Radboud University Medical Centre (Radboudumc), Nijmegen, The Netherlands), Agathe Roubertie (Département de Neuropédiatrie, Pôle Femme Mère Enfant, CHU de Montpellier, France) and the neurosurgeons Thomas Roujeau (Service de Neurochirurgie Pédiatrique, Département de Neurosurgery, CHU de Montpellier, France) and

Karl Kiening (Heidelberg University Hospital, Germany). In addition, Lisa Flint (AADC Research Trust, London, U.K.), representing the International Association of Parents of Children with AADCD was recruited as a lay member of the group.

The suitability for an expert role in the present Delphi survey was determined on the basis of the respective professional qualifications in the field of neurotransmitter disorders and pediatric neurosurgery. The experts were consulted via online tools. Feedback to the group of experts was provided by e-mail after each Delphi rounds.

Seventy-one statements were derived from the expert survey and the feedback from national academic societies and included in the Delphi process.

The iterative process was as follows: In order to make the process efficient, the statements were entered into a web-based program, in which the experts could make suggestions for adapting the statements. In case the statements were imprecise or missing, the experts had the option to modify or supplement them by citing scientific literature. Statements were then integrated into the online survey software LimeSurvey, so that the statements could be evaluated in a 3-point Likert scale (Accept = I accept the statement, Reject = I reject the statement, Adjust = I would like the statement to be adjusted; for detailed results see supplementary material). The results of the individual statements were evaluated on the basis of the following reference values: If the rate of agreement ("Accept") exceeded 80%, the statement was included in the catalog of consensus statements as an expert opinion. If the approval rate was ≤80% or the rate of suggested change ("Adjust") was >50%, the statement was adjusted on the basis of the free-text feedback and was voted on again in a subsequent Delphi round. If the rate of rejection ("Reject") was above 50%, the statement was rejected without further processing. A time window of 10 days per round was specified for processing the online survey. After each round, feedback on the results was provided to the experts. By documenting IP addresses, it was ensured that each expert could only evaluate the statements once per round.

A consensus was reached already after the first Delphi round for most of the statements (74%). Twenty-five percent of statement were rated as "Adjust." Of these, 82% were accepted in the second Delphi round while for three statements (18%) adaptions were suggested which led to a final statement phrasing.

3 | RESULTS

The following sections summarize the structural and professional qualifications necessary to achieve high quality in the therapy and aftercare process and to ensure patient safety. The individual points are, of course, only suggestions and can be adapted to local conditions.

3.1 | Structural and professional requirements for an AADC gene therapy center

AADC gene therapy places special demands on the structural and professional resources of the treatment center due to the vulnerable patient population, type of application and scope of care. Resources for the diagnosis, treatment, and multidisciplinary care of AADCD are generally located in tertiary care pediatric hospitals. Physicians experienced in the care of these patients are best positioned to make the initial referral for gene therapy.

Patient care before, during, and after intracerebral use of the product requires collaboration among the following disciplines: Neuropediatrics, Metabolic Medicine, Neurosurgery, Anesthesiology, Clinical Pharmacology, Pediatric Intensive Care, and Rehabilitation Pediatricians. Thus, this therapy requires a multiprofessional treatment center. It is necessary that each of the disciplines involved have a clear knowledge of the standard operating procedures that govern clinical, radiologic, and radiochemical diagnosis, as well as outpatient and inpatient monitoring. Table 1 provides an overview of the technical and infrastructural requirements of all participating disciplines.

Planning and preparation require accurate, written documentation of the disease course to date from a neuropediatric and physical therapy perspective, as well as a summary of previous drug treatments, including their effects on the patient's symptomatology. Physical therapists should be trained in the administration of standardized motor tests (e.g., GMFM-88) and have experience with pediatric patients with neurodevelopmental disorders.

Timely involvement of pediatric neurosurgery and anesthesiology for joint planning of the surgical approach is required. The treatment center should have an in-house pharmacy that must be involved early in the utilization planning process to ensure proper product handling and timely delivery to the surgical team. The hospital pharmacy must meet infrastructural requirements, such as a separate room for the preparation/reproduction of ATMPs (European Union: according to Biosafety Level 1, BSL, under EU Directive 2000/54/EC and Biological Substances Regulation; https://osha.europa.eu/en/legislation/directives/exposure-to-biological-agents, assessed 31.03.2023).

In addition to inpatient treatment, structured outpatient follow-up is a critical step in ensuring patient safety. Patients who participated in clinical trials experienced in the months after gene therapy transient side effects such as hyperkinesia, sleep disturbances, and

TABLE 1 Consensus recommendations for the professional, organizational, infrastructural, and personnel requirements of gene therapy treatment centers.

1) Experience in the treatment of rare movement disorders

a. General experience in the diagnosis and care of children with rare and unexplained movement disorders (documented by treatment of ≥10 cases with this diagnosis at the center within 2 years).

b. Regular performance of stereotactic procedures on children and adolescents.

c. Specific experience with interdisciplinary care and drug treatment of patients with AADC deficiency, documented by drug cessation of at least 3 patients within 3 years.

d. Documentation of treatment outcomes through longitudinal recording of motor and developmental neurological functions in patient registries.

2) Personnel and professional requirements for the treatment center

a. Requirement for the qualification of the medical staff

- Coordination: The physician responsible for the treatment with Eladocagene exuparvovec and his/her deputy must be specialists in pediatrics and adolescent medicine with a specialization in neuropediatrics. They must have at least 2 years of professional experience in the care of children with rare and unexplained movement disorders.
- Neurosurgery: trained specialists in neurosurgery with a focus on stereotactic neurosurgery with at least 5 years of professional experience in stereotaxic surgery.
- Intensive care medicine: trained specialists in pediatric and adolescent medicine with a focus on pediatric intensive care medicine.

b. Requirements for the qualification of physiotherapists

- At least two physiotherapists should be available in the treatment center who have at least 2 years of experience in physiotherapeutic diagnosis and treatment of children with movement disorders. They should be trained in the performance of standardized motor tests and, if possible, have practical expertise in standardized test procedures (e.g., in the context of clinical studies).

c. Requirements for the qualification of psychotherapists

- At least one clinical psychologist who has at least 2 years of experience in the psychological diagnosis and treatment of children with movement disorders must be available in the treatment center. He/she must be trained in the administration of standardized psychological testing and have practical expertise in standardized testing procedures (e.g., in the context of clinical trials).

d. Availability of a psychosocial team.

- The center must have social team with experience in the care of patients with rare diseases to ensure adequate psychosocial care for the children and their families.

3) Requirements for infrastructure and organization of the treatment center

a. The center has inpatient care capabilities including pediatric intensive care with ventilator spaces, stereotactic neurosurgery, MRI/CCT imaging for multiprofessional care of children with rare movement disorders including AADC deficiency

b. There is an SOP for clinical, instrumental, and laboratory monitoring before, during, and after treatment with Eladocagene exuparvovec. Planning of the therapy by professional case management is recommended.

c. Physician supervision according to specialist standards (pediatric and adolescent medicine) must be continuously available for inpatient care of patients treated with Eladocagene exuparvovec.

d. The treatment center maintains appropriate resources to allow newly diagnosed patients with AADC deficiency to present within 4 weeks of contacting the center.

e. Eladocagene exuparvovec preparation and operation:

- The treatment center has its own or hospital-supplied pharmacy with a certified department for the preparation/reconstitution of sterile drugs (sterile department). SOPs are in place for aseptic manufacturing, hygiene management, and behavior in case of release of hazardous substances according to biological protection level 1. The pharmacy ideally has a separate room for manufacturing/reconstitution of ATMP (minimum requirement is the possibility of campaign manufacturing). The pharmacy has validated and qualified drug refrigerators with 24-h monitoring. The pharmacy ensures 24-h accessibility (on-call).
- The treatment center has a department of neurosurgery with equipment for surgical stereotaxy, including preoperative neuroradiological imaging by cranial CT/MRI and intraoperative equipment (pediatric carbon frames, short clamps, pediatric pins, planning software, ZD target sheet, cannulation and tubing).

f. Outpatient follow-up:

- Medical care according to specialist standards (pediatrics and adolescent medicine, focus on neuropediatric) must be available at all times on weekdays for outpatient follow-up of patients treated with Eladocagene exuparvovec.
- A telephone emergency contact and emergency outpatient clinic must be continuously available.

g. Documentation:

- The treatment facility actively participates in a patient registry (e.g., iNTD patient registry) and must maintain the staffing and structural requirements to include patients in the registry and other required documentation systems, as appropriate.

(Continues)

TABLE 1 (Continued)

- Over a period of at least 5 years, documentation must include:
  - Prior therapies
  - Adverse drug reactions
  - Documentation of motor function by standardized tests
  - Documentation of metabolic status through specific metabolic tests
  - Documentation of neurocognitive development by standardized tests
  - Overall survival

postoperative respiratory complications, which in some cases required hospitalization and intensive care (personal communications TO).

3.2 | Consideration for the practical implementation

3.2.1 | Preparation/prestationary phase

Due to the broad phenotypic spectrum of AADCD patients, the indication for intracerebral gene therapy is of particular importance. The therapeutic decision must be made by a pediatric specialist with a focus on neuropediatrics and several years of experience in the care of children with neurometabolic diseases and rare movement disorders. The diagnosis must be confirmed by genetic evidence of biallelic variants of DDC plus a biochemical marker (abnormal cerebrospinal fluid (CSF) profile OR abnormal plasma AADC activity[5]).

After biochemical and/or genetic diagnosis, the first presentation should be an outpatient consultation (prescreen, approximately 3 months before surgery, see Table 2). Treatment centers maintain adequate resources to offer newly diagnosed patients with AADCD an appointment at the center within 4 weeks of initial contact. In this meeting, the clinical picture of AADCD and the available therapy options including potential benefits and risks are presented in detail. In addition to taking a detailed and standardized medical history, current and previous symptoms have to be documented. If molecular genetic confirmation of the diagnosis has not been performed by this time, this will be arranged.

The various treatment options for the phenotypic spectrum of AADCD should be discussed with the family: currently (as of July, 2023), there is only a gene therapy approval for patients with a severe phenotype and an age of 18 months or older. Since the severity of the clinical phenotype may not become apparent until later in life, all individuals diagnosed in infancy should receive a therapeutic trial of medication according to the consensus guideline.[5] In particular, patients with a mild to moderate phenotype may respond well to drug treatment. In the severe phenotype, that is, with no apparent development of motor milestones, drug therapy helps to optimize clinical symptoms and provide some developmental benefits prior to gene therapy. The continuation of drug treatment after gene therapy has been performed must be assessed individually and depending on the clinical course.

As next step and according to health care systems specific to each country, cost coverage will then be discussed and if applicable an application for cost coverage will be submitted to the responsible insurance company.

After confirmation that all costs will be covered, a (partial) inpatient screening visit (15–30 days prior to surgery) takes place. This serves to evaluate the patient in detail from a (neuro-) pediatric, metabolic, neurosurgical, and physiotherapeutic perspective and includes the following key points:

- Medical history and physical examination as well as initial contact with neurosurgery: co-assessment of principal surgical capability.
- Enrollment into the (iNTD) Registry Study (if not already done) to document the treatment and the follow up of the patients in an industry independent approach. The international iNTD patient registry already contains the clinical, biochemical and diagnostic data of around 70 patients with AADCD as well as their development under the different drug therapies.[2,20] Recently, the registry has been extended by a specific gene therapy module, which allows standardized data collection in a longitudinal approach after gene therapy, independent from the surgical target.
- Metabolic laboratory analyses including presurgical CSF profile containing biogenic amines, 5-methyltetrahydrofolate (5-MTHF) and pterins.
- AAV2 serology and titer can be investigated for research purposes (according to Upstaza® package leaflet not required for routine care).
- Vaccination status: vaccinations should be performed for patient and caregivers according to the current recommendations of national guidelines as well as seasonal recommendations up to a maximum of 2 weeks before surgery. The suggested safety intervals for vaccinations following gene therapy should be taken from the manufacturer's technical information.

TABLE 2 Treatment algorithm for AADC gene therapy including suggested time intervals and examinations before, during, and after administration of the gene therapy.

	Preoperative		Operative						Postoperative								
	Outpatient	Inpatient	Inpatient						Outpatient				Inpatient	Outpatient			Inpatient
	Pre-Screen	Screen	D-1	D0	D1	D2	D3	D4[a]	W1	W2	M1	M2	M3	M6	M12	M18	M24
Medical history	•	•	•	-	-	-	-	-	•	•	•[b]	•[b]	•	•	•	•	•
Physical examination (including neurological status)	•	•	•	-	•	•	•	•	•	•	•[b]	•[b]	•	•	•	•	•
Postoperative monitoring (intensive/peripheral)	-	-	-	-	•	•[a]	•[a]	•[a]	-	-	-	-	-	-	-	-	-
Order preparation (pharmacy)	-	•	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
(iNTD) Register survey	-	•	-	•	-	-	-	•	•	-	-	-	•	•	•	•	•
Documentation "adverse events"			•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Molecular genetics	•[c]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lab examinations	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
• Metabolic investigations (U/DBS)	-	•[d]	•[d]	-	-	-	-	-	•[d]	-	•[d]	-	•[d]	•[d]	•[d]	•[d]	•[d]
• Metabolic investigations (CSF)		•[e]	-	-	-	-	-	-	-	-	-	-	•[e]	-	-	-	•[e]
• Preoperative safety lab	-	-	•[f]	-	-	-	-	-	-	-	-	-	-	-	-	-	-
• AAV2 antibody titer (for research purpose only)	-	•[g]	-	-	-	-	-	-	-	-	-	-	•	-	-	-	•
Vaccination status	-	•	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
12 channel ECG/Echo	-	•	-	-	-	-	-	-	-	-	-	-	•	-	-	-	•
Reconnaissance/Presentation Neurosurgery	-	•	•	-	-	-	-	-	-	-	-	-	•	-	-	-	-
Reconnaissance anesthesia	-	-	•	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Intracerebral application	-	-	-	•	-	-	-	-	-	-	-	-	-	-	-	-	-
Brain MRI	-	•[h]	-	•[h]	-	-	-	-	-	-	-	-	-	-	-	-	•
Intra−/postoperative MRI		-	-	•[i]	(•)[i]		-	-	-	-	-	-	-	-	-	-	-
F-DOPA PET Scan / DAT SPECT Scan	-	(•)[j]	-	-	-	-	-	-	-	-	-	-	(•)[j]	-	-	-	(•)[j]
Physiotherapy status	-	•[k]	-	-	-	-	-	-	-	-	•[k]	-	•[k]	•[k]	•[k]	•[k]	•[k]
Neurodevelopmental assessment	-	•[l]	-	-	-	-	-	-	-	-	-	-	-	-	•[l]	-	•[l]

(Continues)

TABLE 2 (Continued)

	Preoperative		Operative						Postoperative								
	Outpatient	Inpatient	Inpatient						Outpatient				Inpatient	Outpatient			Inpatient
	Pre-Screen	Screen	D-1	D0	D1	D2	D3	D4[a]	W1	W2	M1	M2	M3	M6	M12	M18	M24
Social worker counseling	-	•	-	-	-	-	-	-	-	-	-	-	•				•
Request for cost coverage	•	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
24 h availability for emergencies	-	-	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•

Abbreviations: AAV2-AK, adeno-associated virus type 2 antibody; BGA, blood gas analysis; CSF, cerebrospinal fluid; CT, computed tomography; D, day; DBS, dried blood spot; iNTD, International Working Group on Neurotransmitter related Disorders; M, month; MRI, magnetic resonance imaging; U, urine.

[a]Mandatory initial postoperative monitoring in the intensive care unit. In the course, monitoring in peripheral ward possible. Duration of intensive care and inpatient monitoring dependent on clinical presentation (e.g., hyperkinesias, postoperative complications).

[b]Weekly (telephone) consultations take place between M1 and M3 rounds to allow early detection of postoperative dyskinesias.

[c]If not available.

[d]3-OMD in dried blood spot; organic acids in urine.

[e]Biogenic amines, 5-methyltetrahydrofolate (5-MTHF) and pterins in CSF.

[f]Preoperative diagnostics: blood count, transaminases (GOT, GPT), creatinine, coagulation diagnostics (Quick, pTT) and bleeding time, cross blood, electrolytes (Na, K, Ca), ABG.

[g]AAV2 antibody titer. Not needed for clinical routine according to UPSTAZA® drug leaflet. Research purpose only.

[h]Planning brain MRI and matching with stereotactic CCT; alternative stereotactic intraoperative planning MRI. If cranial imaging is already available, it should be submitted.

[i]Ideally, intraoperative cranial MRI imaging to exclude hemorrhage and stroke. If no intraoperative MRI available, cranial MRI after 48 h and, if necessary, further cranial imaging during the course, depending on clinical symptoms.

[j]Optional.

[k]Physical therapy assessment including GMFM-88 survey and video documentation; clarification of postoperative outpatient physical therapy needs, assistive devices, etc.

[l]Psychological testing when possible; developmental age using Peabody Developmental Motor Scales 2nd Edition (PDMS-2) or Bayley Scales of Infant Development, 3rd Edition, in addition assessment of limitation using Pediatric Evaluation of Disability Inventory (PEDI); behavioral analysis using Vineland Adaptive Behavior Scale/Patient's Global Impression of Change (PGI-C); and quality of life questionnaire Pediatric Quality of Life Inventory (PedsQL).

- Ordering of the gene therapy vector by clinic pharmacy. Details and recommendations for the ordering process and delivery times will be requested in advance from the manufacturer.
- MRI of the head with and without contrast for surgical planning (alternatively stereotactic planning MRI intraoperatively).
- Optional: F-DOPA PET Scan/DAT SPECT Scan (likely to be performed only in the context of a research protocol).
- Motor and developmental neurological assessment of the patient according to the information in Table 2.
- Social counseling (determination of the need for social security measures, assistance regarding planning of implementation and follow-up).

It is recommended that further visit planning at the center be implemented through professional case management. Parents should have a reliable contact person to coordinate upcoming appointments and multispecialist care. Scheduling must be transparent for all parties involved.

3.2.2 | Inpatient phase (surgery and therapy)

The treatment part follows a clear and regularly updated standard operating procedure (SOP) in the treatment center. To perform the application of Eladocagene exuparvovec, the inpatient admission in the treatment center is done at least 24 h prior to surgery to ensure that the patient is currently stable for surgery. The patient's accommodation should be in accordance with the applicable hygiene guidelines of the center, but must meet the handling of pathogens corresponding to biological protection level 1.

One day before surgery

This includes informing the patient's legal guardian/caregiver about the anesthesiology and the surgical procedure as well as performing any preoperative blood sampling. During the preoperative blood collection (see Table 2), a peripheral intravenous catheter is inserted. Parenteral hydration with a weight- and age-adapted 10% glucose/electrolyte solution is carried out via this catheter from the evening before the operation (caution: patients with AADCD have increased risk of hypoglycemia during the preoperative fasting phase). Anesthesia related pharmacological management should follow the recommendations.[5,21]

Surgery

The AAV2-hAADC is prepared in the affiliated pharmacy according to the manufacturer's instructions. The preparation is stored in the pharmacy at a minimum of −60°C and thawed only shortly before application and prepared for use in a Biosafety Level 1 qualified room. The preparation is transported directly to the neurosurgical operating room. The transfer of the preparation to the surgeon must be documented. The period between thawing and application of the vector must not exceed 6 h (for details see product information sheets). This is followed by the neurosurgical procedure using stereotactic CT/MRI and the application of AAV2-hAADC. For this purpose, a cannula is inserted into the putamen or substantia nigra (with MRI guidance) and the product is applied with gradual withdrawal of the cannula. After removal of the cannula, an intraoperative or postoperative MRI is performed to rule out any complications such as bleeding or ischemia. Disposal of any equipment that has come into contact with the preparation must be carried out in compliance with the applicable disposal standards.

Postoperative care

After surgery, the patient is transferred to a pediatric intensive care unit (caution: disease-related risk of acute neurologic deterioration, hypoglycemia, and sudden cardiac death). Early extubation of the patient is desired. Attention should be paid to any signs of neurological change, which would suggest the presence of hemorrhage, ischemia or other complication of the neurosurgical procedure and would require appropriate diagnostics and treatment. Depending on the postoperative course and the clinical general condition, transfer to a peripheral or intermediate care (IMC) ward takes place on the third postoperative day at the earliest. An interdisciplinary team of neuropediatricians, neurosurgeons, and other necessary disciplines determines the duration of inpatient monitoring and plans outpatient follow-up.

3.2.3 | Postoperative follow up phase

Due to preexisting hypersensitivity in the dopamine system, the occurrence of (transient) dyskinesia can be expected after 2–6 postoperative weeks as a result of the increase in endogenous dopamine production. In the context of increasing dyskinesias, a gradual reduction of the previous medication must take place. The procedure must be individually adapted to the patient. Therefore, a close-meshed consultation as well as a 24-h availability of a specialist physician of the treatment center who is familiar with the treatment of patients with acute dystonia/dystonic crises must be ensured. Although the dyskinesias were transient in the previous studies, it may become necessary to provide (intensive) medical care to the patient again.[12,17]

Adapted to established approaches in spinal muscular atrophy[19] patients should return to the treatment center for outpatient follow-up in defined intervals for the first 2 years to monitor for treatment-related side effects and clinical progress. (The patient may also be followed by a local physician close to home, but ideally this would be in addition to, not instead of, follow-up at the treatment center; Table 2). All follow-up visits should be documented in a standardized manner in an industry-independent international registry. Only an international approach will reach the critical mass of patients after gene therapy for a detailed and reliable scientific data evaluation.

The iNTD patient registry, 10 years since its establishment in a purely academic setting, has broad international coverage and contains over 500 patients with various neurotransmitter related disorders, 70 of them with AADCD.[2,20] The registry follows all current recommendations of the European Rare Disease Registry Infrastructure (ERDRI) and it hereby reaches by the use of common data elements, structured and controlled vocabulary of the Human Phenotype Ontology and the coding system of the Human Metabolome Database a high semantic interoperability. The newly established gene therapy module provides ideal conditions for the standardized data collection in a longitudinal approach after gene therapy, independent from the surgical target and is therefore highly suitable for postauthorization surveillance studies.

Long-term follow-up after gene therapy with Eladocagene exuparvovec and other vectors is necessary until at least 15 years, considering the personnel, professional and structural requirements of the treatment of rare diseases, after 2 years at least once a year, in order to scientifically document long-term outcomes. Long-term follow-up will be important to document whether clinical benefits, with regard to both symptoms and developmental progress, are sustained and continue to improve over time. It will also be critical to monitor for any delayed complications that may emerge. Gene therapy for AADCD is likely to continue to evolve, considering ongoing clinical trials to investigate midbrain gene delivery, and the potential for future therapeutic approaches that aim to address both dopamine and serotonin deficiency.

4 | CONCLUSION FOR PRACTICE

The approval of Eladocagene exuparvovec in 2022 represents the first approved intracerebral gene therapy for pediatric and adolescent AADCD patients in Europe. The intracerebral application, which has so far been designed as a single administration, requires multiple inpatient and outpatient visits with high-intensity care. The diagnostic and therapeutic procedure must be accompanied by a multi-professional team in specialized treatment centers that meet structural and professional requirements for safe administration of the drug. This consensus statement compiles the recommendations for these prerequisites; this statement should be reviewed and updated at regular intervals, and collection of patients' data in an industry-independent international registry will help understand patients´ courses after gene therapy.

AUTHOR CONTRIBUTIONS

Conception of the work Thomas Opladen, Agathe Roubertie, Toni S. Pearson, Roser Pons, Heiko Brennenstuhl, Oya Kuseyri Hübschmann; Execution: Thomas Opladen, Heiko Brennenstuhl and Oya Kuseyri Hübschmann developed the Delphi questions; All authors participated in the Delphi procedure; Data evaluation: Heiko Brennenstuhl, Oya Kuseyri Hübschmann, Thomas Opladen, Toni S. Pearson, Roser Pons; Writing of the First draft: Heiko Brennenstuhl, Thomas Opladen, Agathe Roubertie; Review and Critique: All authors.

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CONFLICT OF INTEREST STATEMENT

Thomas Opladen, Agathe Roubertie, and Thomas Roujeau received speaker and research honorarium from PTC Therapeutics. Roser Pons received speaker honoraria from PTC therapeutics and has participated in Scientific advisory boards organized by PTC therapeutics. Oya Kuseyri Hübschmann and Bruria Ben Zeev received speaker honorarium from PTC Therapeutics. Manju A. Kurian is Co-founder of Bloomsbury Genetic Therapies, Consultant to Bloomsbury Genetic Therapies and received honorarium from PTC. All other authors declared no conflict of interests.

DATA AVAILABILITY STATEMENT

All data supporting the Delphi results are available from the corresponding author.

ETHICS STATEMENT

This article does not contain any studies with human or animal subjects performed by any of the authors.

Aromatic L-amino acid decarboxylase–AADCD–gene therapy–Eladocagene exuparvovec—neurotransmitter—iNTD registry All data supporting the Delphi results are available from the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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