Eladocagene Exuparvovec: First Approval

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Abstract
Eladocagene exuparvovec (Upstaza™) is a gene therapy developed by PTC Therapeutics for the treatment of human aromatic L-amino acid decarboxylase (AADC) deficiency. Eladocagene exuparvovec comprises an adeno-associated virus vector that delivers the dopa decarboxylase (DDC) gene, the gene for human AADC. Eladocagene exuparvovec was approved in July 2022 in the EU for the treatment of patients aged 18 months and older with a clinical, molecular, and genetically confirmed diagnosis of AADC deficiency with a severe phenotype (i.e. patients who cannot sit, stand or walk). This article summarizes the milestones in the development of eladocagene exuparvovec leading to this first approval for the treatment of patients aged 18 months and older with AADC deficiency.

1 Introduction
Aromatic L-amino acid decarboxylase (AADC) deficiency, a fatal, rare inborn error of neurotransmitter biosynthesis affecting the central nervous system (CNS), results from mutations in the dopa decarboxylase (DDC) gene. The DDC gene encodes the AADC enzyme, which converts L-3,4-dihydroxyphenylalanine (L-DOPA) to dopamine [1–5]. A reduction or absence of AADC enzyme activity due to DDC gene mutations results in a reduction in CNS dopamine levels, as well as reductions in noradrenalin (norepinephrine), adrenalin (epinephrine), serotonin and melatonin levels. In AADC deficiency, the putamen is directly affected by the loss of dopamine synthesis in the striatum [1–5]. Most patients with AADC deficiency have a severe phenotype (i.e. cannot sit, stand or walk), fail to achieve developmental milestones, and show severe disability from the first months of life. Signs and symptoms of AADC deficiency include hypotonia, movement disorders (dystonia, oculogyric crises, hypokinesia), autonomic dysfunction (e.g., ptosis, excessive sweating, impaired regulation of heart rate and blood pressure, nasal congestion, emotional instability and sleep disturbance), intellectual disability, feeding difficulties, frequent vomiting and behavioural problems. A definitive diagnosis of AADC deficiency is made based on the presence of two of the following three core diagnostic keys: DDC pathological mutation; changes in cerebrospinal fluid (CSF) markers of AADC [e.g. decreased concentrations of homovanillic acid (HVA; the dopamine metabolite) or 5-hydroxyindoleacetic acid (5-HIAA; the serotonin metabolite); and decreased AADC enzyme activity in plasma [1].
Historically, there have been no approved disease-modifying therapies for treating AADC deficiency, and the success of symptomatic treatment using combinations of vitamin B6, dopamine agonists and monoamine oxidase inhibitors (all recommended as first-line treatments) is very limited, especially in cases where patients have severe impairments [1, 2]. Ongoing physical, occupational and speech therapy and interventions, including surgery, are often required to manage potentially life-threatening complications such as infections and severe feeding and breathing problems [1]. While the recommended first-line treatments have been associated with treatment benefits, drug-related adverse events are often dose-limiting and may result in treatment discontinuation; thus, other treatment options are required [1, 6]. Based on the rationale, efficacy and safety of intraputaminal delivery of adeno-associated virus serotype 2 (AAV2) gene therapy in Parkinson’s disease [3] and the genetic basis for AADC deficiency [2, 3, 7], AAV2 gene therapy has also been investigated in AADC deficiency [2, 3, 7, 8, 15].

Eladocagene exuparvovec (Upstaza™) is a gene therapy that expresses the human AADC enzyme. It is a non-replicating recombinant AAV2 based vector containing the cDNA of the human DDC gene under the control of the cytomegalovirus immediate-early promoter [5]. Eladocagene exuparvovec is indicated for the treatment of patients aged 18 months and older with a clinical, molecular, and genetically confirmed diagnosis of AADC deficiency with a severe phenotype [5]. The gene therapy is delivered directly into the brain through stereotactic injections. The one-time treatment corrects the underlying genetic defect by delivering a functioning DDC gene directly into the putamen; as a consequence, the AADC enzyme is expressed, dopamine production is restored and motor function develops [3, 5, 8]. Patients receive a one-time total dose of $1.8 \times 10^{11}$ vg delivered as four $0.08 \text{mL} (0.45 \times 10^{11} \text{vg})$ infusions directly to the putamen [one each to the right anterior putamen, right posterior putamen, left anterior putamen, and left posterior putamen] during a single procedure via a minimally invasive stereotactic neurosurgical procedure [5]. Eladocagene exuparvovec should be administered in a centre that is specialised in stereotactic neurosurgery by a qualified neurosurgeon under controlled aseptic conditions and should only be infused with the SmartFlow® ventricular cannula [5, 9]. Post administration, patients should be closely monitored for procedure-related complications, complications related to their underlying disorder, and risks associated with general anaesthesia during the peri-operative period. Patients may experience exacerbations of symptoms of their underlying AADC deficiency as a result of surgery and anaesthesia. The risk of viral shedding is considered to be low because of the very limited systemic distribution of eladocagene exuparvovec; however, waste material handling precautions are recommended in the 14 days after treatment. Patients treated with eladocagene exuparvovec should not donate blood, organs, tissues and cells for transplantation [5].

### 1.1 Company Agreements

In June 2020, PTC Therapeutics entered into a manufacturing agreement with MassBiologics for the manufacture of eladocagene exuparvovec [10]. In October 2019, PTC Therapeutics entered into a strategic collaboration with Aldevron, LLC to support GMP plasmid manufacturing capacity for PTC Therapeutic’s gene therapy portfolio, including programmes for AADC deficiency [11]. In August 2018, PTC Therapeutics acquired Aglis Biotherapeutics [10].

In June 2016, Aglis Biotherapeutics and the US National Center for Accelerating Translational Sciences (NCATS) signed a letter of intent for the Cooperative Research and Development Agreement (CRADA) under the National Institutes of Health’s Therapeutics for Rare and Neglected Diseases (TRND) programme, to facilitate development activities in support of registration of eladocagene exuparvovec for the treatment of AADC deficiency [12].
In December 2015, Agilis entered into an exclusive licensing agreement with the National Taiwan University (NTU) for the treatment of AADC deficiency using the gene therapy product, eladocagene exuparvovec, developed at NTU. Under the agreement terms, PTC Therapeutics sponsored ongoing research and development of the eladocagene exuparvovec gene therapy in collaboration with NTU, including the conduct of ongoing clinical work and completion of non-clinical testing in advance of the observational studies. PTC Therapeutics is also supporting ongoing manufacturing efforts for the gene therapy [13, 14]. In September 2015, Agilis entered into collaboration agreement with NTU to conduct research and clinical trials for AADC deficiency gene therapy. Under the agreement, NTU was responsible for conducting the research and clinical trials and Agilis provided funding and was responsible for regulatory filings [14].

2 Scientific Summary

2.1 Pharmacodynamics

Eladocagene exuparvovec is produced in human embryonic kidney cells by recombinant DNA technology [5]. After infusion of eladocagene exuparvovec into the putamen, the AADC enzyme is thought to be expressed through the direct transduction of medium spiny neurons and/or monoenzymatic/dienzymatic neurons in the putamen [3]), leading to the production of dopamine and consequently, the development of motor function in treated AADC deficient patients [5].

The measurement of L-6-[18F]fluoro-3, 4-dihydroxyphenylalanine (18F-DOPA) uptake in the putamen using positron emission tomography (PET) imaging has been used to assess the success and stability of AADC gene transduction and de novo dopamine production in the brain of patients with severe AADC deficiency after administration of eladocagene exuparvovec [5]. In two clinical studies [AADC-010 (NCT01395641; n = 10) and AADC-011 (NCT02926066; n = 10)], small, sustained increases in PET-specific uptake in the putamen were seen in most patients, with the increases from baseline seen as early as 6 months after treatment. Baseline PET-specific uptake was 0.27 (n = 20); the change from baseline to month 12 (0.32; n = 17) and month 24 (0.36; n = 15) was sustained at month 60 (0.39; n = 4) [5]. At 6 months after gene transfer in the earliest study in patients with AADC deficiency (AADC-CU-1601; n = 4), an increase in 18F-DOPA using PET imaging was also evident [7]. PET data at 1, 2 and 5 years after administration of eladocagene exuparvovec in all three clinical studies (AADC-CU-1601, NCT01395641 and NCT02926066) showed the mean 18F-DOPA-specific uptake increasing from baseline of 0.23 (n = 24) to 0.48 at 12 months (n = 24; p < 0.001 vs baseline), 0.55 at 2 years (n = 15; p = 0.003) and 0.60 at 5 years (n = 13; p < 0.001) [15].

CSF HVA levels at 12 months after administration of eladocagene exuparvovec were significantly increased from baseline (6.6 vs 30.2 nmol/L; p < 0.001) in the three eladocagene exuparvovec clinical studies (AADC-CU-1601, NCT01395641 and NCT02926066); as expected, CSF 5-HIAA levels did not differ significantly from baseline in all three clinical trials, because serotonergic nuclei were not targeted [15].

2.2 Pharmacokinetics

Eladocagene exuparvovec is infused directly into the brain and does not distribute outside the central nervous system. There was no evidence of detectable viral vector in blood or urine (measured using a validated real-time quantitative polymerase chain reaction assay) at baseline or through the 12 months after administration of eladocagene exuparvovec in patients with AADC deficiency [5].

Features and properties of Eladocagene exuparvovec

| Alternative names | Upstaza, PTC-AADC, AGIL-AADC; AAV2-hAADC, GT-AADC, AAV-hAADC-gene-therapy-PTC Therapeutics/National-Taiwan-University |
|-------------------|-------------------------------------------------------------------------------------------------------------------|
| Class             | Gene therapies                                                                                                     |
| Mechanism of action| Aromatic-L-amino-acid decarboxylase replacements; Gene transference                                               |
| Route of administration | Intracerebral infusion (one time treatment)                                                                         |
| Pharmacodynamics  | Increases from baseline in 18F-DOPA using PET imaging were evident from as early as 6 months after administration and sustained through 5 years |
| Pharmacokinetics  | No evidence of detectable viral vector in blood or urine at baseline or through 12 months after administration |
| Adverse events    | Most frequent: Dyskinesia, initial insomnia and irritability, salivary hypersecretion                                |
| Related to neurosurgery | Anemia, cerebrospinal fluid leakage                                                                                   |
| ATC codes         | WHO ATC code: N07 (other nervous system drugs)                                                                     |
|                   | EphMRA ATC code: N7 (other CNS drugs)                                                                               |

△ Adis
2.3 Therapeutic Trials

Treatment with eladocagene exuparvovec was associated with acquisition of key milestones in patients with AADC deficiency, together with improvements in cognitive and communication skills, body weight, hypotonia and dystonia and reduction in the frequency and duration of OGC episodes, according to data from two trials [NCT01395641 (AADC-010; \( n = 10 \)) and NCT02926066 (AADC-011; \( n = 10 \))] [5]. Motor milestone achievement was based on the Peabody Developmental Motor Scale, version 2 (PDMS-2); the primary endpoint in these studies was the number of patients who achieved the following PDMS-2 motor milestones (where mastery of skill is a score of 2) at 24 months: full head control; sitting unassisted; standing with support; and walking with support. As early as 12 months after treatment, head control and sitting unassisted was achieved by 6 and 3 patients, respectively; by 60 months, 14 of 20 patients had achieved head control, 13 were sitting unassisted, 6 were standing with support and 2 were walking with support. Not all patients had reached the timepoints specified at the time of data cut [5].

PDMS-2 total scores improved from baseline in all patients treated with eladocagene exuparvovec; at 12 months after treatment, the least squares mean (LSM) change from baseline was 76.1 points. At 24 months the LSM change from baseline had increased to 104.4 points and this improvement was maintained through 60 months (LSM change from baseline of 108.2 points). Patients who were administered eladocagene exuparvovec at a younger age showed a more rapid response and a higher final PDMS-2 total score [5]. Cognition and communication skills, evaluated by the total language score [combined score for receptive and expressive communication subscales of Bayley-III]; total score of 97), improved gradually after administration of eladocagene exuparvovec. The mean score at baseline was 17.70 (\( n = 20 \)); mean change from baseline at month 12 after administration was 7.35 (\( n = 17 \)), increasing to 9.87 at month 24 (\( n = 15 \)) and 12.60 at month 36 (\( n = 10 \)) [5].

At month 12 after treatment with eladocagene exuparvovec in the two trials, most patients maintained (16/17 patients) or increased (8/17) body weight, and the number of patients with hypotonia symptoms reduced from 77.8% at baseline (\( n = 20 \)) to 46.7% (\( n = 17 \)). At baseline (\( n = 20 \)), 66.7% of patients experienced limb dystonia and 11.1% experienced stimulus-provoked dystonia; at 12 months post treatment, none of the patients experienced limb dystonia or stimulus-provoked dystonia [5]. The duration of oculogyric crisis episodes after eladocagene exuparvovec treatment was reduced by 1.85 h/week by month 3 (\( n = 16 \)) and by 3.66 h/week by month 12 (\( n = 6 \)) from a mean 12.3 h/week at baseline (\( n = 20 \)) [5].

Both trials enrolled patients with severe AADC deficiency, diagnosed by decreased HVA and CSF 5-HIAA levels and elevated L-DOPA levels in CSF, the presence of DDC gene mutation in both alleles, and the presence of clinical symptoms of AADC deficiency (including developmental delay, hypotonia, dystonia, and oculogyric crisis). Patients were aged 19 months–8.5 years and had not achieved motor development milestones, including the ability to sit, stand or walk [5, 15]. Patients were treated with a total dose of \( 1.8 \times 10^{11} \) vg (\( n = 13 \)) or \( 2.4 \times 10^{11} \) vg (\( n = 7 \)) during a single operative session. The results for efficacy parameters were similar between the two doses [5].

Similar results to the AADC-010 (NCT01395641) [8, 15] and AADC-011 (NCT02926066) [15] studies were seen in the earlier phase 1 compassionate use study (AADC-CU/1601; \( n = 8 \)) [7, 16] that used an older treatment manufacturing process for eladocagene exuparvovec, and benefits were maintained up to 5 years [5, 7, 16]. Combined data from these three trials in 26 patients who completed 1-year evaluations [15] showed that PDMS-2 scores increased from a mean baseline score of 10.4 (\( n = 25 \)) to 80.5 (\( n = 25 \)) at 1 year, 114.5 (\( n = 22 \)) at 2 years and 116.1 (\( n = 11 \)) at 5 years (all \( p < 0.01 \) vs baseline). Alberta Infant Motor Scale (AIMS) scores increased from a mean baseline score of 1.8 to 18.8 at 1 year post treatment, 26.9 at 2 years, and 24.5 at 5 years (all \( p < 0.001 \) vs baseline). Three patients, all of whom had been treated at a young age (2.5, 4.2 and 2.0 years, respectively), could walk freely without assistance at 2.9, 2.4 and 2.2 years, respectively, after treatment with eladocagene exuparvovec [15]. At baseline, 21 of 26 patients had a body weight < 3rd percentile of normal; after treatment, significantly fewer (11 of 23) patients with >1 year of follow-up had a body weight < 3rd percentile of normal at the latest visit (\( p = 0.02 \)). A retrospective survey of caregivers (\( n = 17 \)) [using a symptom severity questionnaire and the World Health Organization Quality of Life (WHOQOL)-BREF (Taiwan version)] indicated that the severity of bad mood, excessive sweating, temperature instability and oculogyric crises all decreased significantly from baseline (\( p < 0.001 \) and caregiver quality of life had significantly improved after gene therapy (\( p \leq 0.006 \) vs baseline for all 5 domains) [15]. Age at the time of treatment correlated significantly with the response to therapy as measured by 1-year (\( p < 0.001 \)) and 2-year (\( p < 0.001 \)) post-treatment PDMS-2 scale (younger age was associated with better outcomes) and a strong correlation between post treatment HVA levels and PDMS-2 scores was also evident [15].
Key clinical trials of Eladocagene exuparvovec

| Drug(s)            | Indication      | Phase | Status   | Location(s)          | Sponsor                  | Identifier                        |
|--------------------|-----------------|-------|----------|--------------------|--------------------------|-----------------------------------|
| Eladocagene exuparvovec | AADC deficiency | 2     | Ongoing  | USA, Israel, Taiwan | PTC Therapeutics          | NCT04903288, PTC-AADC-GT-002     |
| Eladocagene exuparvovec | AADC deficiency | 2     | Completed | Taiwan            | National Taiwan University Hospital | NCT02926066, NTUH-AADC-011, EudraCT 2019-003072-39 |
| Eladocagene exuparvovec | AADC deficiency | 1/2   | Completed | Taiwan            | National Taiwan University Hospital | NCT01395641, NTUH-AADC-010, EudraCT 2019-003032-23 |
| Eladocagene exuparvovec | AADC deficiency | CU    | Completed | Taiwan            | National Taiwan University Hospital | AADC-CU-1601                      |

AADC aromatic L-amino acid decarboxylase, CU compassionate use

2.4 Adverse Events

Dyskinesia, which was reported in 24 of 28 patients (85.7%) and is due to dopamine sensitivity, was the most frequent adverse reaction reported in patients enrolled in the three open-label clinical studies of eladocagene exuparvovec in children with AADC deficiency (AADC-CU-1601, NCT01395641 and NCT029260660) [5]. Most of the dyskinesia events occurred within 2 months of treatment (mean time to onset 25.8 days), were mild to moderate (33/35 events) or severe (2/35) and responded to standard pharmacological treatment, including anti-dopaminergic treatment (e.g., risperidone). Most resolved in ≈ 2 months, and by 7 months after treatment, all cases had resolved [5, 15]. Other adverse reactions occurring in two or more patients in these trials were initial insomnia and irritability and salivary hypersecretion. Adverse reactions relating to neurosurgery included anemia and cerebrospinal fluid leakage [5]. In the three studies, patients were aged 19 months to 8.5 years at time of treatment with eladocagene exuparvovec and were followed for a median 52.3 months (range 3.1 months to 9.63 years) [5].

Prior to treatment with eladocagene exuparvovec, all patients had anti-AAV2 titres ≤ 1:20. In the first 12 months after treatment, most patients (n = 18) were positive for anti-AAV2 antibodies at least once [5, 15]. Antibodies generally stabilized or declined over time [5]. Immune responses are not expected to affect localized brain gene therapy [15]; in clinical studies, the presence of anti-AAV2 antibodies was not associated with decreased efficacy or an increase in the frequency or severity of adverse reactions [5]. The immune response to the transgene and cellular immune response was not measured [5].

2.5 Ongoing Clinical Trials

A phase 2 trial plus extension (NCT04903288) to assess the safety of the SmartFlow® magnetic resonance compatible ventricular cannula for administering eladocagene exuparvovec, together with pharmacodynamic measures and efficacy in AADC deficiency is being conducted in Taiwan, the USA and Israel.

3 Current Status

Eladocagene exuparvovec received its first approval on 20 July 2022 for the treatment of patients aged 18 months and older with a clinical, molecular, and genetically confirmed diagnosis of AADC deficiency with a severe phenotype (i.e. cannot sit, stand or walk) in the EU [5, 17].

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