SMC2586

eladocagene exuparvovec solution for infusion (Upstaza®)

PTC Therapeutics Ltd

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The Scottish Medicines Consortium (SMC) has completed its initial assessment of the evidence for the above product using the ultra-orphan framework:

Indication under review: for the treatment of patients aged 18 months and older with a clinical, molecular, and genetically confirmed diagnosis of aromatic L-amino acid decarboxylase (AADC) deficiency with a severe phenotype.

Key points:

- Severe AADC deficiency is a rare genetic disorder associated with debilitating symptoms, significant impairment in normal motor development milestones, and a high risk of death in young children. Eladocagene exuparvovec is the first medicine licensed for severe AADC deficiency.
- In three open-label, single-arm studies in children with severe AADC deficiency, eladocagene exuparvovec treatment resulted in patients achieving key motor milestones (with most achieving head control and sitting unassisted); the number who achieved these key motor milestones appeared to increase over time. Total Peabody Developmental Motor Scales - Second Edition (PDMS-2) scores also improved from baseline. These suggested that improvements in motor development were deemed clinically meaningful. There were also improvements in neurological symptoms and scores that assess cognitive development.
- There are limited data available in small numbers of patients. There is a lack of efficacy and safety data for eladocagene exuparvovec in children over the age of 12 years, as well as adults. There are limited longer-term efficacy and safety data. All three studies were carried out in Taiwan, meaning generalisability to Scottish clinical practice is uncertain.
- Patients' health related quality of life (HRQoL) could not be clinically assessed. However, carers' HRQoL was assessed retrospectively in a subset of carers and these findings were promising. Health state utilities were also used in the economic case with appropriate values used from a sample of the general population.
- The costs of eladocagene are high relative to the expected health outcomes, and there are considerable uncertainties in the economic case which may result in the true cost of eladocagene being considerably higher or lower than the base case estimates.

Chair
Scottish Medicines Consortium

SMC ultra-orphan designation

Eladocagene exuparvovec has been validated as meeting SMC ultra-orphan criteria:

- The prevalence of AADC deficiency is estimated to be ≤1 in 50,000.
- Eladocagene exuparvovec has GB orphan designation for the treatment of AADC deficiency and this was maintained at the time of Marketing Authorisation.
- AADC deficiency is a chronic and severely disabling condition that has a major impact on quality of life of patients and their families. The majority of patients present a severe phenotype with early onset hypotonia, oculogyric crises, ptosis, dystonia, hypokinesia, impaired development and autonomic dysfunction.
- This condition requires highly specialised management for diagnosis and the administration of treatment.

1. Clinical context

1.1. Background

Eladocagene exuparvovec is a parenteral gene replacement therapy that contains an active biological substance. It consists of a recombinant adeno-associated virus serotype 2 (AAV2) vector containing the human complementary DNA (cDNA) for the dopa decarboxylase (*DDC*) gene. After administration into the putamen, the product results in the expression of the AADC enzyme (which metabolises levodopa and 5-hydroxytryptophan to produce the neurotransmitters dopamine and serotonin, respectively) and the subsequent restoration of dopamine production is anticipated to improve AADC deficiency symptoms, including motor function.[1, 2]

Eladocagene exuparvovec is a single-dose gene replacement therapy. Patients are expected to receive a total dose of 1.8×10^{11} vector genomes (vg), which is delivered as four 0.08mL (0.45×10^{11} vg) separate infusions of equal volume to the right anterior putamen, right posterior putamen, left anterior putamen and left posterior putamen in one surgical session. Treatment should be administered in a centre that is specialised in stereotactic neurosurgery, by a qualified neurosurgeon under controlled aseptic conditions.[1]

1.2. Nature of condition

AADC deficiency is a rare autosomal recessive genetic disorder caused by mutations in the *DDC* gene. This ultimately results in the reduced expression and availability of the AADC enzyme, and a consequential reduction in the levels of dopamine, as well as other neurotransmitters such as serotonin, noradrenaline and adrenaline.[2, 3] The global incidence of AADC deficiency is unknown but the predicted birth rates of children with AADC deficiency is 1 in 118,000 births in the European Union[4]; the condition appears to be more prevalent in certain Asian populations, such as in Taiwan and Japan.[2, 3] Clinical experts consulted by SMC advised that there are currently no known patients with AADC deficiency in Scotland; it is estimated that there are between 8 to 12 patients with AADC deficiency in the UK.[5]

Diagnosis of AADC deficiency is difficult and many individuals with this genetic disorder have not been diagnosed, or have a delayed diagnosis.[3, 4] All patients with AADC deficiency have symptoms within the first few months of life. However, despite the early onset of symptoms, the median age of diagnosis is 13 months, with a range of 2 months to 23 years, highlighting the difficulty in recognising the disease and the subsequent delays in its diagnosis.[2, 3]

People with AADC deficiency can present with a range of signs and symptoms including: hypotonia; movement disorders (such as oculogyric crises, dystonia and hypokinesia); autonomic disorders (such as ptosis, excessive sweating and nasal congestion); non-neurological symptoms (such as diarrhoea, constipation and feeding difficulties); sleeping and behavioural difficulties (such as irritability, dysphoria and excessive crying); and delayed cognitive, motor and speech development. The behavioural difficulties, as well as the oculogyric crises (seizure-like episodes where patients can experience involuntary upper movements of the eye, spasms, tremors, agitation and involuntary tongue biting), can be very distressing symptoms for patients and caregivers.[2, 3] Patients with AACD deficiency are at an increased risk of infections as a secondary complication of the condition.[3]

The disease severity can range from mild, where patients have the ability to walk independently and have functional independence in daily activities, to severe; approximately 80% of patients have the severe phenotype. These patients fail to achieve key motor milestones.[2, 3] Patients with severe AADC deficiency will be completely dependent on carers, and require round-the-clock care with all aspects of daily living.[2, 3]

Survival data are very limited, though studies and clinical expert opinion suggest that death is common in the first decade of life, but there are some documented cases of adult patients with AADC deficiency.[3, 6-8]

There are no other licensed treatments for AADC deficiency, and existing treatments do not modify the disease itself.[2, 3] At present, the treatment approach to AADC deficiency (based on international consensus guidelines) is symptomatic management through specialist multidisciplinary input and pharmacological treatment which mainly targets the dopamine pathway; this includes dopamine agonists, monoamine oxidase inhibitors (MAOIs), pyridoxal phosphate, and pyridoxine.[2, 3] However, the majority of patients, especially those with severe AADC deficiency (no motor development), do not respond to these treatments.[2, 3, 9]

2. Impact of new technology

Comparative efficacy

The key evidence to support the efficacy and safety of eladocagene exuparvovec comes from the AADC-010, AADC-011 and AADC-CU/1601 studies. Details are summarised in Table 2.1.

Table 2.1 Overview of relevant studies.[2, 10-12]

Criteria	AADC-010, AADC-011, AADC-CU/1601
Study design	Single-centre, open-label, single-arm (all conducted in Taiwan) studies. AADC-010 and AADC-011 were prospective; AADC-CU/1601 was retrospective and observational.[a]
Eligible patients	• Patients aged ≥2 years or (in AADC-010 and AADC-011 only) head circumference big enough for surgery. • Confirmed diagnosis of AADC deficiency, including cerebrospinal fluid analysis to show reduced levels of neurotransmitter metabolites, HVA and 5-HIAA, and higher L-DOPA, and more than one mutation within AADC gene. • Classical clinical characteristics of AADC deficiency, such as oculogyric crises, hypotonia and developmental retardation.
Treatments	Patients were injected with eladocagene exuparvovec into the putamen during one operating session within a stereotactic neurosurgery centre. Patients received the licensed dose of eladocagene exuparvovec, except nine patients in AADC-011, who received a higher total dose of 2.4×10^{11} vg. Treatments that affected the production of dopamine were prohibited for 1 to 12 months after surgery, including dopamine agonists, MAOIs and anti-cholinergic drugs. Medicines that only provided symptomatic relief were permitted.
Primary outcomes	Cumulative number of patients achieving four key motor milestones (full head control, sitting unassisted, standing with support, walking with assistance) assessed using PDMS-2[b] at[c]: 60 months (AADC-010 and AADC-CU/1601) and 12 months (AADC-011).[10, 12]
Key ad-hoc Secondary outcomes	• Raw scores for the PDMS-2[b] total scores and subscales. • Raw scores for the Bayley-III[d] total and subscales (AADC-010 and AADC-011 only). • Raw scores for the CDIIT[e] total and subscales (AADC-CU/1601 only). • Neurologic examination findings with respect to muscle tone (i.e. floppiness), oculogyric crisis episodes, dystonia, muscle power, and deep tendon reflex response (every month for the first year of follow-up).
Statistical analysis	No formal statistical analysis was carried out in AADC-011, and no formal sample size calculation was carried out for any of the studies due to the ultra-rare nature of the disease with very limited patient numbers. It is uncertain whether the studies were sufficiently powered to detect statistically significant results. In AADC-010, the primary outcome was computed at 24 months post gene replacement therapy. One-sided exact binomial tests were used to test the null hypothesis for each milestone (head control, sitting unassisted, standing with support and walking with assistance). Summary statistics (that is descriptive statistics) were computed for the secondary outcomes (including the change from baseline in PDMS-2 total scores).

[a]AADC-CU/1601 was a single-centre, observational study that summarised and analysed data from a single-arm, compassionate use interventional study designed to evaluate the safety and long-term benefits of administration of eladocagene exuparvovec to patients with AADC deficiency.
[b]PDMS-2 is a validated assessment of a child's motor development up to the developmental age of 5 years old, and assesses both gross and fine motor skills, and with items that specifically capture motor milestone achievement.[1] In the PDMS-2 scale, each item is scored either as 0 (skill not met), 1 (emerging) or 2 (mastery). In the primary outcome for all three studies, a score of 2 (mastery) on the specific PDMS-2 item was required for a key motor milestone to be achieved. However, a regulatory authority also deemed a score of 1 to be clinically relevant.
[c]The original pre-specified timepoint for efficacy assessment was 12 months in all three studies; however, this was subsequently increased to 24-months and 60-months (in AADC-010 and AADC-011 only).
[d]The Bayley-III scale assessed infant and toddler development across five domains: language (receptive and expressive), motor (gross and fine), social-emotional, and adaptive.
[e]CDIIT evaluates development in infants and toddlers in the domains of cognition, language, motor skills, social skills, and self-care skills. Patients received a numerical score that correlated developmental milestones. The whole CDIIT scores were calculated by adding the subtest scores.

Abbreviations: HVA = homovanillic acid; 5-HIAA = 5-hydroxyindoleacetic acid; AADC = aromatic L-amino acid decarboxylase; Bayley-III: Bayley Scales of Infant Development – Third Edition; CDIIT = Comprehensive Developmental Inventory for Infants and Toddlers; MAOI = monoamine oxidase inhibitors; L-DOPA = levodopa; PDMS-2 = Peabody Developmental Motor Scales – Second Edition; vg = vector genomes.

All three studies have been completed and the submitting company report that the data submitted are not beyond 12 months (AADC-011) and 60 months (AADC-010 and AADC-CU/1601) of follow-up for the respective studies.[2, 10, 12]

The submitting company used the intention-to-treat (ITT) populations from all three studies (n=28) to inform the clinical evidence. Data at 12 months (in all three studies), and at 60 months (AADC-010 and AADC-CU/1601), showed that at least some patients had achieved mastery (PDMS-2 score of 2 in the relevant item) of four key motor milestone achievements; the number who achieved milestones increased with time.[2]

A pooled analysis of studies AADC-010 and AADC-011, at a February 2020 data cut-off, is presented in Table 2.2. However, not all patients reached the timepoints specified in Table 2.2 at the time of the unspecified data cut-off.[2] In this pooled analysis, patients were treated with a total dose of 1.8×10^{11} vg (n=13) or 2.4×10^{11} vg (n=7) eladocagene exuparvovec during a single operative session. The results for efficacy and safety parameters were similar between the two doses.[1, 2]

Table 2.2 Primary outcomes from a pooled analysis of the AADC-010 (n=10) and AADC-011 (n=10) studies (data cut-off February 2020).[1]

	Baseline	Time interval post-treatment (months)						Overall (cumulative) post-treatment
Motor milestone (PDMS-2)	Pre-treatment N=20	0 to 3 N=20	3 to 12 N=17	12 to 24 N=17	24 to 36 N=13	36 to 48 N=8	48 to 60 N=6	From 0 to 60 months N=20
Full head control	0	1	5	6	2	0	0	14
Sitting unassisted	0	1	2	6	2	1	1	13
Standing with support	0	0	0	4	1	1	0	6
Walking with assistance	0	0	0	0	2	0	0	2

The cumulative column includes all patients who achieved that particular milestone at any point during the study up to 60 months; patients needed to reach the score of 2 (indicative of mastery of the skill) on a milestone item to be rated as having achieved that milestone.
Abbreviations: PDMS-2 = Peabody Developmental Motor Scales – Second Edition.

Study AADC-CU/1601 was conducted with therapy from an older manufacturing process, and enrolled eight patients who all received a dose of 1.8×10^{11} vg;[1] this study showed similar results at the 24-month and 60-month timepoints and are presented in Table 2.3.[2]

Table 2.3: Primary outcomes from the AADC-CU/1601 study (n=8).[2]

Motor Milestone (PDMS-2)	Timepoint	Number assessed at the timepoint	Number who achieved milestone up to the timepoint
No motor function	Baseline	8	8
Full head control	Baseline	8	0
	Month 12	8	4
	Month 24	8	4
	Month 60	6[a]	4
Sitting unassisted	Baseline	8	0
	Month 12	8	2
	Month 24	8	4
	Month 60	6[a]	4
Standing with support	Baseline	8	0
	Month 12	8	0
	Month 24	8	0
	Month 60	6[a]	2
Walking with assistance	Baseline	8	0
	Month 12	8	0
	Month 24	8	0
	Month 60	6[a]	0

[a]2 of 8 patients did not attend for voluntary assessments after month 24.
Abbreviations: PDMS-2 = Peabody Developmental Motor Scales – Second Edition.

Subgroup analyses of the three studies appear to show that the improvements in motor milestones were independent of age, gender or dose.[2]

There is also additional information from five patients from the AADC-CU/1601 study who have had ≥60 months of follow-up (ranging from 6 to 10 years); three of these patients had stable PDMS-2 scores. The other two patients experienced a decline in motor scores associated with non-gene therapy related events; prior to gene therapy.[11]

PDMS-2 data were used to inform the cost-effectiveness analysis, as a predictor of final motor milestone achievement. PDMS-2 total score was a secondary outcome in all three studies. The maximal scores are 450 (<12 month of age) to 482 (>12 months of age).[1] All patients treated with eladocagene exuparvovec showed increases in mean PDMS-2 total scores over time.[2] At a March 2019 data cut-off, the least squares mean of change from baseline in PDMS-2 total scores were: 63.3, 94.3, and 113.1 at the 12-month (all three studies), 24-month (AADC-010 and AADC/CU-1601), and 60-month (data available in AADC-010 only) timepoints respectively;

these were deemed clinically meaningful by a regulatory authority.[2] Updated results from a December 2020 data cut-off provide further reassurance.[11]

A pooled analysis of studies AADC-010 and AADC-011, at the March 2019 data cut-off (confirmed upon request by the submitting company), showed that most patients had improvements in neurological examination findings. From baseline to the data cut-off, there were reductions in the number of patients with floppiness (78% to 47%), limb dystonia (67% to 0%), and stimulus-provoked dystonia (11% to 0%).[1, 2] However, few patients had an improvement in oculogyric crisis episodes following gene therapy.[2] There were modest reductions in the frequency and duration of oculogyric crisis episodes, and this effect was sustained over time and up to 12 months after treatment. The mean time in oculogyric crisis was 12.3 hours per week at baseline; this was reduced by 1.9 hours per week at 3 months (n=16) and 3.7 hours per week at 12 months (n=6).[1, 2]

Cognitive development was also evaluated using the Comprehensive Developmental Inventory for Infants and Toddlers (AADC-CU/1601) and Bayley-III (AADC-010 and AADC-011) instruments. Across all three studies, eladocagene exuparvovec was associated with clinically meaningful improvement compared with natural history control in cognitive function.[2]

Patients' Health-related quality of life (HRQoL) data were not measured in studies AADC-010, AADC-011 or AADC-CU/1601. Carers' HRQoL was assessed retrospectively in a subset of carers of patients in the eladocagene exuparvovec studies (n=17) who completed the World Health Organisation (WHO)-BREF survey (Taiwanese version). They reported improved quality of life after gene therapy in all five domains: overall ($p<0.001$), physical health ($p<0.001$), psychological ($p<0.001$), social relationship ($p=0.006$) and environment ($p<0.001$).[11]

In the absence of direct evidence comparing eladocagene exuparvovec with best supportive care (BSC), a naive indirect treatment comparison (ITC), using pooled studies AADC-010, AADC-011 and AADC-CU/1601 for eladocagene exuparvovec and a natural history database (NHDB) for BSC, informed motor milestone achievements in the economic case. The NHDB was created as part of the regulatory approval process to serve as a control in the assessment of comparative efficacy. The naive ITC included 28 patients treated with eladocagene exuparvovec and 49 patients from the NHDB who were classified (based on a review by two independent clinical experts) as having a similar 'severe' phenotype (that is, AADC deficiency with no or poor head control by age 2 years). The submitting company also conducted a propensity score analysis but considered that this was unfeasible to use in the economic case. Further details are provided in Table 2.4.

Table 2.4: Summary of indirect treatment comparison.

Criteria	Overview
Design	A naive indirect treatment comparison. A propensity score analysis was conducted but was not used in the economic base case or scenario analysis.
Population	Patients with AADC deficiency. Severe phenotype was not specified in the systematic literature review but was defined by the submitting company as 'no or poor head control by 2 years of age'. Motor milestone achievement was assessed on a 'per statement basis' by two independent reviewers of qualitative descriptions and quantitative data, who created a scoring system anchored to PDMS-2 items.
Comparators	Best supportive care (BSC).
Studies included	Data for eladocagene exuparvovec were taken from a pooled analysis of 28 patients from the three key single-arm studies (AADC-010[10, 11], AADC-011[11, 12], AADC-CU/1601[2]). Data for BSC were taken from a NHDB, which was commissioned by the submitting company.[13, 14]
Outcomes	The proportion of patients who achieved key motor milestones (full head control, sitting unassisted, standing with support, walking with assistance) from year 1 to year 5 was assessed.
Results	The results of the naive analysis suggested that 96% of patients (47/49) with severe AADC deficiency who receive BSC achieve no motor milestones (including full head alignment, sitting, stepping and walking with assistance) over 5 years. This contrasts with results from the eladocagene studies, where the majority of patients attained motor milestones over time.

Abbreviations: AADC = aromatic L-amino acid decarboxylase; NHDB = natural history database; PDMS-2 = Peabody Developmental Motor Scales – Second Edition.

Comparative safety

No comparative safety data are available. Refer to the summary of product characteristics (SPC) for details.

A pooled safety analysis of all three studies (AADC-010, AADC-011 and AADC-CU/1601) was performed which included 25 patients who had completed at least 12 months of follow-up and one patient who had completed 6 months of follow-up after receiving eladocagene exuparvovec. The median duration of follow-up in the pooled safety analysis set was 45.7 months (range 6.1 to 68.3 months). Most adverse events (AEs) were mild or moderate in intensity, and occurred within the first 12 months following eladocagene exuparvovec treatment.[2]

The most common adverse reaction that was considered treatment related was dyskinesia. This was reported in 23 of 26 patients, and was prevalent during the first 2 months post-treatment; however, dyskinesia tended to decrease over time as sensitivity to the improved dopamine levels reduced.[2] Other treatment-related AEs were initial insomnia, irritability, salivary hypersecretion and feeding disorder.[1, 2]

Data on moderate to severe AEs that affected ≥5% of patients within the first 12 months of follow-up informed the economic model. Of 26 patients, 23 had experienced a serious AE, with pneumonia (13 patients) and gastroenteritis (11 patients) being the most commonly reported; these were presumed to be related to the underlying disease rather than the treatment.[2] AEs related to the neurosurgery to administer eladocagene exuparvovec included cerebrospinal fluid leakage (3 patients), hypotension (6 patients), endotracheal intubation complication (1

patient), post-operative skull defect (1 patient), skin injury (1 patient) and subcutaneous haematoma (1 patient).[2, 11]

Most patients (n=18) had a positive anti-AAV2 antibody response within the first 12 months following eladocagene exuparvovec treatment; in general, these antibody levels stabilised or declined with time. There was no specific follow-up program to capture potential immunogenicity reactions in any of the clinical studies. However, the presence of anti-AAV2 antibodies in the clinical studies was not reported to be associated with increase in severity, number of adverse reactions or with decreased efficacy.[2, 11]

Clinical effectiveness issues

The key strengths and uncertainties of the clinical case are summarised below.

Key strengths:

- Eladocagene exuparvovec is the first medicine licensed for severe AADC deficiency, with a mode of action that aims to treat the cause of the condition itself, whilst current treatments are used off-label in an attempt to manage symptoms associated with the disease.[2, 3, 9] Clinical experts identified by SMC confirmed that there is a high unmet need in this condition.
- In three clinical studies (AADC-010, AADC-011 and AADC-CU/1601), eladocagene exuparvovec treatment resulted in patients achieving key motor milestones, with most achieving head control and sitting unassisted; the number who achieved these key motor milestones appeared to increase over time. Total PDMS-2 scores also improved from baseline. These improvements in motor development were deemed clinically meaningful.[2] There were also improvements in neurological symptoms and scores that assess cognitive development.

Key uncertainties:

- The main evidence to support the use of eladocagene exuparvovec comes from three small, open-label, single-arm studies. Whilst there are legitimate ethical and practical reasons for these study design limitations, there still remained the potential for assessments to be biased by the investigators. Additionally, there were no reported centralised or independent assessments for any of the outcomes in any of the studies, which would further reduce any bias relating to knowledge of the intervention and assessment of outcomes.
- There is a lack of efficacy and safety data for eladocagene exuparvovec in patients over the age of 12 years.[1, 2] The AADC-011 study had a maximum age of 6 years in their inclusion criteria, whilst the age range of patients at the time of receiving eladocagene exuparvovec was 19 months to 8.5 years old.[1]

- There are long-term data beyond the originally specified 12-month assessment timepoint in all three studies. However, long-term data are not available for all the enrolled patients and the outcomes for those not followed-up long-term are unknown. It is unclear whether all the participants who did not attend for the voluntary follow-up assessments beyond 12 months differed to those who did attend.[2, 5]

- In all three studies, no missing value imputation was to be used and all analyses were to be based on the observed data; this essentially means the last observation was carried forward (LOCF).[2, 5] For all three studies, the safety and efficacy analysis populations were to include all enrolled patients treated with eladocagene exuparvovec. However, the primary outcome in the AADC-011 study used the number of patients assessed at each 3-month timepoint as the denominator (which contrasted with AADC-010 and AADC-CU/1601). This could bias the results of the primary outcome in favour of eladocagene exuparvovec.[5]

- This is an ultra-rare condition and the three studies likely comprise a significant proportion of all the people diagnosed with the condition worldwide. All three studies were carried out in Taiwan, and all but one patient were of Chinese descent.[11] As a result, all patients had the AADC deficiency founder mutation (IVS6+4A>T) which is uncommon in patients not from an Asian family background.[2, 4] However, there is no established correlation between genotype and phenotype in AADC deficiency at present.[3, 4] It is suggested that genotype would unlikely affect the efficacy and safety of eladocagene exuparvovec, because it restores the faulty *DDC* gene irrespective of the specific mutation type.[5]

- The results of the ITC are highly uncertain due to the naive methods used and the limited quality of the data sources, including three single-arm studies for eladocagene exuparvovec and non-randomised data from a NHDB for BSC, with high levels of missing data. In particular, there was only limited information in the NHDB about which treatments patients received as part of BSC. A propensity score analysis was conducted to account for differences but due to poor overlap between the populations, the effective sample size was reduced considerably and the weights were considered highly unstable. Therefore, the submitting company concluded that the ITC was unfeasible to use in the economic base case. Furthermore, they noted that results of the naive analysis favoured BSC. The statistician consulted by SMC considered that a naive analysis was probably reasonable given the inherent limitations with the data, but noted that limitations in the presentation of the results increased uncertainty.

Eladocagene exuparvovec has received marketing authorisation under exceptional circumstances (it does not have a conditional marketing authorisation). The European regulator has included a number of obligations:

- In order to further characterise the long-term efficacy and safety of eladocagene exuparvovec in patients with AADC deficiency and with a severe phenotype, the submitting company shall submit the results of the AADC-1602 study, a 10-year follow-up of the patient population enrolled in the clinical studies AADC-CU/1601, AADC-010 and AADC-

011. The submitting company are required to provide annual submissions to the European Medicines Agency (EMA), and then a final report by 30 June 2030 (10 years follow-up).[2]

- In order to further characterise the long-term efficacy and safety of eladocagene exuparvovec in patients with AADC deficiency and with a severe phenotype, the submitting company shall conduct and submit the results of study PTC-AADC-MA-406, an observational, multicentre and longitudinal study of patients treated globally with the commercial product, based on data from a registry, according to an agreed protocol.[2]
- The Medicines and Healthcare products Regulatory Agency (MHRA) will review any additional information every year and update the SPC as necessary.[2, 15]

3. Impact beyond direct health benefits and on specialist services

Compared with a lifetime of no motor function and severe symptoms, the achievement of key motor milestones and improvements in cognition and language could be profound and life changing for patients and their carers. These benefits could allow patients to attend school, participate in activities of daily living, and potentially contribute to family life and wider society. There is also the consideration that a healthier child will reduce the emotional and physical burdens faced by their families; this would increase their quality of life.

The administration of this new gene replacement therapy will have service implications. It is anticipated that the neurosurgery procedure would be carried out at a specialised centre in England (Great Ormond Street Hospital); therefore, the increased demand on services in NHS Scotland is unlikely to be significant. If eladocagene exuparvovec results in an improved prognosis, the care requirements of patients may change over time, but patients are likely to continue to need multi-disciplinary management.

The extremely high upfront acquisition cost for this single-dose treatment is associated with financial risk to the service if the long-term predicted clinical benefits do not materialise.

4. Patient and carer involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from The AADC Research Trust Children's Charity, which is a registered charity.
- The AADC Research Trust Children's Charity has not received any pharmaceutical company funding in the past two years.
- AADC deficiency is a multifaceted life-threatening disease causing major physical, autonomic and emotional dysfunction in children suffering the disease. Symptoms are variable amongst patients but almost all suffer hypotonia and oculogyric crisis (OGC) with a greatly reduced quality of life. The majority require 24-hour care and the use of multiple mobility aids. AADC deficient children have difficulty with speech and swallowing, with a

high risk of aspiration and pneumonia. The impact on the carer of a child with AADC deficiency is extreme, the myriad of symptoms suffered can be extremely painful with little to no way of communicating their needs to a carer.

- Current treatment for AADC deficiency relies on repurposed antiparkinsonian medications in an attempt to help, support and reduce symptoms. Medications, originally developed for patients with movement disorders, are used off-label in infants and children with AADC deficiency, and are often unhelpful, difficult to titrate and cause significant and dangerous side effects.
- Gene therapy has the potential to change the course of the disease, providing patients with an opportunity to lead a more independent life and offering their families the chance to see their children grow and flourish beyond what was once thought possible. A parent described how eladocagene exuparvovec and physiotherapy had transformed the life of their child with AADC deficiency and in turn their whole family's life.
- The major disadvantages of the new medicine are the risks of undergoing invasive brain surgery and the side effects during recovery. It is not a cure but given that re-purposed medications do not significantly help most children with AADC deficiency, the new gene therapy is considered worthwhile, in spite of the risks.

5. Value for money

5.1. Economic case

The economic evaluation provided a cost-utility analysis of eladocagene exuparvovec compared with best supportive care for patients aged 18 months and older with a diagnosis of AADC deficiency with a severe phenotype.

Table 5.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost utility analysis
Time horizon	Lifetime (100 years).
Population	The model considered patients aged 18 months and older with a diagnosis of AADC deficiency with a severe phenotype. There was no positioning as there are currently no other licensed therapies for AADC deficiency
Comparators	Best supportive care (although eladocagene exuparvovec patients also receive best supportive care as it amounts to management of symptoms). Symptom management options included MAOIs, dopamine agonists and vitamin B6, plus potentially anticholinergic agents, benzodiazepines, melatonin, nasal decongestants – depending on the health state of the patient, and clonidine use was assumed for 10% of patients in each state.
Model description	The perspective for the economic evaluation was NHS Scotland and social work. A cohort model with five motor milestone states (plus death) was used to estimate costs and utilities over a lifetime time horizon. The motor milestone states were 1) no motor function, 2) full head control, 3) sitting unassisted, 4) standing with support and 5) walking with assistance. Model cycle length was 3 months.

Clinical data	Clinical data for the model came from the three studies listed in the clinical evidence sections of the NPAF, namely AADC-010, AADC-011 and AADC-CU/1604. As these studies were not comparative, data for the best supportive care comparator came from a natural history database of 49 patients assumed to have the severe phenotype of AADC, based on the information in each reported case study. An indirect comparison was attempted but owing to the amount of information on variables that could be used to match natural history patients to eladocagene exuparvovec patients being minimal, the submitting company did not proceed with this and so the treatment comparison is naïve.
Extrapolation	A Bayesian growth model predicts PDMS-2 scores over 12 years for the intervention group, based on observed PDMS-2 scores observed from the study up to a maximum of five years. The submitting company has clarified that they used a 12 year time frame to be consistent with the duration of motor function development in a healthy child. There is considerable overlap between the observed and predicted scores up to five years, and beyond that there is negligible further growth (or otherwise) predicted in the absence of observed data. The predicted PDMS-2 scores are then used as an explanatory variable in an ordered logit model whereby the dependent variable is the five motor milestone states. Final predicted motor milestone achievement after the development phase timeframe is used as the basis for predicting long-term survival, which was based on a study on cerebral palsy patients (Brooks et al 2014), although tested in scenario analysis.
Quality of life	Utility scores were derived from a published Time to Trade Off (TTO) exercise for this submission. Standard gamble and discrete choice experiment alternatives (also found in the literature having been conducted for this submission) were tested in scenario analysis. Values used in the base case were as follows: 0.494 (no motor function), 0.537 (full head control), 0.631 (sitting unassisted), 0.676 (standing with support) and 0.728 (walking with assistance).
Costs and resource use	Model costs include acquisition costs of treatment, medicines costs for best supportive care, resource use incurred from visits to multi-disciplinary staff, imaging and laboratory tests, mobility equipment (e.g. wheelchairs) and the cost of treating adverse events
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.

5.2. Results

SMC would wish to present the with-PAS cost-effectiveness estimates that were assessed by SMC. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. List price results were also confidential and therefore no base case or sensitivity analysis results can be presented.

Sensitivity analyses

The one-way sensitivity analysis indicated that results were sensitive to utilities and resource use incurred in the no motor function and sitting unassisted health states for occupational therapy and physiotherapy. Scenario analysis showed that the results were sensitive to aspects such as the inclusion of carer effects, assumptions surrounding the

developmental phase in the model, the time horizon for the analysis, and the inclusion of travel and accommodation costs for patients and their families.

5.3. Key strengths:

- Clinical data available for the relevant patient population, even though sample sizes are small and the studies are not comparative.
- Most choices regarding parameter selection in the model have been well-researched; literature reviews have been conducted for relevant published sources of information and the company also elicited UK expert opinion which is particularly useful given how rare this condition is. Considerable effort has gone into the inclusion of carer disutilities and cost considerations (in scenario analysis) for travel and accommodation costs needed for NHS Scotland patients to access treatment in England.

5.4. Key uncertainties:

- The assumptions surrounding PDMS-2 scores and motor milestone health states. These seem overly predicted compared to what may be necessary given the observed data. The rationale for predicting data could have been reasonable in this situation, for example, the initial Bayesian growth component may have been used as a way to minimise missing data for the later ordered logit regression that specifies the motor milestone state based on predicted PDMS-2 score, because otherwise missing values would have been excluded and the sample size for this study population is already small due to the nature of the disease. However, it remains necessary to try to clarify the extent to which the data informing the ordered logit model uses predicted data from the earlier Bayesian growth model and if using observed only data were possible.
- In the Bayesian growth model, changes in predicted model state beyond the timeframe for which observed data were available were minimal, but particularly with regard to the possibility of deterioration or treatment waning in the longer term no deterioration is assumed either, and structurally this may be difficult to amend in the model, which is potentially an issue because it also remains unclear whether there is consistency between the economic and clinical results due to the data cut-off time points.
- A time horizon of 100 years is long compared to what might be expected in this patient population. The base case ICERs are considerably higher when this is reduced to 10, 20, 30 and 40 years respectively. The handling of deaths in the longer term applies mortality for cerebral palsy patients from the literature as the best proxy for long-term survival depending on final motor state achieved after the development phase. Upon clarification the company confirmed that clinical experts had agreed cerebral palsy patients offered a more suitable proxy than spinal muscular atrophy patients (although survival based on this group of patients was used in scenario analysis and lowered the ICER). However, the submitting company also noted cerebral palsy deaths were being used to inform mortality in the

development phase of the model as well (in addition to all-cause mortality from routine ONS data). The use of cerebral palsy mortality in the development phase of the model adds some uncertainty.

- For best supportive care patients the natural history database did not contain enough information to allow matching against intervention patients, so the comparison is naïve.
- The proportion of available patients who had the severe phenotype from the natural history database seemed small in comparison to what has been said about the epidemiology of the severe phenotype in practice. 30.6% were missing information on symptomatic treatments used. However, the submitting company has clarified that there are differences in how disease severity is defined in the literature, and in some cases there was insufficient information reported to determine disease severity that would allow inclusion into the natural history data used to inform the best supportive care arm of the model.
- The extent of uncertainty in the results was tested with combined scenario analyses; for example by limiting the development phase for the intervention group to equivalent to BSC (5 years) plus reducing the time horizon and using the appropriate 3.5% discount rate. An analysis was also provided that used the scenario analysis utilities from a discrete choice experiment and survival extrapolation based on spinal muscular atrophy patients.
- There was also discussion of uncertainty around any potential benefits on cognitive function and the impact that this could have on the patient and carer.

*Other data were also assessed but remain confidential.**

6. Costs to NHS and Personal Social Services

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

7. Guidelines and protocols

In 2017, the International Working Group on Neurotransmitter Related Disorders (consisting of experts in paediatric neurology and biochemistry) published a consensus guideline on the diagnosis and treatment of AADC deficiency.[3]

8. Additional information

8.1. Product availability date

25 January 2023.

Table 8.1 List price of medicine under review

Medicine	Dose Regimen	Cost per course (£)
Eladocagene exuparvovec 2.8 vector genomes (vg)/0.5mL solution for infusion	A total dose of 1.8×10^{11} vg, administered as four 0.08mL (0.45×10^{11} vg) infusions (two per putamen).	£3,010,451

Doses are for general comparison and do not imply therapeutic equivalence. Costs are from the submitting company's NPAF on 13 June 2023. Costs calculated using the full cost of vials assuming wastage. Costs do not take any patient access schemes into consideration.

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This assessment is based on data submitted by the applicant company up to and including 14 July 2023.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC assessment report.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When a medicine is available through the ultra-orphan pathway, a set of guidance notes on the operation of the patient access scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC assessment report.

Assessment report context:

No part of the assessment summary on page one may be used without the whole of the summary being quoted in full.

This assessment represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.